Health-Economic modeling using Markov model and application in R

Master Thesis

Master in *Sciences, Technologies and Health*,
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Auteur
Yonatan Carlos CARRANZA ALARCON

Superviseurs
Benoit LIQUET
Louise BASCHET
Sebastien MARQUE

Lieu de stage
UFR Sciences et Techniques de la Cote Basque - Anglet

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Abstract

Les modèles markoviens sont des outils statistiques puissants pour analyser et évaluer les consequences en coût et en santé des nouvelles interventions de soins de santé (i.e. une evaluation médico-économique). Ceux-ci étant souvent utilisés par des économistes de la santé qui ont essayés de les mettre en œuvre à l'aide d'outils simples à utiliser mais pas forcément les plus adaptés ou évolutifs.

Ainsi, la recherche des outils pour mettre en œuvre ce genre de modèle est devenu un enjeu majeur, car l'utilisation de tableurs (de type Microsoft Excel) est source d'erreurs et limite la traçabilité et le contrôle qualité, en outre, ils ne sont pas non plus spécialisés pour résoudre des problèmes statistiques.

Capionis, société de conseil en biostatistiques, cherche à présent à améliorer leur processus de mise en œuvre en s'appuyant sur des outils qui puissent optimiser et/ou automatiser un sous-processus du processus global (e.g. automatisation du compte-rendu de graphiques d'analyse de sensibilité).

Pour cela, le paquet *Heemod* de R est une alternative qui nous a semblé intéressante. Nous nous sommes donc attachés à évaluer et analyser le paquet, en mettant en œuvre plusieurs cas réels d'évaluation médico-économique, déjà développés et validés par l'équipe de biostatistiques chez *Capionis*.

Malgré la nouveauté du paquet et les difficultés rencontrées en reproduisant les résultats médico-économiques due aux caractéristiques manquantes, nous n'avons pas trouvé de problème de précision des résultats numériques, néanmoins, sa flexibilité pour implémenter ou migrer des cas réels n'est pas satisfaisante contrairement à l'outil Microsoft Excel. Nous ne pouvons donc pas prétendre de juger l'efficacité et l'efficience du paquet *Heemod* par rapport à Microsoft Excel aussitôt, étant donné que ce dernier est utilisé depuis plus de 20 ans contrairement au paquet *Heemod* (environs 1an).

En outre, nous avons aussi développé une "petite" plate-forme web pour l'utilisateur final et/ou la communauté. Cette plate-forme, utilise le paquet *Heemod*, et a été implémentée entièrement sur R avec Shiny.

Mots clés: Markov multi-état, Coût-efficacité, Médico Economie, simulation Monte Carlo, Shiny.

Abstract

Markov models are powerful statistical tools for analyzing and assessing the cost and health consequences of new health-care interventions (i.e., a health-economic evaluation). These are often used by health economists who have tried to implement them using tools that are simple to use but not necessarily the most adapted or scalable.

Thus, the search for the tools to implement this kind of model has become a major challenge because the use of spreadsheets (of the Microsoft Office Excel type) is a source of errors and limits the traceability and the quality control, in addition, they are not specialized in solving statistical problems.

Capionis, a biostatistics consulting firm, is now seeking to improve their implementation process based on tools that can optimize and/or automate a subprocess of the global process (e.g. automated graphics reporting Sensitivity analysis).

For this, the Heemod package of R is an alternative which has seemed to us interesting. We have therefore focused to evaluate and analyze the package, implementing several real cases of health-economic evaluation, already developed and validated by the team of biostatistics at Capionis.

Despite the novelty of the package and the difficulties encountered in reproducing health-economic results due to the missing characteristics, we have not found any problem with the accuracy of numerical results, but its flexibility to implement or migrate real cases is not satisfactory in contrast to the Microsoft Excel tool. Then, we can not pretend to judge the efficiency and efficiency of the *Heemod* package compared to Microsoft Excel, since it has been used for over 20 years unlike the package (around 1 year).

In addition, we have also developed a "simple" web platform for the end user and/or the community. This platform uses Heemod package, and was fully implemented in R with Shiny.

Keywords: Multi-state Markov, Cost-effectiveness, Health-economic, Monte Carlo simulation, Shiny.

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Remerciements

I would like to thank my supervisors Benoit LIQUET, Sebastien MARQUE and Louise BASCHET who taught me, guided, followed and oriented and who answered all my questions and other problems encountered during this modest work. I would also like to thank my parents, especially my mother Gladys ALARCON VERA, who have always supported me, encouraged and helped

Chapter I

Introduction

What is health-economic evaluation?

We could define the health-economic evaluation as the comparison of a base intervention[1] (or current intervention) against one or more alternatives interventions for the traitement of a specific pathology (e.g. fever, liver cancer, heart disease,...), in terms of costs and consequences to long-term, or else, we can also cite the definition given by *High Authority of Healthcare in France* (H.A.S. in French).

> "Health-economic evaluations consists about comparing the medical interest of an act, a practice, a medical product, an innovative organization or a screening program, etc, and costs which they generate. It provides informations to governments and healthcare professionals on the economic consequences of diagnostique or therapeutic practices or on screening programs".

However, the first questions that arise me were: ***what is the value of a health-economic evaluation and why is it important to do so?***.

Due to scarce healthcare resources of the government, is that healthcare decision-makers require of suitable information in order to efficiently allocate them. Therefore, the health-economic evaluation serves to evidence the costs and benefits of a new intervention versus the old intervention, so that, Decision-makers can allocate resources efficiently to "well-deserved" intervention.

How can we implement a health-economic evaluation?

In figure 1.1, we have drawn up a simple scheme of stages to model health-economic evaluations. Firstly, we start to choose a ***decision model*** that reflects well the problematic of intervention to evaluate, and we also collect in parallel summarized data from all clinical trials, meta-analysis, registers or hypotheses which are well founded and justified in an ***"evidence-based medicine"*** approach. Then, we should choose a *economic evaluation* method that can give us relevant information to make a decision by taking advantage in terms of costs and consequences.

In the third stage, we could analyze the uncertainty related to input data that affect outcomes of our decision model. Finally, the health decision-makers can make decision.

So, what is the current problematic in Capionis?

Currently, Capionis is a consulting firm which is specialized on statistics applied to life sciences and healthcare (epidemiology, clinical research, health-economics), besides it was created in 2007 by ***Sébastien MARQUE*** and ***Stéphane OUARY***. In the context of the consulting in health-economic, collaborators (including ***Louise BASCHET***) validate or create new health-economic models using ***Microsoft Office***

[1] An intervention is a combination of program elements or strategies designed to produce behavior changes or improve health status among individuals or an entire population, for more information on http://health.mo.gov/data/interventionmica/index_4.html.

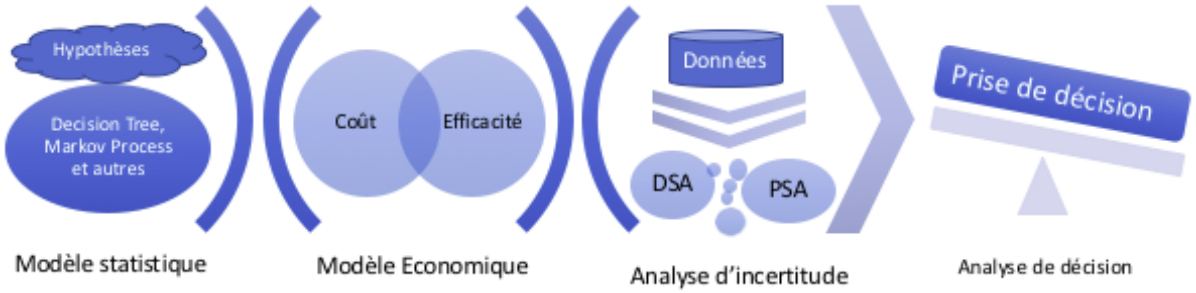


Figure 1.1 – Base scheme for implementing a health-economic evaluation

Excel as a software tool to implement them. This last being the only trustworthy for healthcare authorities, because of that the methods and guidelines have been created by English economists and they have chose "Excel" as the easiest to use. In addition, this tool is in some situations a source of errors and have limits of traceability and quality control, as well as other drawbacks. Therefore, the search for a software tool implementing this kind of model has become a major issue in the health sector, as well as the final results certification for trustworthy using of healthcare authorities.

What was the internship objective?

As part of my internship as a statistician in Capionis. I aimed to find out a solution to the problem presented previously and to achieve it. Firstly, I started to learn the theoretical and practical part that involves setting up a health-economic evaluation. Then, I had to search for a package on R language that satisfies the necessary requirements and validates the usage flexibility (i.e. design) as well as the accuracy of results compared to some cases already implemented by Capionis.

In addition, I have developed a *rudimentary* demo web application in R-Shiny to display the results of a case health-economic evaluation, as well as being able to modify the entries of the model, thus, it refreshes the results obtained beforehand (i.e. interactive interface).

In summary, the rest of memoir is organized in the following way. Chapter 2 describes the decision models as well as the economic evaluation models for the healthcare context. Chapter 3 deals with the search for the package and validation at the conceptual level, that is, if it meets the needs. Chapter 4 shows the implementation of an intermediate-level real case of health-economic evaluation. Chapter 5 discusses a web package coded in R-Shinny, in order to display the results obtained, and also, to modify model entries. Finally, in chapter 6, we will make a complete assessment and the conclusion of the internship, in addition to possible future work.

Chapter II

State of the art

The aim of this chapter is to discuss about existing decision models to implement and to evaluate health-economic studies. Theses models have to be necessarily simplifications of the reality as well as taking into account all possible particularities of real clinical studies, since it isn't possible to consider everything. We'll also learn how to quantify the uncertainty around decision models by using sensitivity analyses methods for health-economic models.

At the end of the chapter, we'll have enough information to be able to choose correctly an adequate decision model that reflects the healthcare case to evaluate. Moreover, we'll see that a real clinical trial designed to evaluate a prospective cost-effectiveness analysis during a long-term follow-up may be most costly because this one needs to employ a staff for collecting, cleaning and reporting safety and other data for a long time (e.g. 20 or 30 years).

Furthermore, it's not purpose of this chapter to provide a extend information about decision model for health-economic evaluations. But, we can find more good information in [Briggs et al., 2006], [Drummond et al., 2005], [Gold, 1996], and [Sloan, 1996].

Contents

What is a Decision Model?

When we are faced with a problem of decision making, there are some questions we often ask ourselves; ***What are the best actions we must take in order to have the maximum gain and the minimum of losing?*** and how must we proceed to model (or structuration) our decisions affected by internal or external factors in the context of the problem?, as well as, how can we transparently quantify decision-making under uncertainty?.

The Decision Model provides us a way (or a vehicle) to visualize the sequences of events (or actions) in logical framework [Kuntz et al., 2013], as well as a systematic approach to decision-making under conditions of uncertainty, in which the probability of each possible event, along with the consequences of those events, is explicitly stated. [Kielhorn and Von der Schulenburg, 2000].

We can generically formulate this decision problem, in our context, as given a discrete space of strategies $\mathcal{S} = \{s_1, ..., s_M\}$, a discrete space of decisions $\mathcal{D} = \{d_1, d_2, ..., d_N\}$ containing each one a payoff[1], such as costs $\mathcal{C} = \{c_1, ..., c_N\}$ and consequeces $\mathcal{E} = \{e_1, ..., e_N\}$.

In the context of the internship, we will limit to evaluating in practical cases (chapter IV) to only two different strategies (although we can also evaluate several) from a set of decisions containing payoffs, then the strategy space is reduced to $\mathcal{S} = \{s_1, s_2\}$.

In the rest of this chapter, we are going to talk "generically" about of two most often used *Decision Models* in the context of the *Health-Economics Evaluation*, such as; *Decision Tree Models* and *Multi-state Models*.

2.1 Decision Tree Models

The decision makers are faced to analyze multiple strategies $\mathcal{S}$ involving to make several successive decisions $\mathcal{D}$, rather than just a single decision. This latter being able to be drawn as a *tree-shaped diagram* (or decision tree, Fig. 2.1) which represents the sequence of events taken under uncertainty (since we don't know with certainty *the correct pathway* because of incomplete knowledge of the problem).

A typical decision tree model structure is shown in Figure 2.1, where this one must be constructed from left to right, starting with:

- A decision question that represents the ***decision node*** (i.e. *square symbol*) which can have more than two *events* as outcomes.
- These events are represented by ***chance nodes*** (i.e. *circular symbols*) which each of them has a probability of *chance* (or occurrence) and payoffs (costs to related to event, and effects such as life-years gained and quality-adjusted life years gained).
- Finally, the outcomes of some chance nodes can finish in ***terminal nodes*** (i.e. *triangle symbols*) that represent the final pathway of the successive events.

Remark 2.1.1 *It should be remarked that we used the word* **"effect"** *to express the notion of consequences (or benefits) of a chosen strategy $s_j \in \mathcal{S}$ which can be defined by different indicators such as the quality average of life gained (QALY), the number of years gained with no adverse events (e.g. a heart attack).*

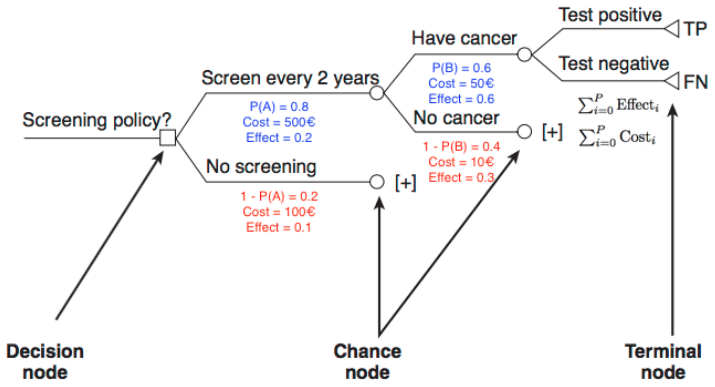


Figure 2.1 – Decision tree model structure: cost-effectiveness and probabilities inputs. [Gray et al., 2010]

The sum of all cost and all effects within of chosen pathway ($\sum_{i=0}^{P} \text{Cost}_i$ and $\sum_{i=0}^{P} \text{Effect}_i$, where P is the size of pathway) represent the overall total spending of the chosen decision d_k at the beginning (i.e. the decision node).

[1] A payoff include a cost and a consequence (or effectiveness) related to each chosen decision[Gray et al., 2010].

This tree decision model is used to analyze the impact of several different alternatives d_k (or pathways) and to evaluate the total spending $\{c_k, e_k\}$ (cost and consequences) of each alternative, as well as quantifying uncertainty about decision-making using *Monte Carlo simulation* (see section 2.5).

However, it's limited in as much as it's designed to capture what happens at a point in time, so it doesn't have an explicit sense of time passing (or patient history in clinical trials), as well as its complexity when the trees became bushy, e.g. in Figure 2.1, we've only got two possible outcomes given a screening in the first two years, and if we want a screening in the next two years, we'll get four possible outcomes, consequently, if the patient follow-up is during 40 years we'll get 40 possibles outcomes!!. That's why decision trees aren't made to model longitudinal studies such as clinical trials.

In the next section, we are going to talk about a model adapted to longitudinal studies (i.e. multi-state model).

2.2 Multi-state model

A multi-state model is a generalization of a survival model observing several events of interest [M. Machado et al., 2009]. In this section, we will review briefly these concepts (see appendix VI for more information about longitudinal study and survival model).

We define a continuous time stochastic process $\{X(t), t \in \mathbb{R}^+\}$ with values in a discrete set of states $E = \{1, 2, 3, ..., r\}$. The change of state is called a transition, or occurrence of event, and these states can be classified in transient or absorbing (i.e. non transition). We can, therefore, generalize the equation of transition intensities of the appendix VI-6.1:

$$\alpha_{hj}(t; \mathcal{F}_{t^-}) = \lim_{\Delta t \to 0^+} \frac{p_{hj}(t, t + \Delta t | \mathcal{F}_{t^-})}{\Delta t}, h, j \in E \tag{2.1}$$

where $p_{hj}(t, t + \Delta) = \mathbb{P}(X(t + \Delta t) = j | X(t) = h, \mathcal{F}_{t^-})$ represent the transition probability and $\mathcal{F}_{t^-}$ is the filtration of the Markov chain $X(t)$ or *"history of the process"* (i.e. clinical history of the patient) representing the set of events observed at time t [Liquet, 2009].

In Figure 2.2, we can see some well-known *multi-state models* such as illness-death model (also known as disability model), mortality, bivariate model, or competing risk model.

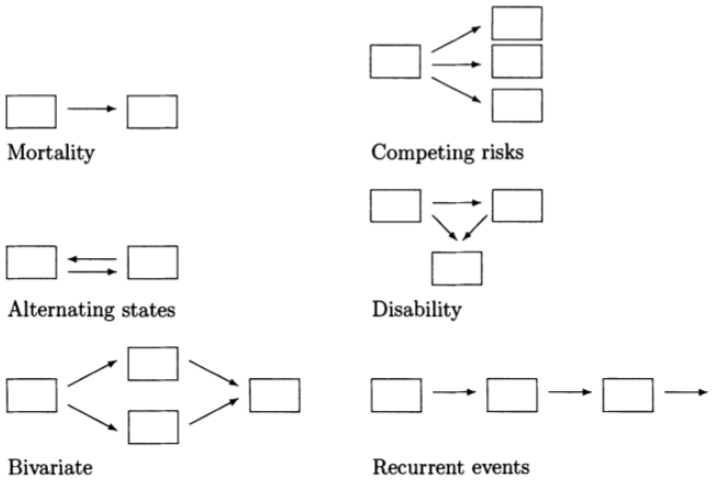


Figure 2.2 – Standards multi-state models

2.2.1 Markov model

Given the continuous-time stochastic process $X(t)$ with values in a discrete set of states (i.e. *multi-state model*), we'll henceforth assume that this process $X(t)$ will be Markovian.

Now, ***due to the fact that the studies of health-economic are evaluated to long-term*** (i.e. long-term patient follow-up) and the available data from clinical trials relevant to the study are of short-term patient follow-up[2], is that we are forced to use the ***extrapolating of survival curves*** for being

[2]Here, we cannot calculate transition probabilities with Kolmogorov's "forward" equations [Cox and Miller, 1977] (i.e. $\frac{\partial P}{\partial t}(s;t) = P(s;t)Q(t)$), because we haven't all available patient-level data at long-term.

able to calculate transition probabilities beyond the duration of follow-up, by performing a ***synthesis of available data*** from all clinical trials relevant to the study.

Extrapolating of survival curves

Due to the fact that the follow-up time in a clinical trial is too short for a health-economic study at long-term (i.e. calculations of costs and consequences on life-long of a patient), it is often necessary to resort to assumptions of extrapolation of short-term data.
According to the methodological guide report of [H.A.S., 2011], hypothesis of extrapolation over a long-term of available data should be justified with statistical methods or meta-analysis.
For example, in the figure 2.3, we have a non-parametric estimation of the survival function that was made with *Kaplan-Meier method*, this one does not allow to extrapolate beyond the duration of follow-up of the clinical study, on the other hand, if we assumption certain hypothesis on the form of the distribution of the survival data, we could use parametric methods allowing to extrapolate beyond the available survival data.

Remark 2.2.1 *The input parameters used by the extrapolation of data have a standard error or a sampling variability since these were calculated from a sample that could not represent all the variability of the studied population. Therefore, it is essential to study the uncertainty of these parameters (see section 2.5).*

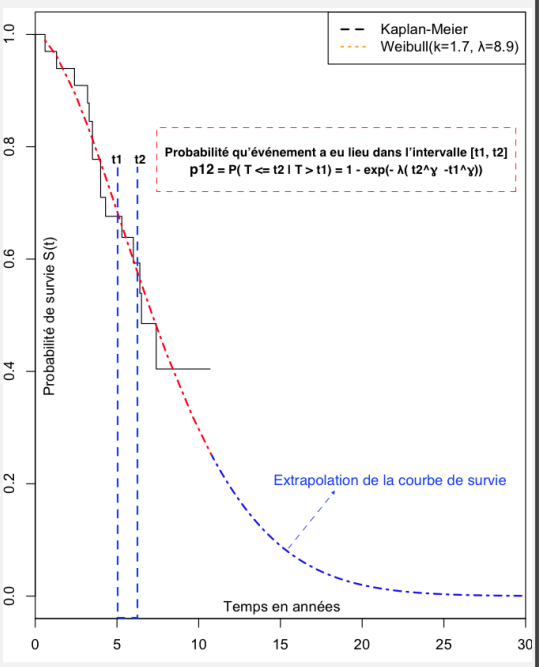


Figure 2.3 – Extrapolation of survival curves

Having said that and taking into account that we cannot estimate changes in a patient's state of health in the Markov process. We're going to constrain the process $X(t)$ to a discrete-time[3] instead.

