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A Probabilistic Graphical Model for Total Knee Arthroplasty

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Thanks

To my wife, Mónica, I gratefully dedicate this work. Thank you for always supporting me.

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Introduction

1.1 Motivation

Probabilistic Graphical Models (PGMs), in particular Bayesian networks and influence diagrams, were developed in the 1980's by researchers in Artificial Intelligence, Mathematics and Economy with the purpose of solving problems whose complexity exceeded the capacity of the methods existing so far. Nowadays, PGMs are applied to many areas and there exists an increasing interest in the academic field as well as in the business world. PGMs allow to deal with problems that could not be addressed with traditional probabilistic methods or other artificial intelligence techniques.

Several Spanish research groups interested on PGMs arose independently in different universities. The work on PGMs at UNED started in 1990 with (Díez, 1994) PhD Thesis, which consisted of the construction of the expert system DIAVAL, a Bayesian network for the diagnosis of heart diseases by echocardiography.

The research of the CISIAD (Centro de Investigación sobre Sistemas Inteligentes de Ayuda a la Decisión)[1], has always been led by concrete medical problems: the needs that have arisen when building diagrams has motivated the development of new models, algorithms, and software tools, which have been later applied to other problems, not only in medicine.

The main objective of this research was the building of an influence diagram to make a cost-utility analysis for the total knee arthroplasty clinical process.

[1]CISIAD is a Research Center on Intelligent Decision-Support Systems, UNED dependent center.

Figure 1.1: Phases in the development of this research.

The main motivation to build this diagram was to confirm two assumptions of the expert who has collaborated in this research, Dr. Rubén García Fraile, which are the following:

1. The main risk factors in order to suffer a perioperative infection after the total knee arthroplasty are: (1) a high body mass index (BMI), (2) being diabetic (diabetes mellitus), and (3) being allergic to antibiotics.

2. For the patients with these three risk factors, the arthroplasty led to a high loss of health and money, because the removal of the prosthesis is needed if the infection is present.

1.2 Objectives

Because of the needs described in the previous section, the objectives of this research can be summarized as follows:

1. To build an influence diagram with super-value nodes representing the total knee arthroplasty clinical process and diagnosis of perioperative prosthesis infection, which we called ArthroNET.

2. To evaluate this diagram.

1.3 Methodology

The methodology followed for achieving the objectives can be divided into three phases, as shown in Figure 1.1.

The first phase consists of building the influence diagram ArthroNET, with the help of the orthopedic and trauma surgeon mentioned in Section 1.1. The

second phase was the validation of the system, which led to the modification of the diagram with the expert's help in an iterative process. Finally, we could evaluate the model and extract some results.

1.4 Organization of the research

This memory is structured in four parts:

1. Part I explains the motivation, objectives, and methodology of this research.
2. Part II reviews the state of the art of two kind of decision support systems: (1) those related to knee arthroplasties, and (2) those based on influence diagrams applied to clinical processes.
3. Part III presents the decision-support system for the diagnosis of total knee arthroplasty perioperative infection.
4. Part IV shows the conclusions and some open lines for future research.

Part II

State of the Art

Chapter 2

State of the Art

In this chapter we present the state of the art of (1) decision support systems (DSS below) for total knee replacements and (2) influence diagrams applied to medicine.

2.1 DSS for Total Knee Arthroplasty

There are few decision support systems for orthopedic surgery. Thereby, the only work with the same objective as ours found at the date of this research is (Hazen et al., 1998), demonstrating how to use influence diagrams augmented by stochastic nodes to analyze a chain of decisions as to whether a patient should proceed to total knee (or hip) replacement surgery or not. The objective of this decision analysis was to calculate the expected costs and effectiveness of each choice. The use of QALYs for the objective was important because an elderly person undergoing joint replacement may not increase his/her life expectancy, but the quality of life improvement can be considerable and, quite possibly, worth the cost.

There is other non-influence diagram based support systems used to help orthopaedic surgeons. Nowadays, the School of Engineering Sciences of the University of Southampton is working on the Decision Support Software for Orthopaedic Surgery project (DeSSOS), whose main objective is to develop both knowledge and software tools providing decision support for orthopaedic surgeons involved in knee arthroplasty. They are trying to offer pre- and intra-operative assistance to determine the prosthetic configuration and position based on the data captured

from each individual patient. Improving the effectiveness of total knee replacement surgery will be done integrating kinematic models into the decision process, so the best possible outlook is offered to the patient.