Definition 2.2.1 *We place in a discrete-time Markov chain* $\{X(t), t \in \mathbb{Z}^+\}$ *with values in a discrete set of states* $E = \{e_1, e_2, e_3, ..., e_r\}$*, where each state will have a cost and a consequence (e.g. effectiveness) equal or greater of zero, i.e. costs* $C = \{c_{e_1}, ..., c_{e_r}\}, c_{e_i} \geq 0$ *and consequences* $D = \{d_{e_1}, ..., d_{e_r}\}, d_{e_i} \geq 0$.

Where $t_{i+1}, t_i \in \mathbb{Z}^+, t_{i+1} - t_i$ represents the size of the Markov cycle (or ***Cycle Length*** in health-economic evaluations).

Cycle Length

An another important concept to be taken into account is *Cycle Length* of each iteration of Markov process (i.e. $t_{i+1} - t_i = l$), this is a crucial decision in each clinical study, because this one represents the minimum amount of time that any individual will spend in a state before the possibility of transition to another state [Gray et al., 2010].
The choice of the length of the cycle must be consistent with the *time horizon* (i.e. the period of evaluation, e.g. 30 years), since it can not be greater than this one (i.e. $l < T$) and it divides the time horizon, in most cases, into equal components of size l, such as weeks, months or years, but it's possible, it can also vary.
Finally, this cycle length affects all inputs of model, for instance, if the cycle length is annual, then the probabilities de transition and payoffs should also be measured annually, in order to run the model and compute the annual values for outcomes.

[3] It's important remark that this approximation can yield biased cost-effectiveness estimation with long cycle periods and if no half-cycle correction is made [van Rosmalen et al., 2013].

Markov process offers us an interesting property in order to simplify the equation 2.1, which tells us that; ***"the necessary information to predict the future state is entirely contained in the present state of the process and does not depend on past states (absence of « memory »)"***, and given the filtration $\mathcal{F}_{t^-}$ that represents the patient's history or past, we can therefore reformulate the equation 2.1:

$$\alpha_{hj}(t) = \lim_{\Delta t \to 0^+} \frac{\mathbb{P}(X(t+\Delta t) = j | X(t) = h)}{\Delta t}, h, j \in E \tag{2.2}$$

The ***synthesis of available data*** can give us a notion of the behavior of each transition intensities $\alpha_{hj}(t)$, this one can be a constant or a time-dependent function. Under these new evidences, we can consider three types of Markov models: ***Homogeneous and Non-Homogeneous***.

Homogeneous Markov

In a homogeneous or time-homogeneous Markov model, all transitions intensities are assumed to be constant, $\alpha_{hj}(t) = \alpha_{hj}$, i.e. any risk of transiting to another state becomes constant, therefore, the transition probabilities $P_{hj}(s,t)$ depends only on $t-s$, i.e. $p_{hj}(s,t) = p_{hj}(0, s-t)$, and by simplicity we note $p_{hj}(s-t)$ [M. Machado et al., 2009], where $l = s - t$ is the cycle length of the discrete-time Markov process and our evaluation study $p_{hj}(l)$ (e.g. 1 years, 6 months, etc).

Example 2.2.1 *We are going to put a three-state model representing the evolution of liver cancer, as well as the mortality in the general population for a long period of time* $\{t_0 = 0, t_1, ...t_{n-1}, t_n = T\}$*, where* T *is the time horizon and* n *is the number of Markov cycles. The health states are; (0)-state:* good health*, (1)-state:* catching liver cancer*, and (2)-state:* death*. Thus, we should convert the transition intensity (or transition rate) to transition probability, see box 2.2.1. We assumed that the transition intensity and the transition probability are measured over a period of one year, in other words, the cycle length is* $l = 1$ *year for the discrete-time Markov process.*

Converting of hazard ratio to transition probability [Fleurence and Hollenbeak, 2007]

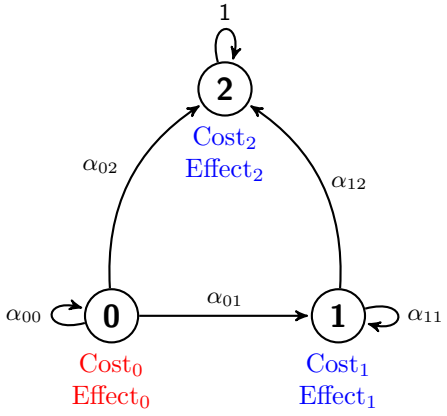
If the event of interest occurs at a constants rate α_{hj} *per time unit* t*, then the probability that an event will occur during time* t *is given by equation following:*

$$p_{hj}(t) = 1 - exp(-\alpha_{hj} t)$$

where the unit of time used in α_{hj} *and* t *must be the same. On the other hand, if we want to convert the probability to a hazard rate:*

$$\alpha_{hj} = -\frac{1}{t} ln(1 - p_{hj}(t))$$

In the appendix VI, we have tried of giving more details and mathematical proof.



$$p_{01}(l) = 1 - exp\left(-\alpha_{01}\right) \tag{2.3}$$
$$p_{02}(l) = 1 - exp\left(-\alpha_{02}\right) \tag{2.4}$$
$$p_{00}(l) = 1 - p_{01} - p_{02} \tag{2.5}$$
$$p_{12}(l) = 1 - exp\left(-\alpha_{12}\right) \tag{2.6}$$
$$p_{11}(l) = 1 - p_{12} \tag{2.7}$$

Figure 2.4 – *Markov Homogeneous to three states.* Each health state of the model is attributed to it a cost and an effectiveness (or quality of life related to the health) which depends on how long a patient has been in its health state. The end of Markov process, we could calculate overall cost expended and efficiency gained (see section 2.4).

Non-Homogeneous Markov

The evolution of a disease, the risk of mortality, or other events that change over time, they can not be considered constant in real life, they always depend on the time elapsed t since the beginning of the process (e.g. birth, disease, ..), on the other words, any risk of transiting depends on temp. Therefore, transition intensities are defined as time-dependent functions $\alpha_{hj}(t)$.

Nonetheless, the Markov process needs the transition probability $p_{hj}(s,t)$. Survival analysis can be helpful here to obtain transition probabilities for Markov process, i.e. $S(t) = exp\left(-\int_0^t \alpha_{hj}(u)du\right) = 1 - \mathbb{P}(T > t)$ ([Collett, 2015], for more concepts of survival analysis).

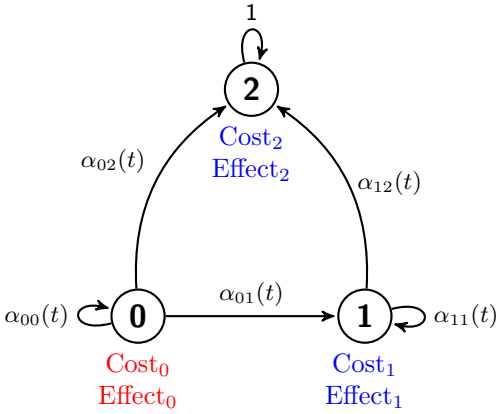
Using survival analysis, we'll estimate the discrete time transition probability $p_{hj}(s,t)$ from transition intensity $\alpha_{hj}(t)$ (or instantaneous hazard rate). We'll take two time points t_i and t_{i+1} of the set of discrete times of the Markov process, where $t_{i+1} > t_i$, and will calculate the probability transition that the event of interest occurs before or equal to t_{i+1} knowing that the event of interest has not yet occurred before t_i, that is, $p_{hj}(t_{i+1}, t_i) = \mathbb{P}(T \leq t_{i+1} \mid T > t_i)$, where the event of interest is the transition of the (j)-state to the (h)-state.

$$
\begin{aligned}
\mathbb{P}(T \leq t_{i+1} \mid T > t_i) &= 1 - \frac{\mathbb{P}(T > t_{i+1} \cup T > t_i)}{\mathbb{P}(T > t_i)}; \quad \text{such as} \quad (T > t_i) \subset T > (t_{i+1}) \\
&= 1 - \frac{\mathbb{P}(T > t_{i+1})}{\mathbb{P}(T > t_i)} = 1 - \frac{S(T > t_{i+1})}{S(T > t_i)} \\
&= 1 - \frac{exp\left(-\int_0^{t_{i+1}} \alpha_{hj}(u)du\right)}{exp\left(-\int_0^{t_i} \alpha_{hj}(u)du\right)} \\
p_{hj}(t_{i+1}, t_i) &= 1 - exp\left(-\int_0^{t_{i+1}} \alpha_{hj}(u)du + \int_0^{t_i} \alpha_{hj}(u)du\right) \\
p_{hj}(t_{i+1}, t_i) &= 1 - exp\left(-\mathcal{H}(t_{i+1}) + \mathcal{H}(t_i)\right) \qquad (2.8)
\end{aligned}
$$

Where $\mathcal{H}(t)$ represents the unknown cumulative hazard rate (or unknown cumulative transition intensity).

Based on longitudinal studies (e.g. trial or cohort study) obtained from a ***synthesis of available data***, we can get the behavior of the time-dependent function of the transition intensity $\alpha_{hj}(u)$, this one being, in most cases, the hazard ratio of a parametric survival function estimated from patient-level data (e.g. Exponential, Weibull, Gamma, ...). In the interest of better understanding, we are going to put the example 2.2.2.

Example 2.2.2 *We'll take up our example 2.2.1 and assume transition intensities as time-dependent functions. We also assume that the parametric survival function, in this example, is an Weibull distribution with λ and γ known parameters for the transition of the (0)-state to (1)-state, and an Exponential distribution with $\lambda_{\mathcal{E}}$ known parameter for the transition of the (0)-state to (2)-state.*



$$
\begin{aligned}
\alpha_{01}(t) &= \lambda\gamma t^{\gamma-1} \\
\mathcal{H}_{01}(t) &= \lambda t^{\gamma} \\
p_{01}(s,t) &= 1 - exp\left(-\lambda s^{\gamma} + \lambda t^{\gamma}\right) \qquad (2.9) \\
\alpha_{02}(t) &= \lambda_{\mathcal{E}} \\
\mathcal{H}_{02}(t) &= \lambda_{\mathcal{E}} t \\
p_{02}(s,t) &= 1 - exp\left(-\lambda_{\mathcal{E}} s + \lambda_{\mathcal{E}} t\right) \qquad (2.10) \\
p_{00}(s,t) &= 1 - p_{01}(s,t) - p_{02}(s,t) \qquad (2.11)
\end{aligned}
$$

Figure 2.5 – *Markov Non-homogeneous to three states.* On the other hand, if we had clinical patient data, we could estimate the transition probabilities using Kolmogorov's equations and helping of the maximum likelihood estimator (MLE).

Another case of Markov model also often used in the clinical trials, it's the Semi-Markov. Therefore, we'll pick up the filtrations $\mathcal{F}_{t^-}$ and we'll review it below.

Semi-Markov

In some longitudinal studies (e.g. epidemiological) can exist a temporal dependence with the patient's past, i.e. a memory, whose the Markov property of *absence of memory* cannot be considered. Let's look at some examples:

Example 2.2.3 *Consider the case where the probability of treatment failure decreases as the treatment time increases, that is, the effect of the new treatment increases their effectiveness in patients over time.*

Example 2.2.4 *Now, consider the case where the patient is in remission after a medical intervention, then, the probability of transiting from the remission state to the death or progress state is dependent on the duration of remission of a patient.*

Thus, we are interested in the variation of the transition probability from the entry to the current state (often named "sojourn time" in Semi-markov model), so we will add a new parameter, T_h, transitions intensities; $\alpha_{hj}(t, T_h)$, by representing the entry time in the h state.

Furthermore, in the context of health-economics modeling, we see a easy way to model this kind of problem by using tunnel states [Hawkins et al., 2005] [Gray et al., 2010, pag. 233] (i.e., non-absorbing states from which reverse transitions are not possible, figure 2.6).

For instance, in the figure 2.6, remission state (1) has been split in four new states, and each state represent an elapsed year without relapse or death (state 5). Thus, the probability from remission state to relapse or death state increase every passing year (i.e. $\alpha_{15}(t, T_h) < \alpha_{25}(t, T_h) < \alpha_{35}(t, T_h) < \alpha_{45}(t, T_h)$, where T_h is the time of the entry at remission state (h)), and that, furthermore, we have also added memory to the Markov model since we now know that patient in state (1.2) (i.e. "Remission after Year 2") have been disease-free survival for two years, and finally, it doesn't exist an other way to get to this state (i.e. path transition).

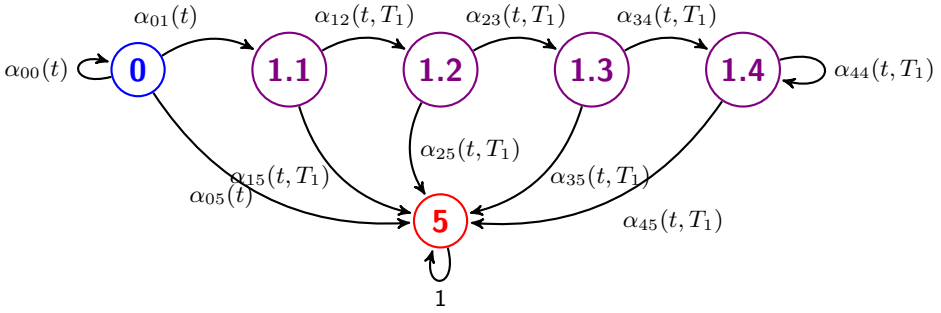


Figure 2.6 – *Semi-Markov implemented with tunnel states.* We transform it to a non-homogeneous discrete-time Markov by dividing state (1) into four states (1.1), (1.2), (1.3) and (1.4).

2.3 Health-Economic Evaluation

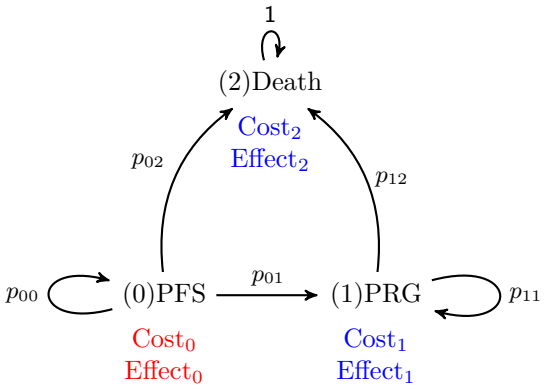
In this section, we would like to introduce briefly different technical and statistical concepts with regard to *Health-Economic Evaluation (HEE)*.

First of all, we must distinguish between statistical models and decision models in the context of HEE, the former we have available the patient-level data such as costs, effects and survival data, then using this data is preferred to build a statistical model, since the latter, ***the patient-level data may not be available*** (due to long-term patient follow-up), and therefore, an alternative approach to model health-economic evaluation is required by using published or summarized data from clinical trials (i.e. a synthesis of available data) [Khan, 2015]. Therefore, we need a ***model decision*** approach in order to compare costs and consequences between all treatments.

Thus, the decision model approach that can be chosen and recommended by the HAS is the Markov model, but ***when do we use Markov Models?***, Markov models are recommended when underlying assumptions are acceptable in terms of pathology, that is, the history of the disease can be simplified into a number of comprehensive and mutually exclusive health states. Furthermore, that health events future must not depend on the patient's prior history, but of the health event current.

Now, we will model a simple clinical case that will be used to better understand the concepts later.

Clinical case 2.3.1 *We'll study the disease of blood cancer named* ***Follicular Lymphoma*** *[Ray et al., 2010], so we are going to model this disease with three health states:*



1. Progression-free survival (PFS) : In this state, patients will receive a first-line treatment and they will be monitored for a response.
2. Progression (PRG): In this state, patients will receive several other line therapies (i.e. second-line, third-line, ...) and experiencing of remissions and relapses.
3. Death: Each patient entering this state ends their follow-up.

2.3.1 Key features for health-economic evaluations

We will now revise some key concepts used by health-economic model, and more specifically, the inputs needed for model configuration and simulation.

2.3.1.1 Strategy

A key concept in health-economic is the strategy or treatment to evaluating (i.e. $s_i \in \mathcal{S}$). In the health-care context, a strategy can be defined as a way more effective and less costly of attacking a health problem. All strategies use the same markov model (e.g. the model 2.3.1), however, each strategy has different input parameters collected of different clinical trials (i.e. costs $c_i \in \mathcal{C}$, effects $e_i \in \mathcal{E}$ and transition probabilities p_{ij}).

2.3.1.2 Payoffs

As decribed in other section, each strategy taken can be attached some sort of cost positive or negative consequence, these can be termed *"payoffs"*. The payoffs chosen for the health-economic evaluation will be consistent with the method economic chosen in the section 2.3.4.

In the context of Markov model, the lifetime of a patient is partitioned in several different health states and each one of them has a different payoff.

Let's get back at case 2.3.1, we can remark that health state have a cost and an effect (or consequence of decision taken), i.e $Cost_i$ and $Effect_i$ such as $i \in \{1, 2, 3\}$. These costs and effects are usually constantes throughout the Markov process, but there are cases where the costs and effects can depend on time, then they will be represented as continuous time-dependent function $Cost_i(t)$ or $Effect_i(t)$ where $t \in \{t_0 = 0, t_1, t_2, ..., T\}$ belongs to Markov cycle.

Furthermore, we can also have costs associated with transitions of two states $h \to j$, $Cost_{hj}$ and initial intervention (e.g. adverse costs).

2.3.1.3 Time Horizon

The time horizon is important because it reflects the period of time for which of health resources are used or are expected to be used [Khan, 2015]. In this period of time, we could like to calculate overall costs and consequences of each determined treatment (or strategy).

It should be noted that the time horizon is greater than the follow-up time in a clinical trial, because It doesn't collect information after the follow-up time could miss important information which could influence in the outcomes, and therefore also, in the decision of decision-maker.

This horizon time represents the length of markov process, i.e. $X(t), t \in \{t_0 = 0, t_1, t_2, ..., T\}$ where T is the time horizon.

2.3.1.4 Discounting

In a Markov process, health states can occur at different times in a patient's lifetime, and how each of them has a payoff, we can define all payoffs of Markov process of example 2.3.1 as:

$$Cost_{e_i}^{t_k} \text{ and } Cost_{e_h,e_j}^{t_k} \text{ and } Effect_{e_i}^{t_k}, e_i \in E, t_k \in \{t_0, t_1, t_2, ..., t_N\}$$

where e_i is a health state at cycle t_k (i.e. $X(t_k) = e_i$), and costs associated with initial interventions are not taken into account for discounting.

However, future playoffs can't be compared in this present time, because from an economist point of view, the payoffs may be worth more today than it would be worth tomorrow, and therefore, we need to reduce that value aggregate in order to compare them with present values.

Thus, discounting is a mathematical operation that allows to compare economic values (i.e. payoffs) that are spread over time, that means it's a procedure for adjusting futures economic values of health-care interventions to "present economic values" [Severens and Milne, 2004]. According to H.A.S., in the health-economic evaluation, it's necessary to discount expected costs and outcomes as soon as the time horizon exceeds 12 months.

In general, the present value (PV) of future payoffs value (PF) are estimated by adjusting them using the discount rate:

$$PV_{t_k}^{e_j} = \frac{PF_{t_k}^{e_j}}{(1+d)^{t_k}} \tag{2.12}$$

where $PV_{t_k}^{e_j}$ represents the present value of the future payoff value $PF_{t_k}^{e_j}$ of the state e_j at cycle t_k, d is the discount value recommended by H.A.S, and finally t_k is the elapsed time of Markov process.

Remark 2.3.1 *The future payoffs can be calculated as soon as we know the number of patients remaining in the state e_j at each cycle (see 2.3.3) in a discrete-time Markov process, for instance, if we assume $\mathbf{p}_{t_k}^{e_j}$ is the number of patients remaining in the state e_j at cycle t_k, then the future costs:*

$$PF_{t_k}^{e_j} = \mathbf{p}_{t_k}^{e_j} * payoffs_{e_j}$$

where $PF_{t_k}^{e_j}$ is the future payoff value of the state e_j at cycle t_k, and where payoffs in clinical case 2.3.1 are the cost and the effect; $PF_{t_k}^{e_j} = \mathbf{p}_{t_k}^{e_j,cost} * costs_{e_j}$ and $PF_{t_k}^{e_j,effect} = \mathbf{p}_{t_k}^{e_j} * effect_{e_j}$

2.3.2 Patient level simulation

According to bibliography, there are two approaches; patient-level simulation and cohort simulation.

Patient-level simulation (or first-order uncertainty), a large number of patients are followed through the model individually, and since an individual patient can only be in on state at a given time they may or may not transit between states in any given cycle. Hence, the path followed by different patients will differ due to chance. Following the patient through the model allows an overall profile of costs and outcomes to be generated for that patient's path [Briggs, 2000].

Cohort simulation (or second-order uncertainty), at the begining of the "virtual" follow-up, a large number of patients are assumed to be in a initial health state selected, and at each cycle the patients begin to move from actual state towards the others in proportions according to the transition probabilities, this is repeated until the final time of the follow-up where it's possible that all patients have reached the state *Death*. In the figure 2.7, we can see a example de cohort simulation.

According to [Briggs, 2000], the patient-level simulation have some drawback of estimation in relation to cohort simulation which is often used for health-economics evaluation, as well as recommended for the H.A.S. That is why *Capionis* uses it in all its health-economic evaluations.

2.3.3 Correction methods

Correction methods are techniques used in health economics evaluations in Markov process to correctly count the number of patients to be transited at each Markov cycle.

A Markov process can be a continuous process, and if we add to that the cohort simulation, the flow of patients between Markov states will be continuous, as shown in the top-left of the figure 2.8. Therefore,

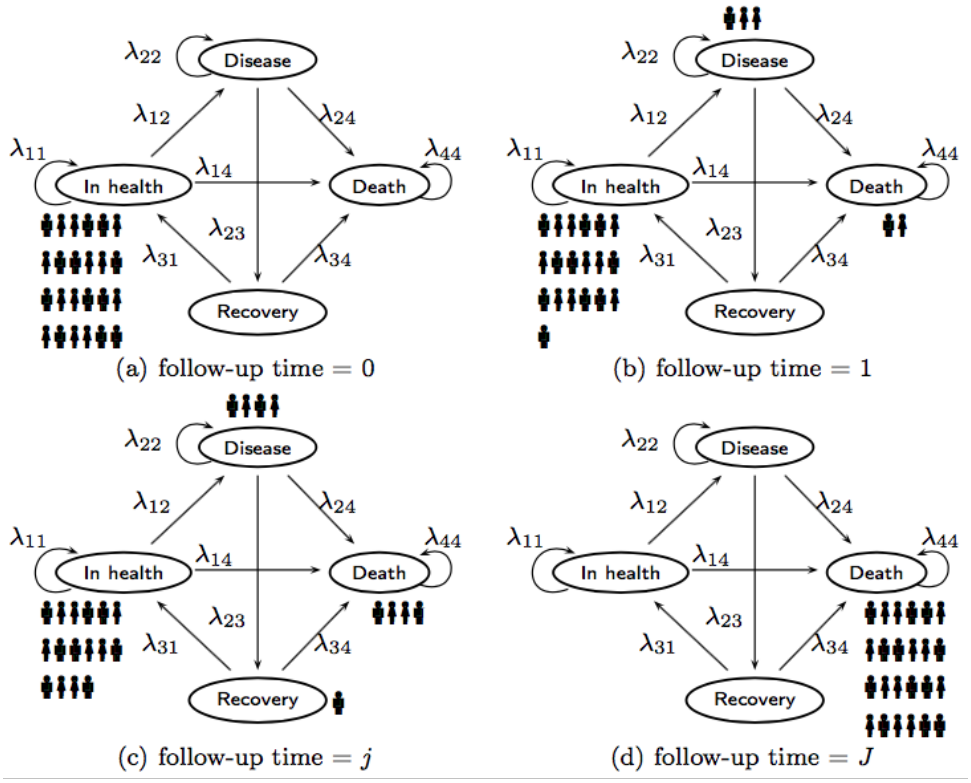


Figure 2.7 – Cohort simulation in Markov process [Baio, 2012]. (a) All patients start in the state *In health*, then in the next cycle (b) a proportion of patients have transited to state *Death*, (c) after some time j, the patients has been distributed to health states, (d) finally, after some time J or at the final time of the follow-up, all patients have reached the state *Death*.

in order to calculate the correct proportion of patients remaining $\mathbf{p}_{e_k}(t-s)$ in the state e_k and in a given interval $[t, s]$ is:

$$\mathbf{p}_{e_k}(t-s) = \int_t^s f_{\mathbf{p}}^{e_k}(u)du$$

Where $f_{\mathbf{p}}^{e_k}(t)$ represents a continuous time-dependent function to calculate the number of patients in a time t. However, this function $f_{\mathbf{p}}^{e_k}(t)$ is unknown, and it's very difficult, almost impossible, to obtain a statistical estimation, but instead, we simplify it using Discrete-time Markov process for counting the number of patients at each cycle. Currently, there are three methods to attack to discrete-time Markov process:

Beginning, In this method, the assumption is that transitions occur at beginning of cycle, as shown in bottom-left of the figure 2.8, then the patients remains in the state e_k is $\mathbf{p}_{e_k}^{start}$. This method in each cycle leads to bias in the form of a overestimated of patients remaining in the state e_k.

Ending, In this method, the assumption is that transitions occur at ending of cycle, as shown in top-right of the figure 2.8, then the patients remains in the state e_k is $\mathbf{p}_{e_k}^{end}$. This method in each cycle leads to bias in the form of a underestimated of patients remaining in the state e_k.

Half cycle, In reality transitions may occur at any time within a cycle, but on average, these occur in the middle of each cycle. Therefore, the assumption here is that transitions occur in the middle of cycle, as shown in bottom-right of the figure 2.8, then the patients remaining in the state e_k is computed:

$$\mathbf{p}_{e_k}^{half} = \frac{\mathbf{p}_{e_k}^{start} + \mathbf{p}_{e_k}^{end}}{2}$$

In most cases, the health-economic evaluations use the half-cycle correction for calculating the number of patients remaining in each health states and at each cycle [Siebert et al., 2012].

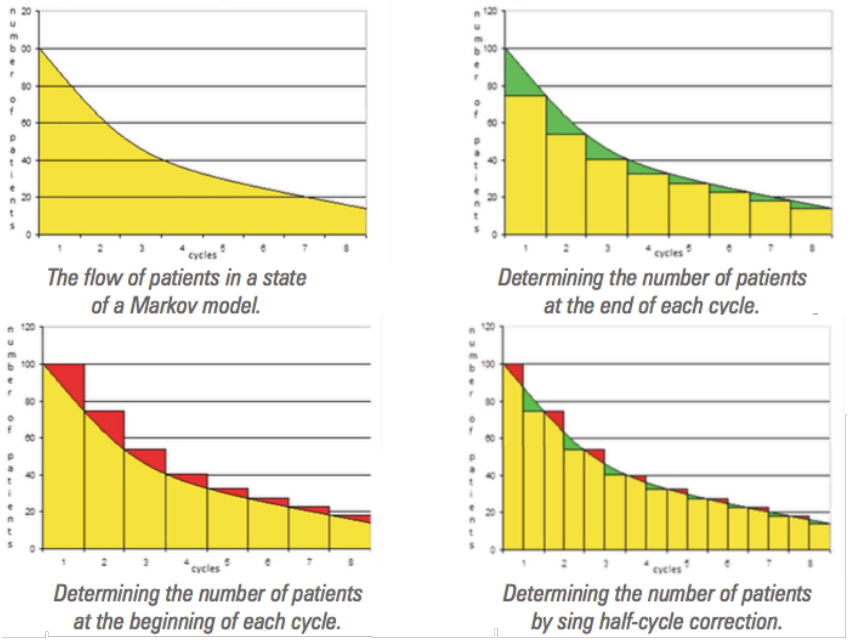


Figure 2.8 – Correction methods [Németh and Szekér, 2014]

2.3.4 Methods for economic evaluation

In order to better evaluate a health-economic case, we use of economic methods based on recognizing what information is necessary for decision-making.

Thus, we can define *economic evaluation methods* as a comparison of several alternatives (or health-care interventions) where each method is focused in comparing some indicators of effectiveness between alternative interventions (i.e. strategies). Economists use often three different method that can vary according to the way in which indicators of performance are chosen; Cost Benefit Analysis (CBA), Cost Utility Analysis (CUA), and Cost Effectiveness Analysis (CEA).

2.3.4.1 Cost-Benefit Analysis (CBA)

Basically, Cost benefit analysis does attempt to place some monetary valuation on health outcomes (or consequences), which means that, it measure and compare costs and consequences (payoffs) of different interventions in monetary units.

Therefore, CBA calculate the different between the monetary value of the benefits and total costs of a intervention (or strategy) in order to know whether this last has a net surplus or net loss, i.e if the total cost was less or greater that the cost of benefits.

Nevertheless, attempting to give a monetary value to health outcomes (benefits) is almost impossible, e.g. the monetary value of a life saved [Cal, 2015]. Moreover, H.A.S. doesn't recommend the cost-benefit analysis as a method of evaluation effectiveness

2.3.4.2 Cost-Effectiveness Analysis (CEA)

In this method, Cost-effectiveness analysis attempt to avoid to place a monetary valuation on health outcomes by expressing the benefits or performances of a intervention by a health indicator, such as; the number of life o year saved, the number of cases treated successfully or avoided, the number of years of major cardiac event-free survival, and so on.

The cost-effectiveness analysis calculates firstly costs and effects (or consequences) of an intervention base and an alternative interventions, then it calculates costs and effects differences in the form of

ratio $\frac{\Delta C}{\Delta E}$, also known as *Increment cost-effectiveness ratio* (ICER, see 2.4.1). Moreover, H.A.S. strongly recommends the cost-effectiveness analysis as a method of evaluation effectiveness.

2.3.4.3 Cost-Utility Analysis (CUA)

In constraint to cost-effectiveness analysis which gives priority to the *lifespan*'s indicator in economic evaluations, the *Cost-Utility Analysis* express the benefits of the intervention through the quality average of life year (QALY) which gained and not the quantity of life year gained of an intervention.

Same as the cost-effectiveness analysis, the CUA calcule the incremental ratio of costs and quality of life (effects), i.e. $\frac{\Delta C}{\Delta Q}$. H.A.S. also recommends to make a cost-utility analysis in addition to cost-effective analysis for health-economic evaluations.

For more good information about disadvantages, special cases, and others about CBA, CEA and CUA methods, in [Cal, 2015].

2.4 Interpretation of deterministic outcomes

By taking the previous example, clinical case 2.3.1, and by putting two different treatments or strategies (A and B) to evaluate in the Markov model, we could calculate total costs and total consequences (effects) of each strategy after the simulation of the Markov model on N times, for example, for the strategy A would be:

$$C_A = \sum_{i=1}^{N} \sum_{s=1}^{S} \mathbf{p}_{t_i}^{e_s} * c_{e_s,A} \quad \text{and} \quad E_A = \sum_{i=1}^{N} \sum_{s=1}^{S} \mathbf{p}_{t_i}^{e_s} * ef_{e_s,A} \tag{2.13}$$

where $\mathbf{p}_{t_i}^{e_s}$ is the number of patients in the e_s state at the cycle t_i, $c_{e_s,A}$ is the cost and $e_{e_s,A}$ is the consequence or health benefit to e_s state of the strategy A, therefore, C_A is the total cost and E_A is the total consequence of the strategy A. The calculations are the same for the strategy B.

We are now going to assume that we are in a ***perfect world*** where all input variables (i.e. probabilities, costs, consequences, etc.) of the decision model to evaluate has no uncertainty, unlike the reality where input variables may vary result on choices or can have uncertainty due to estimation methods, and sample size of studies which its comes from, and also consequently, the final results of the decision model.

We will also use a economic evaluation indicators named ***Incremental Cost Effectiveness Ratios (ICERs)***, in order to be able to interpret the results obtained as well as to make a decision as health decision-maker, in a ***perfect world***.

2.4.1 Incremental Cost Effectiveness Ratios (ICERs)

The incremental cost-effectiveness ratio (ICER) is a statistic used in cost-effectiveness and cost-utility analysis to compare the effectiveness of **two** health-care interventions. Thus, if we have costs (C) and effects (E) of two health-care interventions; A and B, then we can calculate the difference in costs y differences in effects, and also, we can calculate the ICER as the difference in costs divided by the difference in effects, as follows:

$$ICER = \frac{(C_A - C_B)}{(E_A - E_B)} = \frac{\Delta C}{\Delta E} \tag{2.14}$$

where C_A and E_A are the cost and effect in the intervention A (often termed new alternative intervention) and where C_B and E_B are the cost and effect in the intervention B (often termed base intervention). It should remark that effects can be measured in termes of health indicator, such as CEA or CUA, while costs are often measured in monetary value.

The ICER can interpreted as *how much does it cost us for an additional unit of health effect (QALY gained, LY gained, avoided event...)* and the coordinates of the difference in costs and effects $(\Delta E, \Delta C)$ can be displayed on the *cost-effectiveness plane* as shown in figure 2.12. And now, if these value $(\Delta E, \Delta C)$ has been calculated in a *the perfect world*, we could know with certainty in which quadrant would be located. A alternative/new intervention is said “dominante" control, being less costly and more effective (second quadrant), else it is termed “dominated" by the base/old intervention, in other words, the base intervention is the best choice (fourth quadrant). However, It is more often to find of new strategies being more effective and more costly (first quadrant), and this case, we must evaluate if the addition health benefits of the alternative intervention are worth the additional cost (willingness to pay (WTP)), and

finally, the third quadrant could tell us that the alternative intervention is not a good option, if the aim is to reduce spending as much as possible, by restricting at a minimum the loss of efficiency.

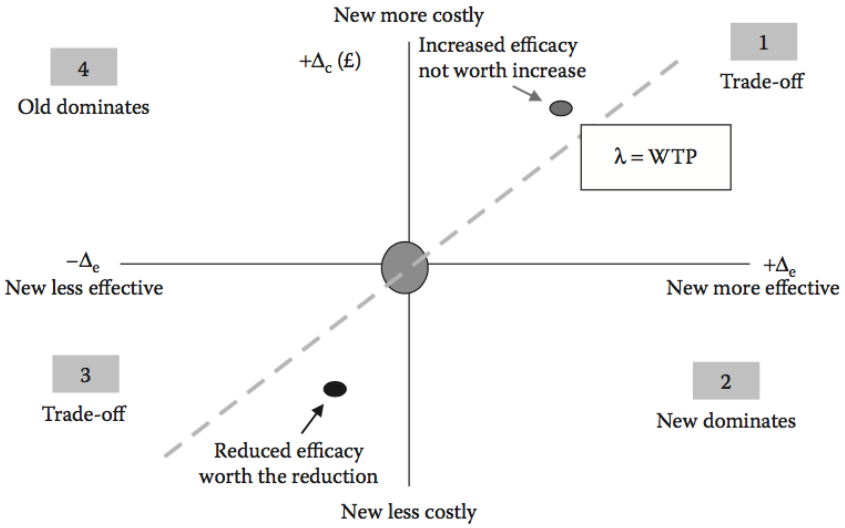


Figure 2.9 – Cost-effectiveness plane of [Khan, 2015]. The slope of the straight line is calculated through $\Delta C/\Delta E$ which can also be taken as the superior acceptable "threshold ratio" $\Delta C/\Delta E < \lambda$ (λ represents the willingness-to-pay for a unit of health gain) that a decision-maker could accept for the alternative treatment.

2.5 Uncertainty analysis in the decision model

In any decision-making, there is always some uncertainty about not making the right decision, because all parameters used in a decision model are estimated of a sample (i.e. a population proportion),and hence, they have some variability issue from ***imperfect models***, and choice. Since we are not unfortunately faced in a *perfect world*, as we had mentioned it in the previous section, so a uncertainty analysis of health-economic models is indispensible.

The uncertainty analysis of a health-economic model can be divided in at least two levels; (1) The uncertainty in the choice of modelling method (e.g. Tree or Markov decision model), also termed *"structural uncertainty"* [Briggs et al., 2012], and (2) The uncertainty in the process of obtaining of the model parameters from clinical trials (i.e. sample not representative of population[4]), also termed *"parameter uncertainty"*. In this work, we'll just consider the uncertainty *parameter uncertainty* varying the values of selected parameters of the decision model.

The uncertainty parameter model can be divided in two: Deterministic sensitivity analysis (DSA) and Probabilistic sensitivity analysis (PSA)

2.5.1 Deterministic sensitivity analysis

The aim of deterministic sensitivity analysis (DSA) is to evaluate how model results can be sensitive to parameter value. Parameter values are changed through upper and lower bounds, and the results are reported [Filipovic-Pierucci et al., 2017].

If we vary the value of an only parameter of the model, we could talk about of ***One-Way Sensitivity Analysis***, whereas if we vary the value of some parameters of the model, we could talk about of ***Multiway Sensitivity Analysis***. The results obtained of this analysis can be presented in a ***Tornado diagram***, see Figure 2.10.

[4]Even if the sample is truly representative of the population, random error in the measurement can result in the captured data not being representative [Edlin et al., 2015, pag. 60].

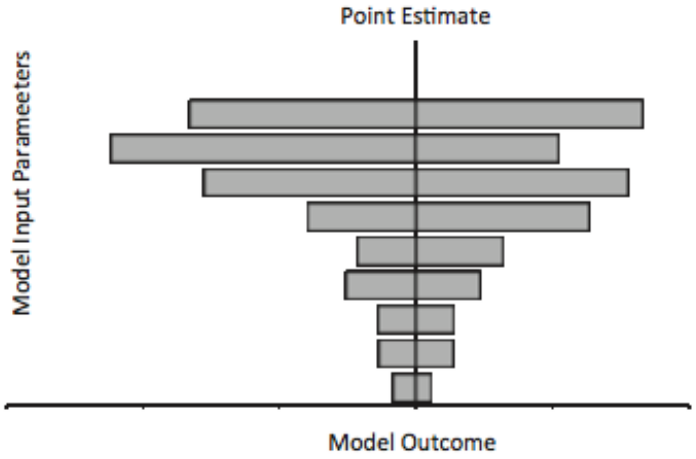


Figure 2.10 – *Tornado diagram showing impact of uncertainty on the outcome of a decision model.* The vertical line represents the parameter value of the reference analysis (i.e. fixed parameters). The horizontal bars represent the value taken by ICER when we vary the values of the parameter between the upper and lower.

2.5.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) is widely used in health economic decision analysis from the 1980s, this one permits us to have a joint uncertainty across all the parameters in the model to be assessed at the same time. This is possible, by making re-sampled the values of all parameters from pre-defined distributions, and then, running again the model with these new parameters as inputs, in order to obtain a distribution by each outcomes, see Figure 2.11, [Critchfield and Willard, 1986], [Gray et al., 2010] and [Filipovic-Pierucci et al., 2017].

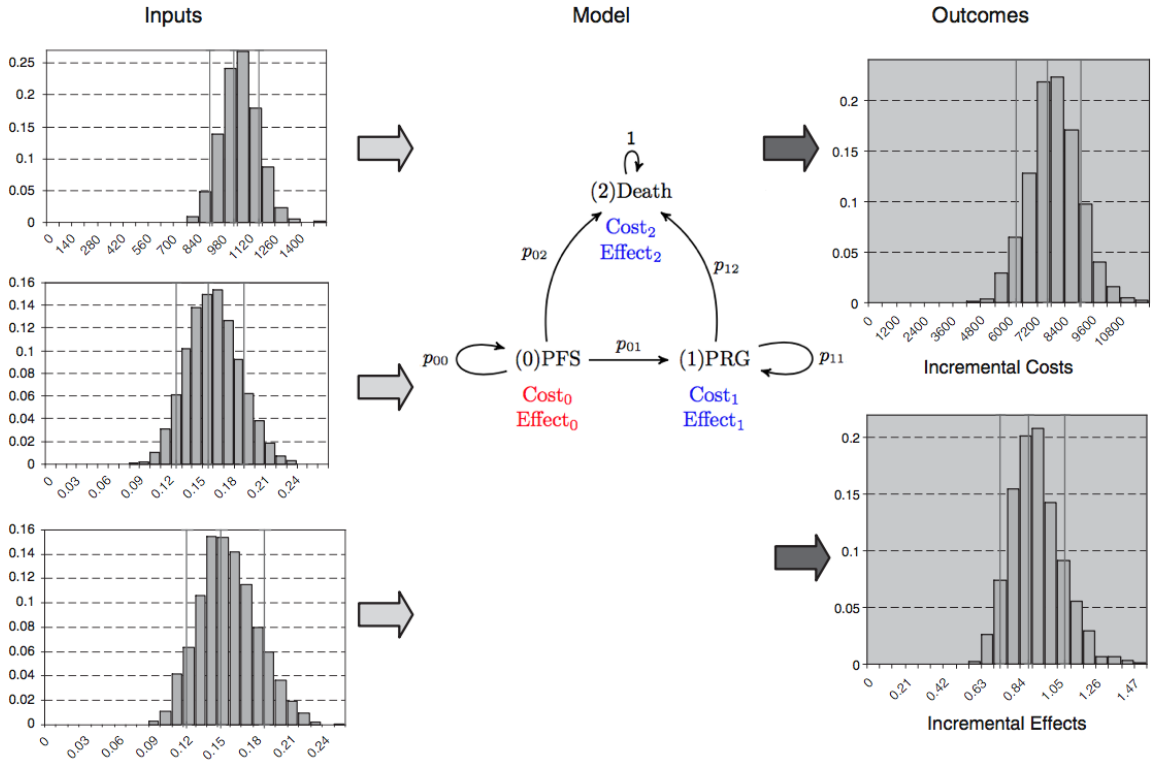


Figure 2.11 – Diagrammatic representation of PSA in health economic decision analytic models. Adapted from [Gray et al., 2010]

Now, the issue is ***how to choose the probability distribution for each input parameter of our decision model?***. The choice of probability distribution should reflects the nature of the parameters, for instance, if the input parameter is a transition probability that can only take values between 0 and 1, then,

a recommended probability distribution may be a *Beta distribution*. On the other hand, in the handbook of [Briggs et al., 2006] we can find more recommendations for choosing a probability distribution.

And, ***is there any correlation between the input parameters?***. It's possible, but not frequent in real cases, to find a certain correlation amongst two inputs parameters. That is, the value of a parameter depends of the information about the second parameter. [Briggs et al., 2006] describe a new approach for defining correlations amongst arbitrary distributions.

2.5.2.1 Outputs from Probabilistic Sensitivity Analysis

Here, we are going to describe briefly outputs from PSA that allows us to take a decision under uncertainty in relation to studied decision model.

1. ***Cost-Effectiveness Plane***

   After having simulated N times the health-economic model, we build up the joint distribution of the difference in costs and consequences $(\Delta E_i, \Delta C_i)_{0<i\leq N}$, in other words, we calculate the difference obtained in costs and consequences of two interventions to evaluate (i.e. $\Delta C_i = C_{i,A} - C_{i,B}$ and $\Delta E_i = E_{i,A} - E_{i,B}$), for each simulation i. This distribution, we plot it in a coordinate plane, see Figure 2.12.

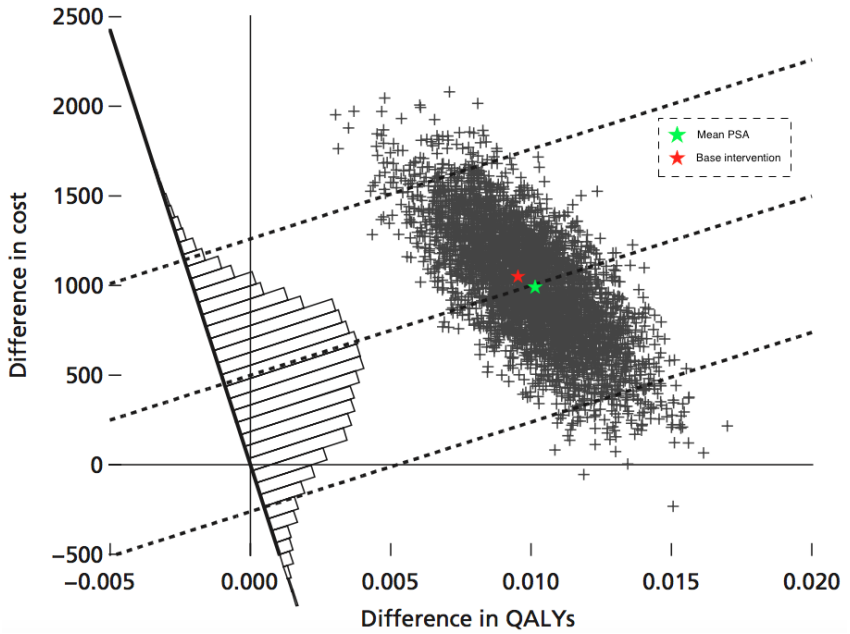


Figure 2.12 – Scatter Plots on the Cost-Effectiveness Plane. Adapted from [Glick et al., 2014]

We plot also the base intervention (i.e. deterministic results obtained), the mean of the distribution simulated (i.e. $\frac{\sum_i^N \Delta E_i}{N}$ and $\frac{\sum_i^N \Delta C_i}{N}$) and a "confiance" interval. These informations are available for health authorities (H.A.S.) in order to make them a decision.

2. ***Cost-Effectiveness Acceptability Curves (CEACs)***

The acceptability curve graphically illustrates the problem of choosing one intervention over another according to the threshold of acceptability allowed for healthcare authorities. Given a threshold value, λ_{max}, defined as the maximum acceptable differential ratio (i.e. $ICER_{real} = \Delta C/\Delta E < \lambda_{max}$, or willingness to pay), the acceptability curve indicates the probability that the *real differential ratio*, $ICER_{real}$, is lower than this value.

In Figure 2.13, we observe that real differential ratio associated to the evaluated intervention (b) has a probability of 50% to be below \$100 000. The probability to be below a threshold of \$70 800 is 25%.

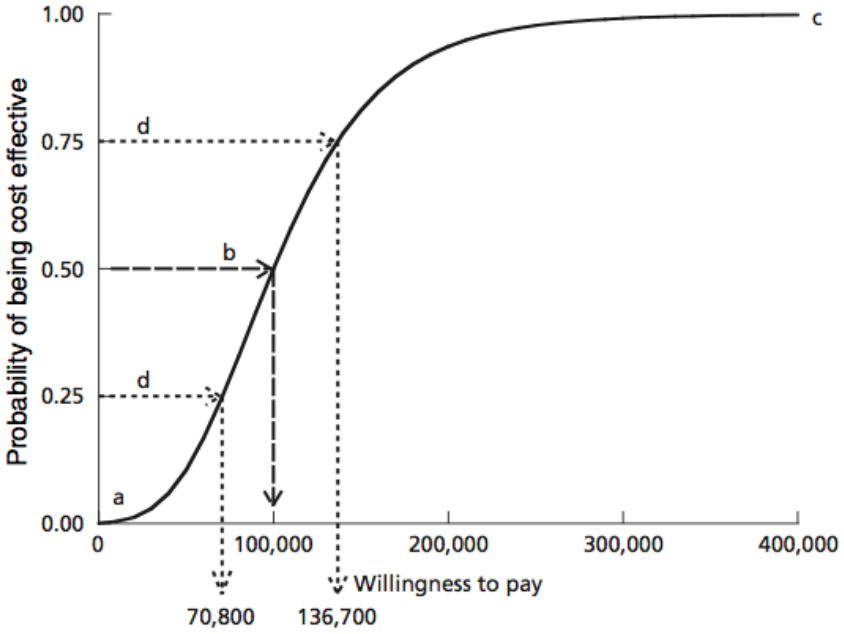


Figure 2.13 – Cost Effectiveness Acceptability Curve

Chapter III

Validation of a health-economic evaluation tool

The aim of the chapter is to briefly explain how I have proceeded to choose the package R for health-economic evaluations in a context Markovian, and why not using *Microsoft Office Excel* as a work tool on long-term.

Contents

3.1 Why is Capionis looking for an alternative to Excel?

In a rapidly changing business environment, the adaptation to change is an obligation in the team's research and innovation, and especially if the usage tools begin to slow down the daily work of collaborators, and therefore, the overall performance of the company.

That's the case of the big projects of health-economic evaluations implement or validate in *Microsoft Office Excel* for the Capionis's collaborators. This tool, in addition to having a private license software, it's sometimes a source of errors due to its limits in traceability, its quality control, and its non-specialized programming language to solve native problems in statistics such as simulations, classification, multivariate regression, and so on. That's why the Capionis's team is actively looking for a tool that responds these needs, the last being one of my aims of the internship.

3.2 A R package for health-economic evaluations

Firstly all, it is important to remind that ***R*** is an open-source programming language, i.e. free license[1], and specialized to solve statistical problems, data analysis, and others. R language has begun to take very strongly in the fields of statistical computing and in the business world of data analysis, already being its implantation in companies a reality.

After having seen the set of concepts for implementing a health-economic case, we have realized that to evaluate an alternative intervention (or new strategy) versus the base intervention or other current interventions (or termed old strategies) in long-term patient follow-up don't need available the patient-level

[1] https://en.wikipedia.org/wiki/Free_license

data, because we extrapolate costs and clinical effectiveness criteria at long-term (e.g. 30 years). Unlike all R package of survival analysis and multi-state Markov models, such as ***SmoothHazard, SemiMarkov, mstate, msm and etm***, which need to the patient-level data for computing transition probabilities using statistical models. A benchmarking matrix of these packages can be found in [Carranza-Alarcon, 2017].

The only two packages currently in R implementing health-economics evaluations are the ***Bayesian Cost-Effectiveness Analysis (BCEA)*** and ***Health Economic Evaluation Modelling (Heemod)***, the former use an Bayesian approach with Markov chain Monte Carlo (MCMC) simulation and the latter use an approach Markov model with Monte Carlo simulation.

Due to the fact that BCEA doesn't use an approach Markov model, as being used in Capionis, I decided to use *Heemod* package, nevertheless, this last conclusion doesn't underestimate the BCEA package.

3.3 Features required

As in all validation studies, we are going to list a set of features required to take in account for validating the *Heemod* package:

1. Flexibility in the usage for coding a health-economic case.
2. Accuracy in the deterministic results.
3. Similar outcomes in the sensitivity analysis
4. Running time of a health-economic model
5. Graphical presentation of results

In order to achieve these requirements, we have also contributed by adding some particular characteristics to ***Heemod*** package [2].

3.4 Drawbacks and Limitations of Heemod package

After having used the Heemod package for implementing some health-economic cases (see chapter IV). We found out some limitations or drawbacks which will be mentioned bellow.

1. Calculating operations with sparse matrix of size $N > 10$ take lots of time in the probabilistic sensitivity analysis (PSA).
2. Need to know an exact formula for the transition probability.
3. Patients in transit not available in each Markov cycle.
4. It is not possible to use a varied discount rate.
5. It is not possible to use a "chained" transitions matrices for calculating the final transition (i.e. $X * Y * Z = T$ such as T is the final transition matrix for the Markov process, et X, Y et Z are three transition matrices intermediate)

In the following of this memoir, we are going to use and to validate the *Heemod* package, if this one satisfies the features referred previously.

[2] Contributors in https://pierucci.org/heemod/authors.html

Chapter IV

Implementation of Health-Economic cases

In this chapter, we'll evaluate of real health-economics cases that have already been validated by *Capionis*. Besides, we could assume that the input data for decision model has already been validated into a preliminary pre-study by *Capionis's* collaborators (e.g. meta-analysis).

During the internship to *Capionis*, I was able to *reproduce* three real health-economics cases and several exercises health-economics cases in order to validate the *Heemod* package. In this chapter, we are going to present a real case of intermediate difficulty and which was published.

In each case, we could firstly proceed by presenting a brief description of case and its implications such as the effectiveness in clinical trials, then we'll draw the transition graph of Markov model that better represents the natural history of a disease in the patient with respect to the intervention to evaluate. Finally, we'll show a sensibility analysis so that health authorities can make a *right* decision between the evaluation of two interventions (base intervention versus alternative intervention).

Health-economic evaluation of drug-eluting stents versus bare-metal stents

Contents

4.1 Objective

The objective is to be able to reproduce the results of the paper published by [Baschet et al., 2016] in order to validate the ***Heemod*** package and make a detailed technical description of the Markov multiple-state model used, as well as an uncertainty analysis for decision making.

4.2 Description

More and more patients in the Worldwide are affected by ***Cardiovascular's disease*** which has become an economic problem in any countries because of the health-care spending and the loss of many billions of dollars in testing other new treatments (e.g. the U.S. in 2006 spent more than $400 billions *[Mensah and Brown, 2007] [Ligthart et al., 2007]*).

In the last decades, patients that have suffered from a **Coronary artery disease** (the most common type of **Cardiovascular's disease**) had been treated with a stent implantation well-known as **Drug-eluting stents (DES)** which made spending to the world market of more than $6 billions in the year 2000, due to their effectiveness on the disease.

Nevertheless, in these last years have emerged other new treatments in order to improve the effectiveness of **DES**. But according to published health scientific articles of randomized controlled trials (RCTs) which compare the new treatment **Bare-metal stents (BMS)** versus the base treatment **Drug-eluting stents (DES)**. I have found a improvement in the number of years of major cardiac event-free survival beyond the first year after stent implantation [Bischof et al., 2009].

Because of a limited health-care budget, the health-care authority (HAS in France) is constrained to evaluate not only the clinical trials performed, also taking into account a cost-effectiveness evaluation to long-term of **BMS** versus **DES** so that decision-makers of health-care authority can make a *"good"* decision.

According to scientific article of [Baschet et al., 2016] which used a model inspired by the model presented by [Bischof et al., 2009], we can model this health-economic case with 3 health states in a Markov model, as pictured below, pointy boxes represent ***a major cardiac event*** that can lead to a transition from the health *state 0* to the health *state 1*.

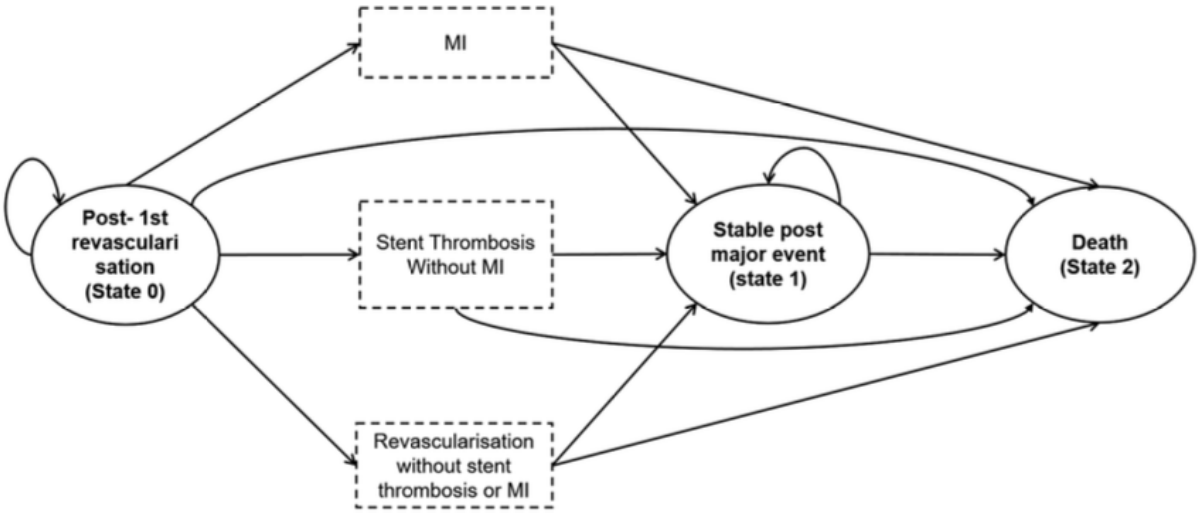


Figure 4.1 – Markov model scheme of [Baschet et al., 2016]

In order to provide a thorough health-economic analysis, we implemented two decision models based on recently published scientific article of [Baschet et al., 2016] comparing **DES** with **BMS**, we also implemented a sensibility analysis to address the joint implication of parameter uncertainty (i.e. uncertainty about the input data) with the purpose that decision makers can make the *good* decision under uncertainty.

4.3 Modeling

4.3.1 Model structure

The cost-effectiveness analysis (or health-economic evaluation) was implemented in two different ways using Markov multiple-state model, with the purpose of simulating the progression of patients affected by the *coronary artery disease* over their lifetime. Therefore, we will present the inputs (i.e. probabilities, costs, effectiveness, ...) and outcomes of each approach below.

4.3.1.1 Markov model to 3 states

The states to be taken into account in this approach has been:

- **Initial:** Patients who have benefited of the first revascularization without complicate. In the cohort simulation, **we assumed that all patients (i.e. cohort) will start in this state** and the health progression of each of them would be followed per six months (i.e. **Markov cycle**).
- **Stable:** In this state, the patients receive a monitoring after surviving a first major cardiac event.
- **Dead:** Each patient that gets into this state, ends their follow-up. No Cost and No Effectiveness.

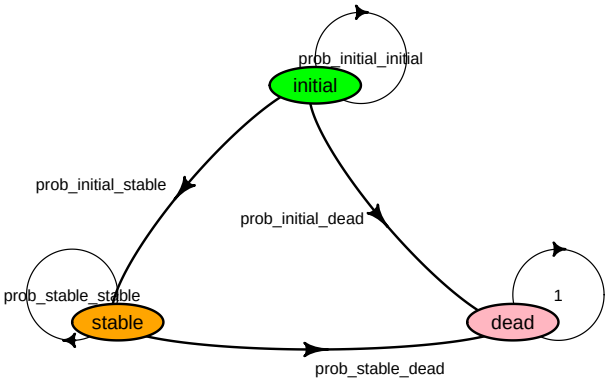


Figure 4.2 – Markov model to 3 states.

4.3.1.2 Markov model to 6 states

The states to be taken into account in this approach has been (see Figure 4.3):

- **Initial:** Patients who have benefited of the first revascularization without complicated. In the cohort simulation, **we assumed that all patients (i.e. cohort) will start in this state** and the health progression of each of them would be followed per six months (i.e. **Markov cycle**).
- **Myocardial infarction (MI):** it's a major cardiac event occurring from the initial state, in addition, patients are visiting, because it's a transient state.
- **Stent thrombosis without (Throm):** it's a major cardiac event occurring from the initial state, in addition, patients are visiting, because it's a transient state.
- **Revascularization (Revas):** it's a major cardiac event occurring from the initial state, in addition, patients are visiting, because it's a transient state.
- **Stable:** In this state the patients receive a monitoring after surviving a first major cardiac event.
- **Dead:** Each patient that gets into this state, ends their follow-up. No Cost and No Effectiveness

4.3.2 Transition probabilities

Here, we'll describe transition probabilities for each approach. Furthermore, for more information about *all transition configurations on [**Baschet et al., 2016**].*

We will first calculate the semi-annual mortality probability in the general population from the annual mortality rate by age and sex given by d'INSEE 2009 [1]. We will declare two random variables A and S that stands for age and sex, i.e. $S \in \{'M','S'\}$ and $A \in \mathbb{Z}^+ - \{0\}$, as well as the constant variables

[1] http://www.ined.fr/fr/france/mortalite_causes_deces/taux_mortalite_sexe_age/

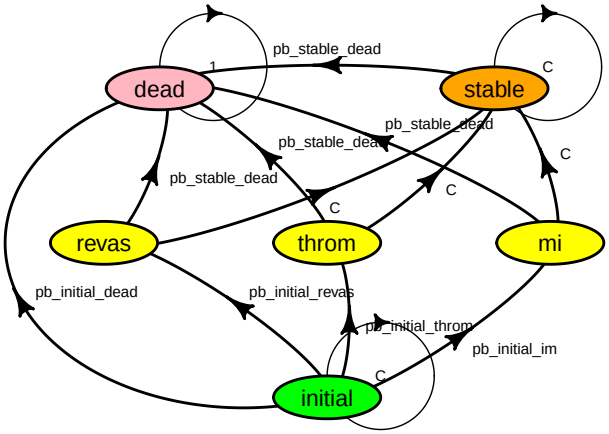


Figure 4.3 – Markov model to 6 states.

$SR = 0.6$ (sex-ratio[2]), $RR = 1$ (relative risk of basic deaths in relation to the general population) and $NCY = 2$ (number of cycle per year). Thus, probabilities by age and sex are:

$$\mathbb{P}(A_{yearly} \leq a, S =' M') = \phi_{p,m}$$
$$\mathbb{P}(A_{yearly} \leq a, S =' F') = \phi_{p,f}$$

The probability of annual mortality in the cohort (i.e. the general population) is:

$$\mathbb{P}(A_{yearly} \leq a, S \in \{'M','F'\}) = (\phi_{p,m} * SR + \phi_{p,f} * (1 - SR)) * RR = \phi_{p,\{m,f\},r,RR}$$

Lastly, the probability of mortality per cycle (6 months) calculated from Appendix VI is:

$$\mathbb{P}(A_{six-monthly} \leq a) = 1 - exp(\frac{ln(1 - \phi_{p,\{m,f\},r,RR})}{NCY}) \tag{4.1}$$
$$\mathbb{P}(A_{six-monthly} \leq a) = 1 - (1 - \phi_{p,\{m,f\},r,RR})^{\frac{1}{NCY}} \tag{4.2}$$

We will henceforth use $\phi_{p,a}$ instead of $\mathbb{P}(A_{six-monthly} \leq a)$.
In code R-Heemod, it would look like to piece of code below :

```
par_mod <- define_parameters(
  year_current = trunc(markov_cycle/2),
  age_base = 60,
  age_cycle = year_current + age_base,
  age_cycle_pr = ifelse(markov_cycle %% 2 == 0, age_cycle-1, age_cycle),
  ratio_sexe = 0.6,
  RR_cardiaque = 1,
  prob_man = look_up(
    data = rate_dead,
    age = trunc(age_cycle_pr),
    value = "prob_h"
  ),
  prob_woman = look_up(
    data = rate_dead,
    age = trunc(age_cycle_pr),
    value = "prob_f"
  ),
  prob_cohort = (prob_man*ratio_sexe + prob_woman*(1-ratio_sexe))*RR_cardiaque,
  prob_dead_gen = 1-(1-prob_cohort)^(1/nb_cycles_an)
)
```

[2] https://fr.wikipedia.org/wiki/Sex-ratio

Where $\phi_{p,a} =$ ***prob_dead_gen*** is the general mortality probability of the population by age during a Markov cycle.

Remarks 3.1:

(a) *In the model, we assume that the probability of death can never be lower than the one in the general population of the same age and the same ratio of man/woman (INSEE).*

(b) *All semiannual outgoing-transition probabilities were calculated from an annual transition rate (or hazard ratio) by assuming that they have a constant risk ([**Fleurence and Hollenbeak, 2007**] and [**Briggs et al., 2006**]).*

(c) *The sum of outgoing transition of a state markov is always one. This is true thanks to one of Markov chain properties. For example: for the health initial state $i = 0$, then, $\sum_{j\in\mathcal{E}} \mathbf{p}_{ij}(t) = 1$ such as $\mathcal{E} = \{0, 1, ..\}$ is the set health state of Markov model.*

(d) *The pieces of code in R (out of appendix) shown in the following sections belong to the drug-eluting stents strategy (i.e. base strategy).*

4.3.2.1 Markov model to 3 states

In this cases, we'll model a Markov model to three main states of health; (0) Initial state, (1) Stable state and (3) Death state.

(0) Initial state
This state has two outgoing transitions towards the stable state and the dead state.

(a) **To stable state**: According to the article [**Baschet et al., 2016**], there are three mutually non-exclusive major cardiac events that can lead the transition from the initial state to the stable state. Based on the calculations in **Appendix VI**, transition probabilities to the stable state from each major cardiac event are:

a.1. Myocardial infarction (MI): It's the transition probability to the stable state knowing that the MI event occurred.

$$\mathbf{p}_{01}(t, E \in \{M\}) = \mathbb{P}(E \in \{M\} \cup A > a) - \mathbb{P}(\text{Death due to MI}) \tag{4.3}$$

a.2. Stent thrombosis without MI: It's the transition probability to the stable state knowing that the stents thrombosis without MI event occurred.

$$\mathbf{p}_{01}(t, E \in \{T\}) = \mathbb{P}[(E \in \{T\}) \cap \overline{(E \in \{M\} \cap (A > a))} \cap (A > a)] - \mathbb{P}(\text{Death due to T}) \tag{4.4}$$

a.3. Revascularization without Stent thrombosis and MI: It's the transition probability to the stable state knowing that the revascularization without thrombosis and without MI event occurred.

$$\mathbf{p}_{01}(t, E \in \{R\}) = \mathbb{P}[(E \in \{R\}) \cap \overline{(E \in \{T\}) \cap \Delta} \cap \Delta] - \mathbb{P}(\text{Death due to R}) \tag{4.5}$$

Lastly, the transition probability from the *(0)-initial state* to the *(1)-stable state* is:

$$\mathbf{p}_{01}(t) = \mathbf{p}_{01}(t, E \in \{M\}) + \mathbf{p}_{01}(t, E \in \{T\}) + \mathbf{p}_{01}(t, E \in \{R\})$$

(b) **To dead state**: According to the article [**Baschet et al., 2016**], the semi-annual mortality probability is that in the general population (i.e. $\phi_{p,a}$) plus deaths due to a percutaneous coronary intervention of each major cardiac event such as myocardial infarction, stents thrombosis and revascularization.

$$\mathbf{p}_{02}(t) = \phi_{p,a} + \mathbb{P}(\text{Death due to M}) + \mathbb{P}(\text{Death due to T}) + \mathbb{P}(\text{Death due to R})$$

(1) Stable state

This state has one outgoing transition towards the dead state.

(a) **To dead state**: According to the article [**Baschet et al., 2016**] and **Appendix VI**, the mortality probability from the stable state can not be lower than the mortality probability in the general population (i.e. $\phi_{p,a}$). Then, the mortality probability of patients in the stable state is:

$$\mathbf{p}_{12}(t) = max(\phi_{p,a}, \mathbb{P}(\text{Deaths in the stable state}))$$

This probability $\mathbb{P}$(Deaths in the stable state) doesn't depend on time.

In code R-Heemod [Briggs et al., 2006] , it would look like to piece of code below, where:

p_01_current $= \mathbb{P}_E(M)$	p_02_current $= \mathbb{P}_E(T)$	p_03_current $= \mathbb{P}_E(R)$
p_15_nu $= \mathbb{P}_D$(D-M)	p_25_nu $= \mathbb{P}_D$(D-T)	p_35_nu $= \mathbb{P}_D$(D-R)
prob_mid_im_net $= \mathbf{p}_{01}(t, E \in \{M\})$	prob_mid_throm_net $= \mathbf{p}_{01}(t, E \in \{T\})$	prob_mid_revas_net $= \mathbf{p}_{01}(t, E \in \{R\})$
prob_initial_initial $= \mathbf{p}_{00}(t)$	prob_initial_dead $= \mathbf{p}_{02}(t)$	prob_initial_stable $= \mathbf{p}_{01}(t)$
prob_stable_dead $= \mathbf{p}_{12}(t)$	prob_stable_stable $= \mathbf{p}_{11}(t) = 1 - \mathbf{p}_{12}(t)$	pb_45_nu $= \mathbb{P}$(Deaths in the stable state)

```
f_pr_best_dead <- function(p_mid_dead, p_dead){
  ifelse(p_mid_dead < p_dead, p_dead, p_mid_dead)
}

par_mod <- modify(
  par_mod,

  prob_mid_im = (1 - prob_dead_gen) * p_01_current,
  prob_mid_throm = (1 - prob_dead_gen - prob_mid_im) * p_02_current,
  prob_mid_revas = (1 - prob_dead_gen - prob_mid_im - prob_mid_throm) * p_03_current,
  prob_im_dead = prob_mid_im * f_pr_best_dead(p_15_nu, prob_dead_gen),
  prob_throm_dead = prob_mid_throm * f_pr_best_dead(p_25_nu, prob_dead_gen),
  prob_revas_dead = prob_mid_revas * f_pr_best_dead(p_35_nu, prob_dead_gen),

  prob_mid_im_net = prob_mid_im - prob_im_dead,
  prob_mid_throm_net = prob_mid_throm - prob_throm_dead,
  prob_mid_revas_net = prob_mid_revas - prob_revas_dead,
  prob_initial_dead = prob_dead_gen + prob_im_dead + prob_throm_dead + prob_revas_dead,
  prob_initial_stable = prob_mid_im_net + prob_mid_throm_net + prob_mid_revas_net,
  prob_initial_initial = 1 - prob_initial_stable - prob_initial_dead,
  prob_stable_dead = f_pr_best_dead(p_45_nu, prob_dead_gen),
  prob_stable_stable = 1 - prob_stable_dead
)
```

(2) Dead state

This state is a absorbing state, therefore, there aren't outgoing transitions.

4.3.2.2 Markov model to 6 states

In this case, we'll model a Markov model to 6 main health states. In this modeling, we split the stable state into four health states, three of them are a major cardiac event (i.e. myocardial infarction, stent thrombosis or Revascularization), and the fourth is the stable state. Therefore, we'll assume these three major cardiac events as health state of the Markov model, and they will be called: *MI-stable, Thrombosis-stable and Revascularization-stable.*

(0) Initial state

This state has four outgoing transitions towards stable state, MI-state, Thrombosis-stable without MI-state, Revascularization-stable without thrombosis-stable and MI state, and Dead state.

According to the article [Baschet et al., 2016] and calculations of the Appendix VI, transition probabilities from the initial state towards the other states are:

(a) **To MI-state**: The transition probability to MI-stable state knowing that the MI event occurred.

$$\mathbf{p}_{01}(t) = \mathbb{P}(E \in \{M\} \cup A > a) - \mathbb{P}(\text{Death due to MI}) \tag{4.6}$$

(b) **To thrombosis-stable without MI-state**: The transition probability to Thrombosis-stable state knowing that the thrombosis stents event occurred.

$$\mathbf{p}_{02}(t) = \mathbb{P}(E \in \{T\} \cup A > a) - \mathbb{P}(\text{Death due to T}) \tag{4.7}$$

(c) **To Revascularization-stable without thrombosis-stable and MI-state**: The transition probability to Revascularization-stable state knowing that the revascularization event occurred.

$$\mathbf{p}_{03}(t) = \mathbb{P}(E \in \{R\} \cup A > a) - \mathbb{P}(\text{Death due to R}) \tag{4.8}$$

(d) **To dead state**:The transition probability to dead state is the semi-annual probability of mortality in the general population, more death probabilities due to each major cardiac event occurred.

$$\mathbf{p}_{05}(t) = \phi_{p,a} + \mathbb{P}(\text{Death due to M}) + \mathbb{P}(\text{Death due to T}) + \mathbb{P}(\text{Death due to R}) \tag{4.9}$$

(1) Myocardial infarction state

This state has two outgoing transitions towards stable state and dead state. As mentioned before, this state is part of the stable state, therefore, the transition probability to dead state is the same as the transition probability from the stable state to the dead state of the Markov model to three states.

(a) **To dead state**: As mentioned in the remark 3.1-a, the probability of death can never be lower than that of general population.

$$\mathbf{p}_{15}(t) = max(\phi_{p,a}, \mathbb{P}(\text{Deaths in the stable state})) \tag{4.10}$$

(b) **To stable state**: Based in the remark 3.1-c, the probability of transition to stable state is the complementary of $\mathbf{p}_{15}(t)$.

$$\mathbf{p}_{14}(t) = 1 - \mathbf{p}_{15}(t) \tag{4.11}$$

(2) Stent thrombosis state without MI

This state has two outgoing transition towards Stable state and Dead state. As mentioned, this state is part of stable state, then, the transition probability to dead state is the same as the transition probability from stable state to dead state.

(a) **To dead state**: As mentioned in the remark 3.1-a, the probability of dying can never be lower than that of the general population.

$$\mathbf{p}_{25}(t) = max(\phi_{p,a}, \mathbb{P}(\text{Deaths in the stable state})) \tag{4.12}$$

(b) **To stable state**: Based in the remark 3.1-c, the transition probability to stable state is the complementary of $\mathbf{p}_{25}(t)$.

$$\mathbf{p}_{24}(t) = 1 - \mathbf{p}_{25}(t) \tag{4.13}$$

(3) Revascularization state without MI and Stent thrombosis

This state has two outgoing transitions towards stable state and dead state. As mentioned before, this state is part of the stable state, therefore, the transition probability to dead state is the same as the transition probability from the stable state to the dead state.

(a) **To dead state**: As mentioned in the remark 3.1-a, the probability of death can never be lower than that of the general population.

$$\mathbf{p}_{35}(t) = max(\phi_{p,a}, \mathbb{P}(\text{Deaths in the stable state})) \tag{4.14}$$

(b) **To stable state**: Based in the remark 3.1-c, the transition probability to stable state is the complementary of $\mathbf{p}_{35}(t)$.

$$\mathbf{p}_{34}(t) = 1 - \mathbf{p}_{35}(t) \tag{4.15}$$

(4) Stable state

This state has two outgoing transitions towards stable state and dead state.

(a) **To dead state**: According to the article [Baschet et al., 2016] and Appendix VI. The probability of mortality from stable state can not be lower than the probability of mortality in the general population (i.e. $\phi_{p,a}$).

$$\mathbf{p}_{45}(t) = max(\phi_{p,a}, \mathbb{P}(\text{Deaths in the stable state})) \tag{4.16}$$

(5) Dead state

This state is a absorbing state, then there aren't outgoing transitions.

In code R-Heemod [Briggs et al., 2006] , it would look like to piece of code below, where:

p_01_current $= \mathbb{P}_E(M)$	p_02_current $= \mathbb{P}_E(T)$	p_03_current $= \mathbb{P}_E(R)$
p_15_nu $= \mathbb{P}_D$(D-M)	p_25_nu $= \mathbb{P}_D$(D-T)	p_35_nu $= \mathbb{P}_D$(D-R)
pb_initial_im $= \mathbf{p}_{01}(t)$	pb_initial_throm $= \mathbf{p}_{02}(t)$	pb_initial_reva $= \mathbf{p}_{03}(t)$
pb_stable_dead $= \mathbf{p}_{45}(t)$	pb_stable_dead $= \mathbf{p}_{15}(t)$	pb_stable_dead $= \mathbf{p}_{25}(t)$
pb_stable_dead $= \mathbf{p}_{35}(t)$	pb_initial_dead $= \mathbf{p}_{05}(t)$	pb_45_nu $= \mathbb{P}$(Deaths in the stable state)

```
f_pr_best_dead <- function(p_mid_dead, p_dead){
  ifelse(p_mid_dead < p_dead, p_dead, p_mid_dead)
}

par_mod <- modify(
  par_mod,

  pb_im = (1 - prob_dead_gen)*p_01_current,
  pb_throm = (1 - prob_dead_gen - pb_im)*p_02_current,
  pb_revas =  (1 - prob_dead_gen - pb_im - pb_throm)*p_03_current,
  pb_im_dead  = pb_im * f_pr_best_dead(p_15_nu, prob_dead_gen),
  pb_throm_dead = pb_throm * f_pr_best_dead(p_25_nu, prob_dead_gen),
  pb_revas_dead = pb_revas * f_pr_best_dead(p_35_nu, prob_dead_gen),
  pb_initial_dead = prob_dead_gen + pb_im_dead + pb_throm_dead + pb_revas_dead,

  pb_initial_im = pb_im - pb_im_dead,
  pb_initial_throm = pb_throm - pb_throm_dead,
  pb_initial_revas = pb_revas - pb_revas_dead,
  pb_stable_dead = f_pr_best_dead(p_45_nu, prob_dead_gen)
)
```

4.3.3 Cost and health utility

The cost and health utility (i.e. payoffs) for each health state and major cardiac event are as follows:

Table IV.1 – Cost/Health utility for health state and major cardiac event

Health state/Cardiac event	Cost	Health utility
Initial	132.725 €	0.77
Myocardial infarction	4322.956 €	0
Stent thrombosis	2696.649 €	0
Revascularization	4430.760 €	0
Stable	132.725 €	0.85
Dead	822.54 €	0

We also have a hospitalization cost per strategy: the hospitalization cost for drug-eluting stents is 3112.003 and the hospitalization cost for bare-metal stents is 3176.173.

4.3.3.1 Markov model to 3 states

As we can remark in table 1 that we have specified costs per patient by having made a major cardiac event (ie, MI, Stents Throms., or Revas.), which have modeled inside of the initial state. Furthermore, *Heemod* provides us only the proportion of patients P_i^j by state j and by current cycle i, such as $i \in \{1, ..., N\}$ whose N is the total number of cycles and $j \in \{1, ..., E\}$ whose E is the total number of states of the Markov model.

Remarks 3.2:

(a) In *Heemod*, we don't have access to the proportion of patients in transit amongst health states. However, *Heemod* provides us the proportion of patients remaining in the j state at current cycle i (i.e. P_i^j). In other words, after subtracting the patients leaving the j state et adding the patients entering the j state at current cycle i.

Therefore, We must extract the proportion of patients from the initial state P_i^0 belonging to each major cardiac event in order to be able to calculate the cost of each event per cycle correctly.

We will now present three finite sequences which stands for the evolution of the cohort of each state of the Markov model throughout the simulation.

$$P_i^0 = P_{i-1}^0 - P_{i-1}^0 * \mathbf{p}_{01}(t_{i-1}) - P_{i-1}^0 * \mathbf{p}_{02}(t_{i-1}) \tag{4.17}$$

$$P_i^1 = P_{i-1}^1 + P_{i-1}^0 * \mathbf{p}_{01}(t_{i-1}) - P_{i-1}^1 * \mathbf{p}_{12}(t_{i-1}) \tag{4.18}$$

$$P_i^2 = P_{i-1}^2 + P_{i-1}^0 * \mathbf{p}_{02}(t_{i-1}) + P_{i-1}^1 * \mathbf{p}_{12}(t_{i-1}) \tag{4.19}$$

Where P_i^0 is the proportion of the cohort of the *(0)-initial* state at cycle i, and $\mathbf{p}_{ij}(t_{i-1})$ is the transition probability from $i-1$ to j state at time t_{i-1} (or cycle $i-1$). Further, at the beginning of the simulation the total number of patients (i.e. cohort) starts up in the *(0)-initial* state (i.e. $P_0^0 = C$), and in the other states, there are no patients (i.e. $P_0^1 = P_0^2 = 0$).

Now, we are going to compute the proportion of patients who had a major cardiac event at the previous cycle $i-1$ from the proportion of patients in the initial state P_i^0 at the current cycle i (P_i^0 is known by *Heemod*).

$$\begin{aligned} P_i^0 &= P_{i-1}^0(1 - \mathbf{p}_{01}(t_{i-1}) - \mathbf{p}_{02}(t_{i-1})) \\ P_i^0 &= P_{i-1}^0 * \mathbf{p}_{00}(t_{i-1}) \\ \frac{P_i^0}{\mathbf{p}_{00}(t_{i-1})} &= P_{i-1}^0 \end{aligned} \tag{4.20}$$

Since $\frac{P_i^0}{\mathbf{p}_{00}(t_{i-1})}$ also stands for the proportion of patients in the *(0)-initial* state at the previous cycle $i-1$ (i.e. P_{i-1}^0). We can now easily compute the cost of each major cardiac event per cycle because P_i^0 is always given by *Heemod* (i.e. the proportion of patients in the initial state at the current cycle i).

$$C_i^{MI} = C_{MI} * \frac{P_i^0}{\mathbf{p}_{00}(t_{i-1})} * \mathbf{p}_{01}(t_i, E \in \{M\}) \tag{4.21}$$

$$C_i^{Throm} = C_{Throm} * \frac{P_i^0}{\mathbf{p}_{00}(t_{i-1})} * \mathbf{p}_{01}(t_i, E \in \{T\}) \tag{4.22}$$

$$C_i^{Revas} = C_{Revas} * \frac{P_i^0}{\mathbf{p}_{00}(t_{i-1})} * \mathbf{p}_{01}(t_i, E \in \{T\}) \tag{4.23}$$

Where $\frac{P_i^0}{\mathbf{p}_{00}(t_{i-1})} * \mathbf{p}_{01}(t_i, E \in \{M\})$ is the propotion of patients who had a myocardial infarction au cycle i, C_{MI} is the cost per patient of having made a myocardial infarction, and C_i^{MI} is the total cost having made a myocardial infarction at cycle i (the same for Thrombosis and Revascularization event).

We also need the proportion of patients who will remain to the ***stable state*** at current cycle i. In other words, it'll be the subtraction of the proportion of patients to the *stable state* at the previous cycle P_{i-1}^1 minus the proportion of patients leaving the *stable state* at the previous cycle $P_{i-1}^1 * \mathbf{p}_{12}(t_{i-1})$, and we can formulate it:

$$P_{i-1}^1 - P_{i-1}^1 * \mathbf{p}_{12}(t_{i-1}) \iff P_{i-1}^1 * (1 - \mathbf{p}_{12}(t_{i-1}))$$

Where $\mathbf{p}_{12}(t_{i-1})$ is the probability of dying from the *stable* state at the previous cycle $i-1$. Furthermore, developing the equation (18) we can have the following equality:

$$\begin{aligned} P_i^1 &= P_{i-1}^1 + P_{i-1}^0 * \mathbf{p}_{01}(t_{i-1}) - P_{i-1}^1 * \mathbf{p}_{12}(t_{i-1}) \\ P_i^1 - P_{i-1}^0 * \mathbf{p}_{01}(t_{i-1}) &= P_{i-1}^1(1 - \mathbf{p}_{12}(t_{i-1})) \\ P_i^1 - P_i^0 * \frac{\mathbf{p}_{01}(t_{i-1})}{\mathbf{p}_{00}(t_{i-1})} &= P_{i-1}^1(1 - \mathbf{p}_{12}(t_{i-1})) \end{aligned} \tag{4.24}$$

Thanks to the equality of the equation (24), we can, therefore, use this proportion of patients $P_i^1 - P_i^0 \frac{\mathbf{p}_{01}(t_{i-1})}{\mathbf{p}_{00}(t_{i-1})}$ in order to properly calculate the cost of patients that remain in the *stable state* and the *initial state*.

$$C_i^{initial} = C_{initial} * (P_i^0 \boldsymbol{- P_i^0 *} \frac{\mathbf{p_{01}(t_{i-1})}}{\mathbf{p_{00}(t_{i-1})}}) \tag{4.25}$$

$$C_i^{stable} = C_{stable} * \boldsymbol{P_i^1} \tag{4.26}$$

Where $C_{initial}$ is the cost in the *initial* state for a patient and $C_i^{initial}$ is the total cost to patients remaining in the *initial* state at the current cycle (the same for the *stable* state).

Finally, we will calculate the total proportion of patients who have died in other health states at the previous cycle.

$$P_{i-1}^0 * \mathbf{p}_{02}(t_{i-1}) - P_{i-1}^1 * \mathbf{p}_{12}(t_{i-1})$$

We know from equations (20) and (24):

$$\begin{aligned} P_{i-1}^0 &= \frac{P_i^0}{\mathbf{p}_{00}(t_{i-1})} \\ P_{i-1}^1 &= \frac{P_i^1}{\mathbf{p}_{11}(t_{i-1})} - P_i^0 * \frac{\mathbf{p}_{01}(t_{i-1})}{\mathbf{p}_{00}(t_{i-1}) * \mathbf{p}_{11}(t_{i-1})} \end{aligned}$$

We can, therefore, calculate the cost of dead event per current cycle:

$$C_i^{dead\_initial} = C_{dead} * P_i^0 * \left[\frac{\mathbf{p}_{02}(t_{i-1})}{\mathbf{p}_{00}(t_{i-1})} - \frac{\mathbf{p}_{01}(t_{i-1})}{\mathbf{p}_{00}(t_{i-1}) * \mathbf{p}_{11}(t_{i-1})}\right] \tag{4.27}$$

$$C_i^{dead\_stable} = C_{dead} * \frac{P_i^1}{\mathbf{p}_{11}(t_{i-1}) * \mathbf{p}_{12}(t_{i-1})} \tag{4.28}$$

Where C_{dead} is the cost of *dying* for a patient and $C_i^{dead\_initial} + C_i^{dead\_stable}$ is the cost total to patients dying at the current cycle i.

In code R-Heemod [Briggs et al., 2006] , it would look like to piece of code below, where:

cost_event_im_net $= C_i^{MI}$	cost_event_im_brute $= C_{MI}$
cost_event_throm_net $= C_i^{Throm}$	cost_event_throm_brute $= C_{Throm}$
cost_event_revas_net $= C_i^{Revas}$	cost_event_revas_brute + cost_2type_revas $= C_{Revas}$
cost_initial_cycle $= C_i^{initial}$	cost_initial $= C_{initial}$
cost_stable_cycle $= C_i^{stable}$	cost_stable $= C_{stable}$
cost_event_dead_brute $= C_{dead}$	cost_event_dead_initial_net $= C_i^{dead\_initial}$
	cost_event_dead_stable_net $= C_i^{dead\_stable}$

```
par_mod <- modify(
  par_mod,

  cost_nu = 550,
  cost_2type_revas = cost_2nd_revas*cost_nu*nb_stents,
  cost_event_im_net = cost_event_im_brute*prob_mid_im_net/prob_initial_initial,
  cost_event_throm_net = cost_event_throm_brute*prob_mid_throm_net/prob_initial_initial,
  cost_event_revas_net = (cost_event_revas_brute + cost_2type_revas)
                          *prob_mid_revas_net/prob_initial_initial,
  # cost_initial_cycle = cost_initial,
  cost_initial_cycle = cost_initial*(1 - prob_initial_stable/prob_initial_initial),
  cost_stable_cycle = cost_stable,
  cost_event_dead_initial_net = cost_event_dead_brute*(prob_initial_dead/prob_initial_initial -
      prob_stable_dead*prob_initial_stable/(prob_initial_initial*prob_stable_stable)),
  cost_event_dead_stable_net = cost_event_dead_brute*prob_stable_dead/prob_stable_stable
)
```

There exists an another way more easy to compute the cost of the proportion of patients remaining in the stable state, in *Heemod*. It's necessary to simulate the concept of ***"semi-Markov" model*** of **Heemod**[3] on the stable state with an expansion of one more transient state (or create a new transition state and using the Markov model of Heemod), this latter would create a new tunnel stable state, graphically it would look like this:

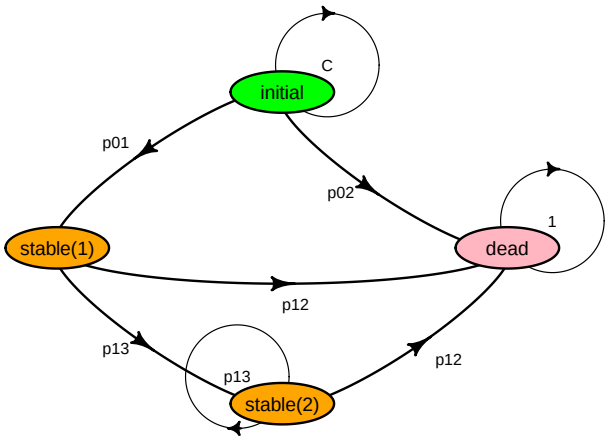


Figure 4.4 – Semi-markov model.

[3]Because in this case, the p_{12} probability depends on the patient's age and not of the semi-Markov cycle which will be reset to zero when entering the stable-(1) state. Note that **Heemod** uses two differents variables to manage the Markov cycle; *"Markov cycle"* for Markov model, and *"state time"* for Semi-Markov model

Then, we'll calculate the cost of the stable state in the state *"stable(2)"* and not in the state *"stable(1)"*, because patients will remain only one Markov cycle in the state *"stable(1)"*. **In code R-Heemod,** we must use the ***state_time*** variable in order to make possible the calculation of the cost only from *stable(2)* state, it would look like to piece of code below:

```
# Definition of stable state
state_stable <- define_state(
  ...
  # Start calculating the cost to the stable state from stable(2) state (state_time < 2)
  cost_state_stable = ifelse(state_time < 2, 0, cost_stable_cycle),
  ...
)

# Declaration of the cost without any transformation.
par_mod <- modify(
  par_mod,

  ...
  cost_initial_cycle = cost_initial,
  ...
)

# Execution of semi-markov model
stents_me <- run_model(
  parameters = par_mod,
  central_strategy = "nu",
  nu = strat_nu,
  act = strat_act,
  ...

  # Expansion of stable state in one more recurrent state
  state_time_limit = list(
    nu = c(stable = 1),
    act = c(stable = 1)
  )
)
```

4.3.3.2 Markov model to 6 states

In this model, it's not necessary to carry out any transformation because we have modeled each major cardiac event as a health state. Therefore, we don't need to calculate the proportion of patients per event.

In code R-Heemod [Briggs et al., 2006] , we assign the cost without any transformation to each health state, as in the piece of code below:

$$\text{cost\_event\_revas\_brute} + \text{cost\_2type\_revas} = C_{Revas}$$

```
state_initial <- define_state(
  ...
  cost_state_initial = cost_initial,
  ...
)
state_im <- define_state(
  cost_event = cost_event_im,
  ...
)
state_throm <- define_state(
```

```
  cost_event = cost_event_throm,
  ...
)
state_revas <- define_state(
  cost_event = dispatch_strategy( nu = cost_event_revas_net,
                                  act = cost_event_revas_act_net),
  ...
)
state_stable <- define_state(
  ...
  cost_state_stable = cost_stable,
  ...
)
# Definition of variables for the drug-eluting stents strategy.
par_mod <- modify (
  par_mod,

  cost_nu = 550,
  cost_2type_revas = cost_2nd_revas*cost_nu*nb_stents,
  cost_event_revas_net = (cost_event_revas + cost_2type_revas)
)
```

4.4 Execution and analysis of results

We are going to proceed to execute and analyze the results of each health-economic model. These models have been implemented with the Heemod package [**Filipovic-Pierucci et al., 2017**] and **the method beginning**[4].

4.4.1 Markov model to 3 states

In this case, we are going to execute the health-economic model to 3 states. The R code can be found in **Appendix VI**. Below, we will show the summary of the execution of health-economic model.

```
# Summmary of health-economic model to 3 states
summary(stents_me)
```

```
## 2 strategies run for 10 cycles.
##
## Initial state counts:
##
## initial = 1
## stable = 0
## dead = 0
##
## Counting method: 'beginning'.
##
## Values:
##
##     cost_event_im cost_event_throm cost_event_revas cost_event_dead
## nu       450.2891         51.15535        1811.7187        52.98680
## act      384.2160         46.30646         989.7879        45.24682
##     cost_state_initial cost_state_stable cost_brute cost_total     qaly
```

[4]The basic idea behind this method is that the flow of patients between Markov states is measured at the beginning of each cycle.

```
## nu            797.5624          418.9792   3582.692   7174.407 3.547677
## act          1020.9333          228.2809   2714.771   6995.405 3.616293
##     life_year
## nu   3.424599
## act  4.077191
##
## Efficiency frontier:
##
## act
##
## Differences:
##
##     Cost Diff. Effect Diff.      ICER Ref.
## act  -179.0014    0.6525929 -274.2926   nu
```

We can remark a cost reduction of 196.3448 € in regard the base treatment (ie. bare-metal stents or **stents nu** in French) quickly, as well as, a similar result which was obtained also by [Baschet et al., 2016].

4.4.1.1 Costs and Evolution Cohort

The total cost obtained with a discount for the base treatment (i.e bare-metal stents or *stents* ***nu*** in French) has been 7240.96 € and for the new strategy (i.e. drug-eluting stents or *stents* ***actif*** in French) has been 7044.61 €. Therefore, we can observe a cost-reduction of 196.34 € and an increase in major cardiac event-free survival, as pictured below on the right in figure 4.5.

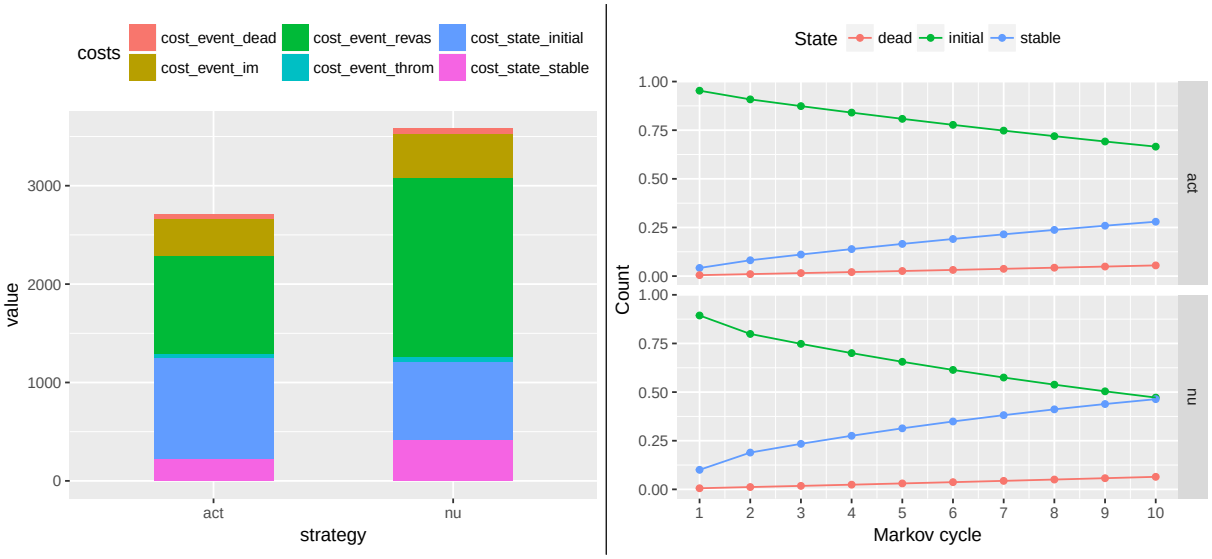


Figure 4.5 – Cost and Evolution of the cohort of the health-economic model to 3 states

4.4.1.2 Health utility

The different health utility obtained with a discount for the base treatment (i.e *stents nu*) has been 3.485392 and for the new strategy (i.e. *stents actif*) has been 4.150208. Therefore, we obtained an increase of 0.665 that hasn't done a first major cardiac event, as pictured below in Figure 4.6.

4.4.2 Markov model to 6 states

In this case, we are going to execute the health-economic model to 6 states. The R code can be found in **Appendix VI**. Below, we show the summary of the execution of the health-economic model.

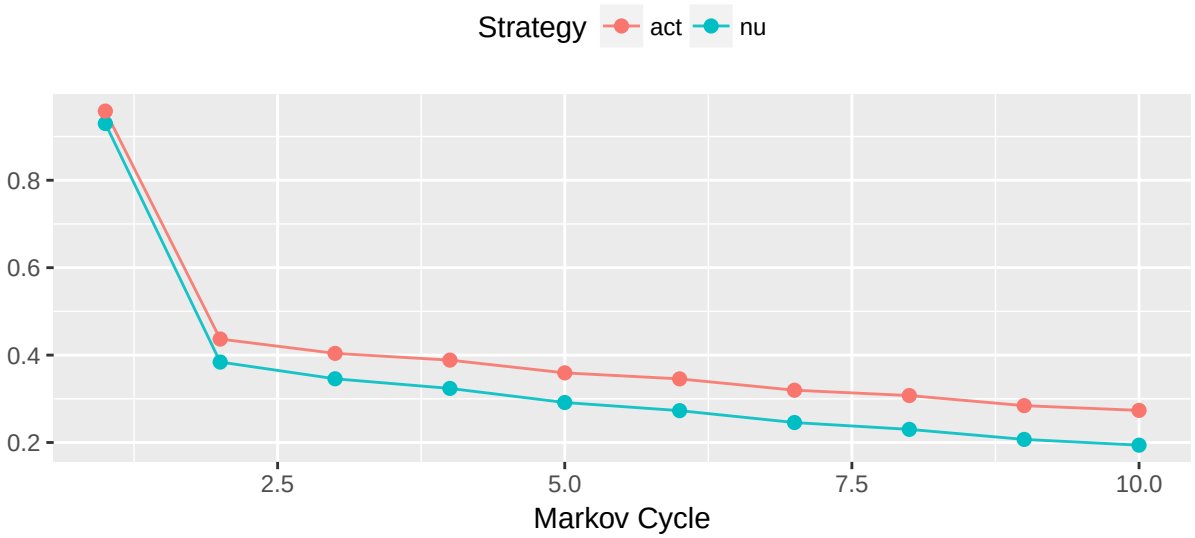


Figure 4.6 – Health utility of the health-economic model to 3 states

```
# Summmary of health-economic model to 3 states
summary(stents_6e_me)
```

```
## 2 strategies run for 10 cycles.
##
## Initial state counts:
##
## initial = 1
## im = 0
## throm = 0
## revas = 0
## stable = 0
## dead = 0
##
## Counting method: 'beginning'.
##
## Values:
##
##     cost_event cost_state_initial cost_state_stable cost_event_dead
## nu    2313.163           862.7017          353.8399        52.98680
## act   1420.310          1059.9521          189.2621        45.24682
##     cost_brute cost_total     qaly life_year
## nu    3582.692   7174.407 3.547677  3.424599
## act   2714.771   6995.405 3.616293  4.077191
##
## Efficiency frontier:
##
## act
##
## Differences:
##
##     Cost Diff. Effect Diff.      ICER Ref.
## act  -179.0014    0.6525929 -274.2926   nu
```

We can quickly remark a result similar to Markov model to three states.

4.4.2.1 Costs and Evolution Cohort

The results are the same that the health-economic model to 3 states.

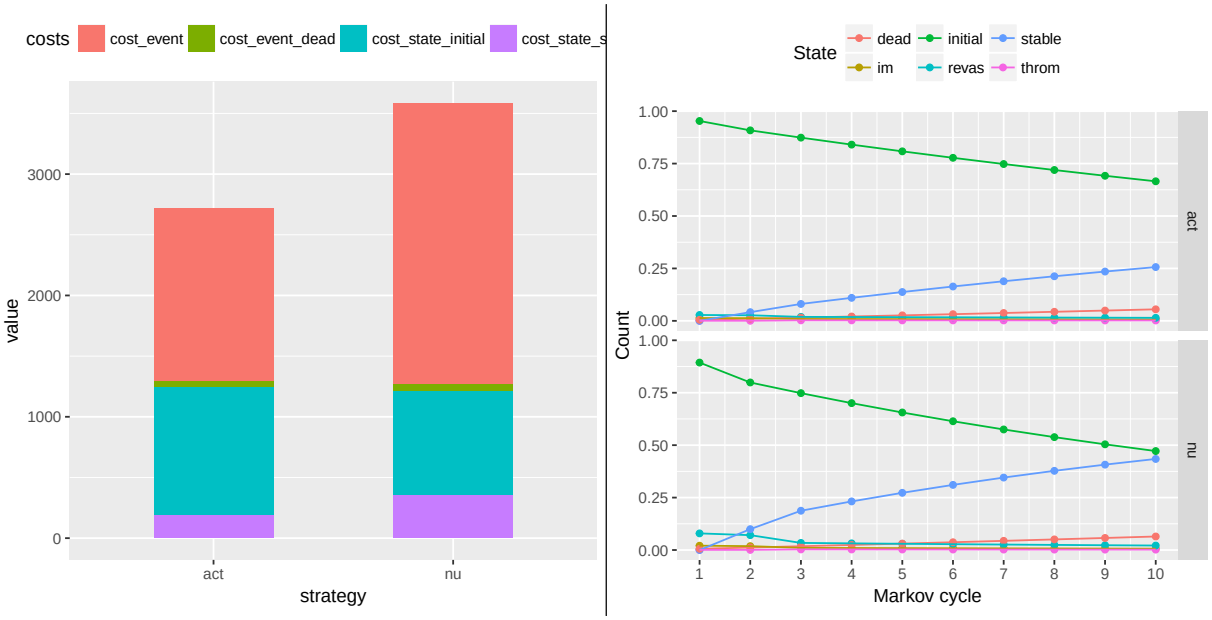


Figure 4.7 – Cost and Evolution of the cohort of the health-economic model to 6 states

4.4.2.2 Health utility

The results are the same that the health-economic model to 3 states.

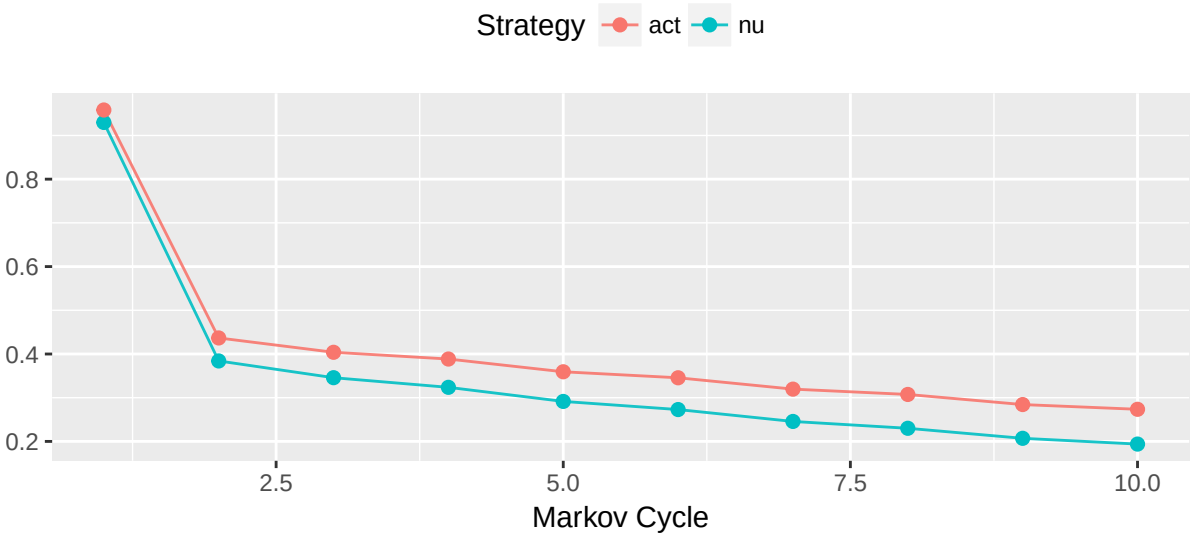


Figure 4.8 – Health utility of the health-economic model to 6 states

4.5 Sentivility analyses

The sensitivity analyses is a methodology used to evaluate the uncertainty either of the statistic model or the estimation parametric (i.e. parameters defined in the model).

In this case, we are going to evaluate parameters uncertainty by putting a priori distribution to each parameter used in the health-economic model, in order to obtain a new random value in each simulation.

We'll use the Probabilistic Sensitivity Analysis (PSA) method configured with **1000** simulations.

Below, we show the table of parameters for the configuration of Probabilistic sensitivity analysis method.

Table IV.2 – Configuration of parameters of health-economic model.

Model Parameter	Distribution	Parameters
Age	Normal	mean: 60, se: 8
Ratio Sex	Beta	$\alpha = 13.8, \theta = 9.2$
Nb. of stents per intervention	Gamma	mean: 1.5, se : 0.5
All rate transition	Beta	α, θ
Cost hospitalization (DES)	Gamma	mean: 3112.0, se : 1505.69
Cost hospitalization (BMS)	Gamma	mean: 3176.17, se : 1505.69
Costs to initial state	Gamma	mean: 132.72, se : 26.545
Costs to stable state	Gamma	mean: 132.72, se : 26.545
Costs of mycoardial infaction event	Gamma	mean: 132.72, se : 26.545
Costs of stent thrombosis event	Gamma	mean: 4322.95, se : 3452.94
Costs of Revascularization event	Gamma	mean: 2696.64, se : 3273.25
Costs of dead event	Gamma	mean: 822.54, se : 164.508
Initial health utility	Gamma	mean: 0.85, se : 0.1
Stable health utility	Gamma	mean: 0.77, se : 0.1

4.5.1 Probabilitic sensitivity analysis for Markov model to 3 states

The spread of simulated points is shown on the left in figure 4.9 and on the right is shown the convergence of Incremental cost-effectiveness ratio (ICER) indicator simulated. This latter tells us that ICER becomes stable with 1000 simulations. The left figure tells us that the new strategy is dominant because he is 53% least costly and most effective.

Figure 4.9 – Uncertainty of the incremental cost and effect of strategies on the cost-effectiveness plane to 3 states, taking the base strategy as a reference.

In the figure below, we show the acceptability curve and the expected value of perfect information (EVPI) curve. The acceptability curve tells us how much the decision-maker is willing to pay for additional

health effectiveness, in this curve, the decision-maker is willing to pay 7500 € per a major cardiac event-free survival year gained which the new strategy has a > 95 % probability of being cost-effective versus the base strategy. The EVPI curve tells us that we must pay between 0 to 10000 € to gather more information and to reduce the risk of taking a wrong decision

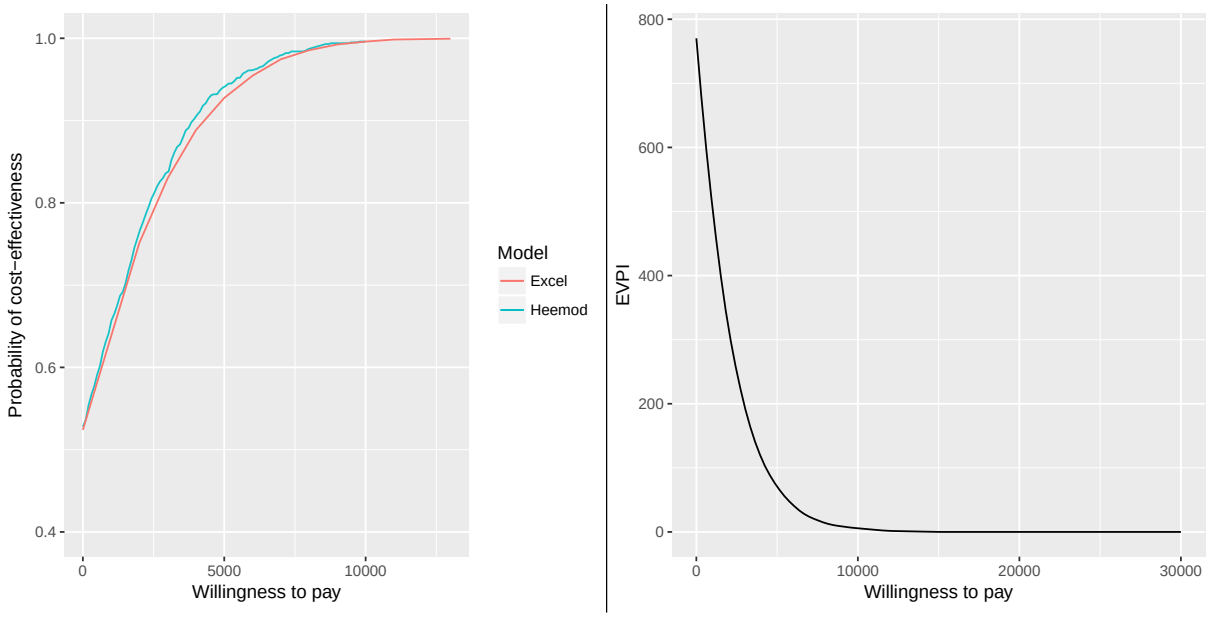


Figure 4.10 – Acceptability curve PSA to 3 states

4.5.2 Probabilitic sensitivity analysis for Markov model to 6 states

The results are almost the same as the health-economic model to 3 states, if there is a slight difference, that is due to the simulation (i.e. random new values for parameters)

Figure 4.11 – Uncertainty of the incremental cost and effect of strategies on the cost-effectiveness plane to 6 states, taking the base strategy as a reference.

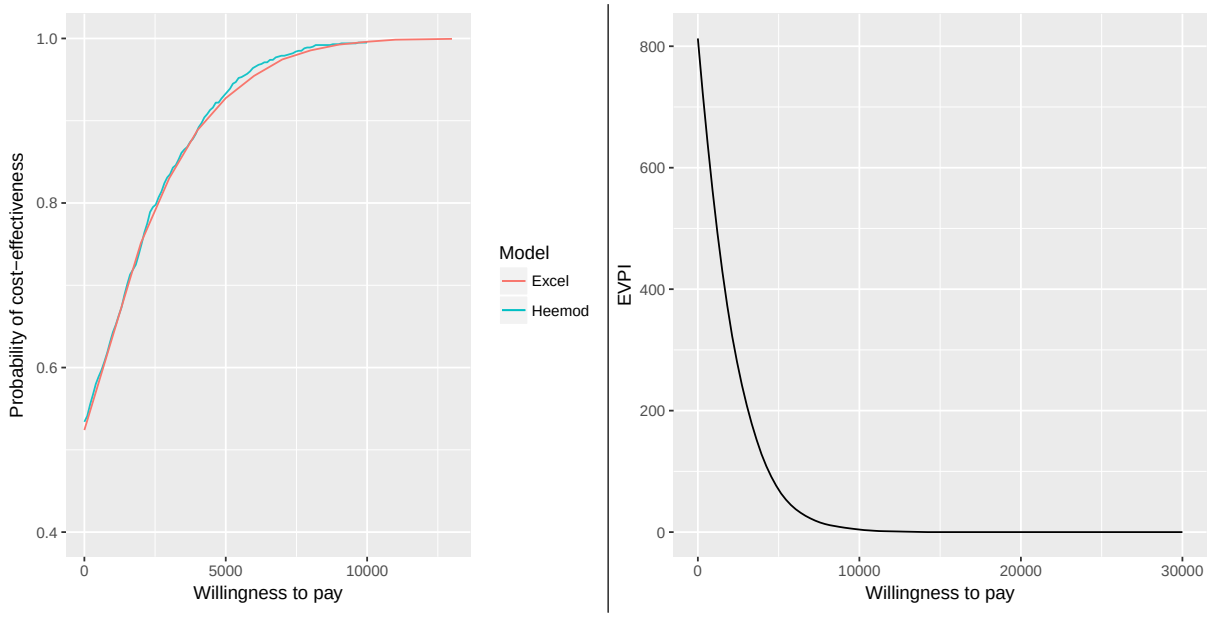


Figure 4.12 – Acceptability curve PSA to 6 states

4.6 Conclusion

After having reproduced and verified that results obtained by **Heemod** are similar to the health-economic evaluation of [Baschet et al., 2016], despite of difficulties found and several missing characteristics in the **Heemod** package. we can conclude that we didn't have a problem due to numerics results, but at the level of design, there isn't still an absolute flexibility to implement or to migrate of cases made in Microsoft excel to Heemod package, for the following reasons:

- We do not have access to patients in transit from one state to another.
- All costs and effects calculated in each cycle are considered in the half-cycle correction, while some transition costs in **Capionis** are not considered.
- Formatting on the presentation of sensitivity analysis results is more generic and slower in *Heemod* because of it, taking into account all the possible scenarios.

However, the use and incremental improvement of the *Heemod* package in the community promises long-term stability and flexibility.

Personally, I highly recommend the use of *Heemod* package because it will evolve and overcome these flaws.

Chapter V

Interface Shiny

As an extra bonus, in this chapter, we'll explain in details how we developed a demo website in ***R-Shiny*** for displaying, setting up and running health-economics evaluations.

This demo website use a web application framework named ***WAHEco*** which has been developed during my internship and published [Carranza-Alarcon et al., 2017] in the conference "Sixth Conference R" (or "Sixièmes Rencontres R" in French) in session "API and Shiny", with the aim of disseminating and popularizing the problematic of the health-economic evaluation, as well as its scientific and practical importance in the decision-making of the health authorities (e.g. H.A.S.)

Contents

5.1 Why a Web Application?

The frequently asked question around companies is ***Why a Web application?***. A web application has several features that can boost economic growth of a company, however, the main reason for developing a website should be the following:

1. An ergonomic web interface for the end user (non-programmers) and the community.
2. Available from a web browser every 7 days / 24 hours.
3. Flexible and scalable to implement for the developer.

It's important to remark that three features have been taken into account for the development of web application framework ***WAHEco***.

5.2 WAHEco a component-based web framework

In order not to reinvents the wheel and having been inspired by recognized architectures such as *AngularJS*[1] and *BlurAdmin*[2], we have developed a ***WAHEco*** package based on components[3], by using *Shiny*[4] as web application framework for R, and integrating it with recognized package in R, such as *Shiny Dashboard*[5] and *Shiny Routes*[6].

[1] https://angularjs.org/
[2] http://akveo.github.io/blur-admin/
[3] A component is a part of an information system that encapsulates a set of related functions.
[4] https://shiny.rstudio.com/
[5] https://rstudio.github.io/shinydashboard/
[6] https://appsilon.github.io/shiny.router/

We have chosen a component-based architecture, for the following reasons:

1. Be able to divide the final web application into various reusable components.
2. Creation and testing of new web components independent of the final web application.
3. Low coupling between components and modules (i.e. a lower interaction between them).
4. Reuse of components and modules in another web application.

The ***WAHEco*** was divided into three main class which should be used to create a web component for the main web application, see Figure 5.1.

1. **AppRoot:** The main core of the Web application, it manages modules.
2. **AppModule :** Abstract class used to create a new module which would contain web components. There is a "base" implementation named ***SimpleModule***.
3. **AppComponent:** Abstract class used to create the custom web interface (i.e. view method (..)) and the Client-Server interaction (i.e. server (..) method).

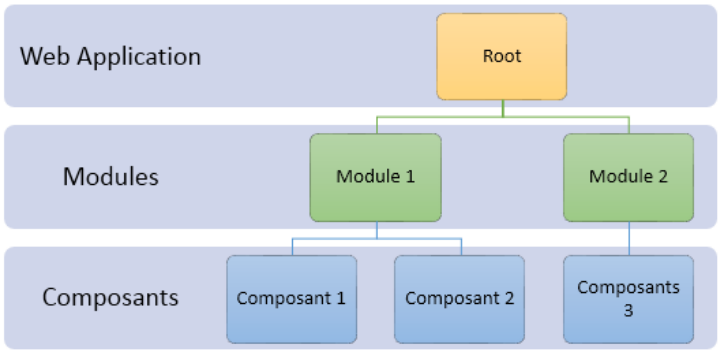


Figure 5.1 – Hierarchy of web components

In Figure 5.2, there is a web visual representation of the last three previously mentioned abstract classes.

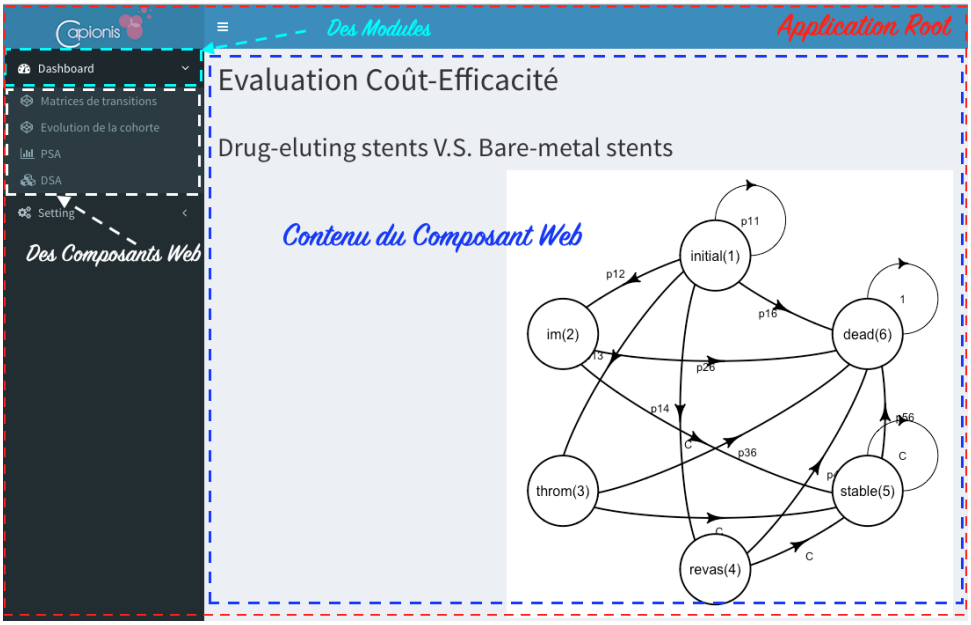


Figure 5.2 – Demo web application for a health-economic evaluation

5.3 Demo web application

During my internship, I used ***WAHEco*** framework for developing a demo web application (Figure 5.2) which can be download from https://github.com/salmuz/WAHEco, section "Demo". This demo has two modules and three components. In Figure 5.3, we can see the component used to sets up a health-economic model in code R and using *Heemod* methods. Any change in the setting of the health-economic model can be done into this web component.

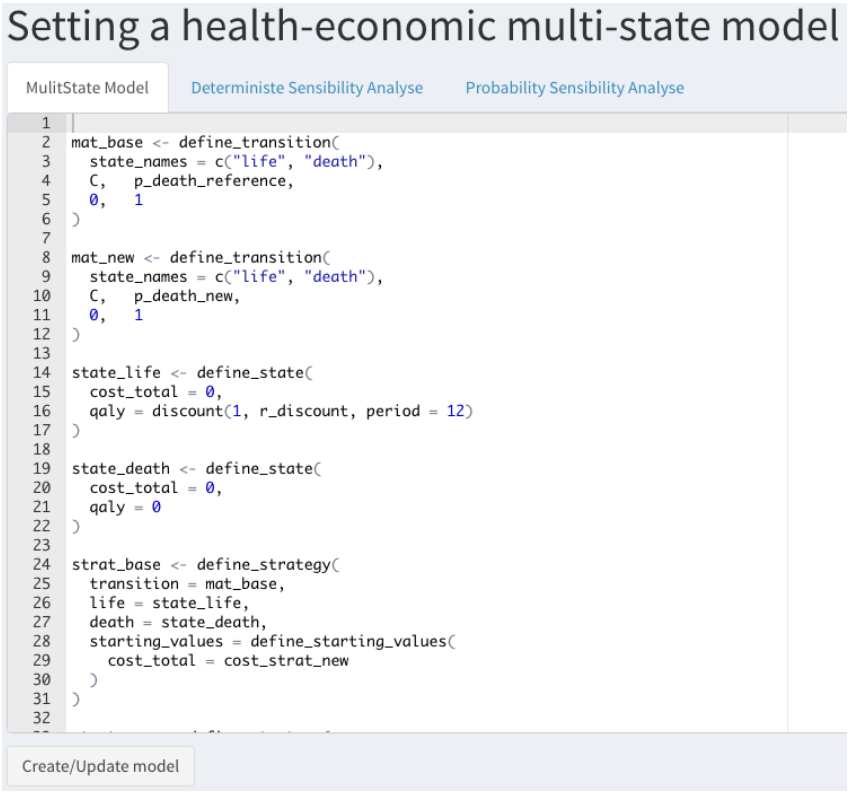


Figure 5.3 – Setting-up of a health-economic model

After having created the model using the previous web component. In Figure 5.4, we can see the evolution over time of patients in each health state, and also, by strategy (i.e. intervention).

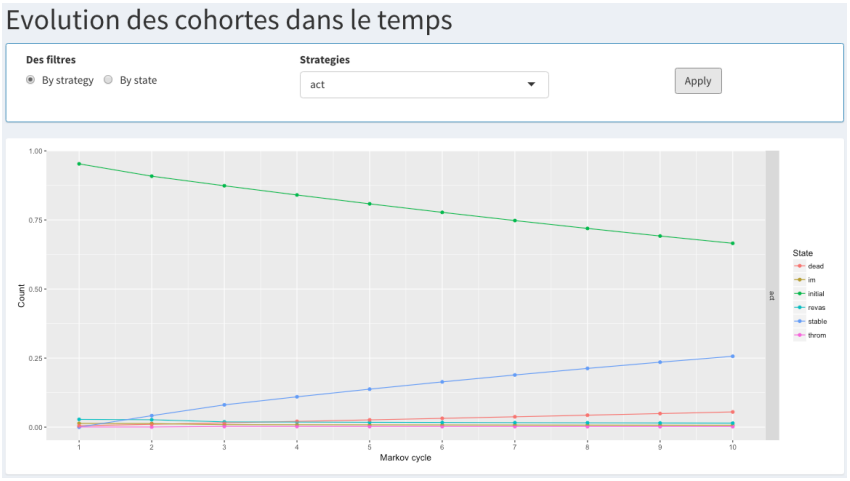


Figure 5.4 – Evolution of cohorts over time

We have also created a web component to display results of the Probabilistic sensitivity analysis (PSA) (see Figure 5.5).

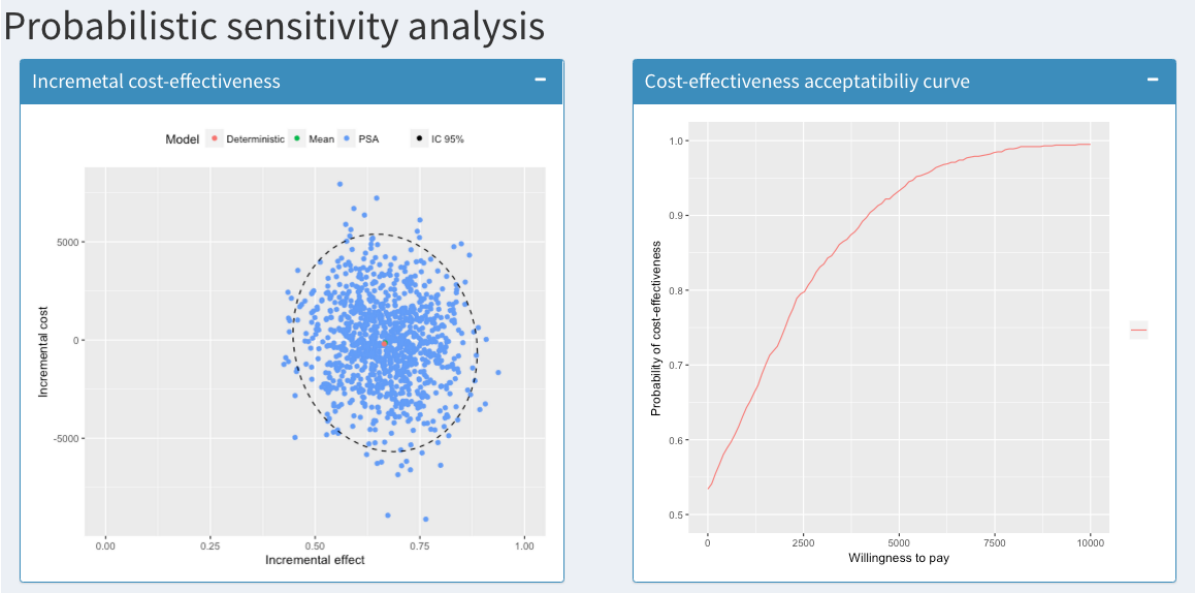


Figure 5.5 – Probabilistic sensitivity analysis

Chapter VII

Conclusion

In closing, I will briefly present below the conclusion of my work achieved as well as future works to be carried out.

Internship assessment

Our results suggest that the evaluation of the *Heemod* package has been a "success", because results obtained are similar to *Capionis* (i.e. validation of deterministic results and sensitivity analysis).

The main disadvantage of *Heemod* is that the implementation could not directly. There are some difficulties in reproducing these results dues to missing features in the *Heemod* package (i.e. initial costs, cost per transition, chained transition matrices, varied discount rates, ...).

Thus, the flexibility to implement real cases of health-economic evaluation using the *Heemod* package has not been satisfactory, since the latter has been designed in a general way in order to address all the existing different cases.

Furthermore, *Heemod* is increasing its used by researchers and companies, so it will surely be able to overcome these weakness, due to the contributions of the community (Capionis includes).

I can finally say that it is still too early to judge the effectiveness and efficiency of the *Heemod* package compared to Microsoft Excel, given the novelty of the package (around 1 year) unlike Microsoft Excel (over 20 years), so we classify this study as a preliminary in nature. However, it may be possible to consider *Heemod* as a sub-process of health-economic evaluations (e.g. sensitivity analysis).

Personal achievement

This 6-month internship at Capionis allowed me to deepen my knowledge in Markov models, or precisely in the simulation of the discrete-time Markov chain subjected to a problem of health-economic evaluation.

The internship was a little difficult at the beginning, because of different techniques and concepts related to health-economic evaluation that I did not know, and that I had to assimilate them. It took me some time to bibliographic research to properly imbibe on the subject, and afterwards, implementing real cases.

The internship also allowed me to apply the lessons which taught me at the university such as stochastic processes, survival analysis and R programming.

Putting into practice the internship allowed me to exchange by mail with the author of the Heemod package, with the aim of making some improvements that I used to implement real cases.

Finally, I also realized that I need a lot of patience and rigor to wait for our final goal.

Further research

I found in the bibliographic search another interesting health-economic approach, as well as their respective R package (BCEA, Bayesian cost-effectiveness analysis), however, due to the constraints of the internship,

I have not been able to implement a real case.

An important feature to be improved are operations with sparse matrix, because the performance of the sensitivity analysis begins to degrade when the multi-state model has around 19 states, taking about 3 hours of execution.

Heemod also has another fairly useful feature, but has not been validated during the internship, this one is the modeling of a semi-Markov process for health-economic evaluations.

Appendix

A.1 - Longitudinal Study

A longitudinal study repeatedly collects information (e.g. medical screening) of different patients (i.e. cohort[1]) exposed a new treatment at prolonged periods of time (patient follow-up) for an in-depth investigation. These information can be extracted of different health states that a patient of the cohort can suffer during the study (e.g. health indicators, cost and effectiveness indicators of a specific treatment).

Further, longitudinal studies are effective in evaluating risk factors for a disease, just like cost-effectiveness of a new treatment (or a new strategy $s_j \in \mathcal{S}$) applied over a long or short period of time, through indicators extracted from the patient. Currently, survival model perfectly attacks this issue as well as the multi-state model (MSM), the former is specific to model longitudinal study focused on an event of interest for longs or short period of time, while the latter can be generalized to several events (or health states) of interest.

Survival model

Survival model is interested in analyzing data where the outcome variable describes time-to-event phenomena as well as the time until the occurrence of the event of interest. The event of interest can be death, heart attack or another organ failure, divorce, defended of master's thesis, etc.

Other examples of an event of interest can be studied as the survival time of a high school teacher until his release, or his internment in a psychiatric hospital or his suicide[2].

First, we assume the time of occurrence of the event of interest as a continuous random variable T with probability density function $f(t)$ and cumulative distribution function $F(t) = \mathbb{P}(T < t)$. And now, if we define a random process $\{X(t), t \in \mathbb{R}^+\}$ to two states $E = \{0, 1\}$; where (0) is initial state (or entered the study) and (1) is state of occurrence of an event of interest(or left the study) [Collett, 2015, p. 323]. We can thus model the survival analysis as a stochastic process, as it's shown in figure 6.1.

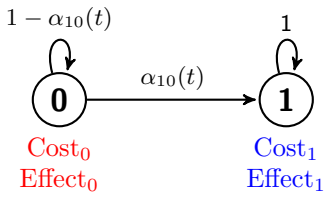


Figure 6.1 – *Survival analysis model to two states.* We have two states, each of them has a cost and an effect (consequence), and to be able to transit from one state to another, due to the transition intensity $\alpha_{10}(t)$ (or hazard ratio function in survival analysis) which express the number of occurrences of an event during a time interval. We can also notice that once we enter state 1, we cannot return to the initial state 0, because the event of interest has already taken place, this kind of state is called an absorbing state.

We can, therefore, define the transition intensity from (0) state to (1) state :

$$\alpha_{01}(t) = \lim_{\Delta t \to 0^+} \frac{\mathbb{P}_{01}(X(t + \Delta t) = 1 | X(t) = 0)}{\Delta t} \tag{6.1}$$

where $\alpha_{01}(t)\Delta t$ is the probability of performing a transition from (0) state to (1) state between t and $t + \Delta t$, for a patient, conditionally on the fact that this patient is in (0) state at time t. In survival analysis, this function is usually called a hazard function which is defined from the random variable T [Liquet, 2009].

[1] Cohort is a group of subjects who share a defining characteristic [https://en.wikipedia.org/wiki/Cohort_(statistics)]
[2] http://zoonek2.free.fr/UNIX/48_R_2004/19.html

$$\alpha(t) = \lim_{\Delta t \to 0^+} \frac{\mathbb{P}_{01}(t < T < t + \ \Delta t | T > t)}{\Delta t} \tag{6.2}$$

From a simplistic point of view, this modeling helps us to make longitudinal studies taking into account the patient's past $X(t)$ before the arrival of the event, and consequently, it is useful for health-economics evaluations having only two different health states of the patient, where each one has a overall cost and consequences as long as a patient has remained there.

Unfortunately, in longitudinal medical studies we observe different health states (or several events of interest) that suffer a patient for a period of time (e.g. good health, sick, relapsed, death), and in order to fully account for all these new elements is that we will approach multi-state models (MSM).

A.2 - Converting of the annual mortality hazard ratio to "different time" probability

***Transform the annual mortality probability to another different Y-time*:** *We're going to assume that the hazard ratio of the Y-time mortality probability is constant during all time of the year. That is, we set a exponential random variable $T_{Y\text{-}time} \sim \mathcal{E}(\lambda)$ which has a constant hazard ratio $h(t) = \lambda$. On the other hand, we also knew by means of Survival Analysis that the hazard ratio can also be formulated as follows:*

$$\begin{aligned} H(t) &= -ln(S(t)) \\ \lambda * t &= -ln(S(t)) \\ \lambda &= -\frac{ln(P(T_{\text{yearly}} > t))}{t} \\ h(t) = \lambda &= -\frac{ln(1 - P(T_{\text{yearly}} \leq t))}{t} \end{aligned} \tag{6.3}$$

where $S(t) = P(T_{Y\text{-}time} > t)$ is survival function, $H(t) = \lambda * t$ is the cumulated hazard and the equation (1) represent the mortality rate of one patient per unit of time t (i.e. hazard ratio). We'll see below some transformations knowing that the annual cumulative probability of mortality is $P(T_{yearly} \leq t)$.

- *If we want to transform it to monthly probability (ie. Y-monthly), then $T_{yearly} = T_{Y\text{-}monthly}/12$*

$$\begin{aligned} \mathbb{P}(T_{\text{Y-monthly}} \leq 12 * t) &= \mathbb{P}(T_{yearly} \leq t) \\ 1 - \mathbb{P}(T_{\text{Y-monthly}} > 12 * t) &= \mathbb{P}(T_{yearly} \leq t) \\ exp(-\lambda_{\text{Y-monthly}} * 12 * t) &= 1 - \mathbb{P}(T_{yearly} \leq t) \\ \lambda_{\text{Y-monthly}} * t &= -\frac{ln(1 - \mathbb{P}(T_{yearly} \leq t)}{12} \\ ln(1 - \mathbb{P}(T_{Y-monthly} \leq t) &= \frac{ln(1 - \mathbb{P}(T_{yearly} \leq t)}{12} \quad \text{of equation (1).} \end{aligned}$$

$$P(T_{\text{Y-monthly}} \leq t) = 1 - exp(\frac{ln(1 - P(T_{yearly} \leq t))}{12}) \tag{6.4}$$

$$P(T_{\text{Y-monthly}} \leq t) = 1 - (1 - P(T_{yearly} \leq t))^{\frac{1}{12}} \tag{6.5}$$

$$P(T_{\text{Y-monthly}} \leq t) = 1 - exp(-\frac{h(t_{yearly})}{12}) \tag{6.6}$$

The (2) or (3) equation stands for the monthly mortality probability with constant hazard ratio for a given age t.

- *If we want to transform it to six-monthly probability (ie. Y-six-monthly), then $T_{yearly} = T_{Y\text{-}six\text{-}monthly}/2$*

$$P(T_{\text{Y-six-monthly}} \leq t) = 1 - exp(\frac{ln(1 - P(T_{yearly} \leq t))}{2}) \tag{6.7}$$

$$P(T_{\text{Y-six-monthly}} \leq t) = 1 - (1 - P(T_{yearly} \leq t))^{\frac{1}{2}} \tag{6.8}$$

$$P(T_{\text{Y-six-monthly}} \leq t) = 1 - exp(-\frac{h(t_{yearly})}{2}) \tag{6.9}$$

A.3 - Compute transation probabilities from each event

We will firstly put a random variable $E \in \{M, T, R\}$ that stands for three major cardiac events (i.e. M : Myocardial infarction, T : Stent Thrombosis, R : Revascularisation), and a random variable $D \in \{\text{D-M}, \text{D-T}, \text{D-R}\}$ that stands for the probability of death after having done one of these last three major cardiac event.

a.1. Myocardial infarction (MI): The probability of making a myocardial infarction ($E \in \{M\}$) to patients who have not died ($A > a$) to the initial state by causes of mortality in the general population during the current cycle is:

$$\mathbb{P}(E \in \{M\} \cap A > a) = (1 - \mathbb{P}(A \leq a)) * \mathbb{P}_E(M) = (1 - \phi_{p,a}) * \mathbb{P}_E(M) \tag{6.10}$$

Assuming the events ($E \in \{M\}$) and ($A > a$) are independent. Furthermore, among patients who suffer MI, one part will die as a result of this event and one part will move to the stable state. In addition, the probability of death due to MI to patients (i.e. $\mathbb{P}_D(\text{D-M})$) can't be lower that the probability of death in the general population (i.e. $\phi_{p,a}$). Thus, the probability of patients who die as a result of MI is:

$$\mathbb{P}(\text{Death due to MI}) = \mathbb{P}(E \in \{M\} \cup A > a) * max(\phi_{p,a}, \mathbb{P}_D(\text{D-M}))$$

Finally, we have the probability of transiting to the stable state from the myocardial infarction event.

$$\mathbf{p}_{01}(t, E \in \{M\}) = \mathbb{P}(E \in \{M\} \cup A > a) - \mathbb{P}(\text{Death due to MI}) \tag{6.11}$$

a.2. Stent thrombosis without MI: The probability of making a stent trombosis without MI to patients who have not died to the initial state during the current state is:

$$\begin{aligned}
\mathbb{P}[(E \in \{T\}) \cap \overline{(E \in \{M\} \cap (A > a))} \cap (A > a)] &= \mathbb{P}[(E \in \{T\}) \cap (E \notin \{M\} \cup \overline{(A > a)}) \cap (A > a)] \\
&= \mathbb{P}[(E \in \{T\}) \cap ((E \notin \{M\} \cap (A > a)) \cup \underbrace{(\overline{(A > a)} \cap (A > a))}_{\emptyset})] \\
&= \mathbb{P}[(E \in \{T\}) \cap (E \notin \{M\} \cap (A > a)] \\
&= \mathbb{P}(E \in \{T\}) * \mathbb{P}(E \notin \{M\}) * \mathbb{P}(A > a) \\
&= \mathbb{P}(A > a) * (1 - \mathbb{P}(E \in \{M\})) * \mathbb{P}(E \in \{T\}) \\
&= (\mathbb{P}(A > a) - \mathbb{P}(E \in \{M\} \cap (A > a))) * \mathbb{P}(E \in \{T\}) \\
&= [1 - \phi_{p,a} - (1 - \phi_{p,a}) * \mathbb{P}_E(M)] * \mathbb{P}_E(T)
\end{aligned} \tag{6.12}$$

Assuming the events ($E \in \{T\}$), ($E \notin \{M\}$) and ($A > a$) are independent. Furthermore, among patients who suffer a stents thrombosis, one part will die as a result of this event and one part will move to the stable state. In addition, the probability of death due to stent thrombosis without MI (i.e. $\mathbb{P}_D(\text{D-T})$) can't be lower that the probability of death in the general population (i.e. $\phi_{p,a}$).Thus, the probability of patients who die as a result of stent thrombosis without MI is:

$$\mathbb{P}(\text{Death due to T}) = \mathbb{P}[(E \in \{T\}) \cap \overline{(E \in \{M\} \cap (A > a))} \cap (A > a)] * max(\phi_{p,a}, \mathbb{P}_D(\text{D-T}))$$

Finally, we have the probability of transiting to the stable state from the stent thrombosis event without MI:

$$\mathbf{p}_{01}(t, E \in \{T\}) = \mathbb{P}[(E \in \{T\}) \cap \overline{(E \in \{M\} \cap (A > a))} \cap (A > a)] - \mathbb{P}(\text{Death due to T}) \tag{6.13}$$

a.3. Revascularisation without Stent thrombosis and MI: The probability to need of a revascularization without MI and stent thrombosis to patients who have not died from initial state during the current cycle is:

$$\mathbb{P}[(E \in \{R\}) \cap \overline{(E \in \{T\}) \cap \overline{(E \in \{M\} \cap (A > a))} \cap (A > a)} \cap \overline{(E \in \{M\} \cap (A > a))} \cap (A > a)]$$

By putting $\Delta = \overline{(E \in \{M\} \cap (A > a))} \cap (A > a) = (E \notin \{M\}) \cap (A > a)$, we have:

$$\begin{aligned}\{(E \in \{R\}) \cap \overline{(E \in \{T\}) \cap \Delta} \cap \Delta\} &= \{(E \in \{R\}) \cap [(E \notin \{T\}) \cup \Delta] \cap \Delta\} \\ &= \{(E \in \{R\}) \cap (E \notin \{T\}) \cap \Delta\} \\ &= \{(E \in \{R\}) \cap (E \notin \{T\}) \cap (E \notin \{M\}) \cap (A > a)\}\end{aligned}$$

Assuming the events are independent. We must therefore calculate $\mathbb{P}[E \in \{R\} \cap ...]$

$$\begin{aligned}&\mathbb{P}[(E \in \{R\}) \cap (E \notin \{T\}) \cap (E \notin \{M\}) \cap (A > a)] = (1 - \mathbb{P}[E \in \{T\}]) * \mathbb{P}[E \notin \{M\}] * \mathbb{P}[A > a] * \mathbb{P}[E \in \{R\}] \\ &= (\mathbb{P}[A > a] * \mathbb{P}[E \notin \{M\}] - \mathbb{P}[E \in \{T\} \cap E \notin \{M\} \cap (A > a)]) * \mathbb{P}[E \in \{R\}]) \\ &= (\mathbb{P}[A > a] * (1 - \mathbb{P}[E \in \{M\}]) - \mathbb{P}[(E \in \{T\}) \cap \overline{(E \in \{M\} \cap (A > a))} \cap (A > a)]) * \mathbb{P}[E \in \{R\}] \\ &= (1 - \mathbb{P}[A \leq a] - \mathbb{P}[E \in \{M\} \cap (A > a)] - \mathbb{P}[(E \in \{T\}) \cap \overline{(E \in \{M\} \cap (A > a))} \cap (A > a)]) * \mathbb{P}[E \in \{R\}])\end{aligned}$$

Using equations (6.10) and (6.12), We will get:

$$\mathbb{P}[E \in \{R\} \cap ...] = [1 - \phi_{p,a} - (1 - \phi_{p,a}) * \mathbb{P}_E(M) - (1 - \phi_{p,a} - (1 - \phi_{p,a}) * \mathbb{P}_E(M)) * \mathbb{P}_E(T)] * \mathbb{P}_E(R) \tag{6.14}$$

As in the previous two cases, the probability of patients who die as result of revascularization without MI and stent thrombosis is:

$$\mathbb{P}(\text{Death due to R}) = \mathbb{P}[E \in \{R\} \cap ...] * max(\phi_{p,a}, \mathbb{P}_D(\text{D-R}))$$

Finally, we have the probability of transiting in a stable state from the revascularization event without thrombosis and myocardial infactus:

$$\mathbf{p}_{01}(t, E \in \{R\}) = \mathbb{P}[E \in \{R\} \cap ...] - \mathbb{P}(\text{Death due to R}) \tag{6.15}$$

A.4 - Markov to 3 state

The source code is in https://www.dropbox.com/s/4846a5hbats7f8b/stents3s_code.pdf?dl=0.

A.5 - Markov to 6 state

The source code is in https://www.dropbox.com/s/2uvaaxd0vq3m0c0/stents6s_code.pdf?dl=0.

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