The same Bioengineering Department where DeSSOS was born, is carrying out other research projects related to knee and hip replacement. Because of their nature, we just want to mention three of them.

In (Strickland et al., 2010), explicit finite element (FE) and multi-body dynamics (MBD) models have been developed to evaluate total knee replacement mechanics as a complement to experimental methods. In conjunction with these models, probabilistic methods have been implemented to predict performance bounds and identify important parameters, subject to uncertainty in component alignment and experimental conditions. Probabilistic methods, such as advanced mean value and response surface method, provide an efficient alternative to the gold standard Monte Carlo simulation technique. The objective of the study was to benchmark models from three platforms (two FE and one MBD) using various probabilistic methods to predict the influence of alignment variability and experimental parameters on TKR mechanics in a simulated gait.

The second study, (Strickland et al., 2009), demonstrates conceptually how probabilistic studies might further provide a framework to explore relationships not just within but between multiple different activities, e.g. intra-operative passive laxity drawer loading and post-operative active gait. Two implants were compared using simulated ISO-gait and passive laxity loading, with factors including mal-positioning and soft-tissue constraint varied using Monte Carlo analysis. The results illustrate that correlations between different activities can be quantified; this demonstration study suggests further research is justified (with detailed clinically representative models) to explore the relationship between passive and active mechanics for specific in vivo conditions.

Polyethylene wear remains a clinically relevant issue affecting total knee replacement performance, with considerable variability observed in both clinical retrieval and experimental wear studies. For this reason the objectives of the latter study, (Pal et al., 2008), were to develop a probabilistic wear prediction model capable of incorporating uncertainty in component alignment, constraint and environmental conditions, to compare computational predictions with experimental results from a knee wear simulator, and to identify the most significant parameters affecting predicted wear performance during simulated gait. The study utilizes a

previously verified wear model; the Archards law-based wear formulation represents a composite measure, incorporating the effects and relative contributions of kinematics and contact pressure. Predicted wear was in reasonable agreement in trend and magnitude with experimental results. After 5 million cycles, the predicted ranges (1–99%) of variability in linear wear penetration and gravimetric wear were 0.13 mm and 25 mg, respectively, for the input variability levels evaluated. Using correlation-based sensitivity factors, the coefficient of friction, insert tilt and femoral flexionextension alignment, and the wear coefficient were identified as the parameters most affecting predicted wear. Comparisons of stability, accuracy and efficiency for the Monte Carlo and advanced mean value probabilistic methods are also described. The probabilistic wear prediction model provides a time and cost efficient framework for evaluating wear performance, including considerations of malalignment and variability during the design phase of new implants.

(Dong and Buxton, 2006), apply a Markov model to compare cost-effectiveness of total knee replacement using computer-assisted surgery (CAS) with that of total knee replacement using a conventional manual method in the absence of formal clinical trial evidence. To this end, a structured search was carried out to identify evidence relating to the clinical outcome, cost and effectiveness of total knee replacement. Nine Markov states were identified based on the progress of the disease after the surgery. Effectiveness was expressed in QALYs. Then, a probabilistic sensitivity analysis was carried out using a Monte Carlo method. The study concludes that compared with conventional total knee replacement, computer-assisted total knee replacement is a cost-saving technology in the long-term and may offer small additional QALYs.

2.2 Influence diagrams based systems applied to clinical processes

Before listing the influence diagram applications, we offer a short description of influence diagrams, extracted from (Luque Gallego, 2009).

2.2.1 Influence diagrams

An *influence diagram* (ID) is basically a Bayesian network augmented with decision nodes and value nodes. Thus, an ID consists of an acyclic directed graph $G = (\mathbf{V}, \mathbf{E})$, where the set $\mathbf{V}$ has three types of nodes: *chance nodes* $\mathbf{V_C}$, *decision nodes* $\mathbf{V_D}$ and *utility nodes* $\mathbf{V_U}$.

As in Bayesian networks, chance nodes (drawn as circles) represent chance variables, i.e., events which are not under the direct control of the decision maker. Decision nodes (drawn as rectangles) correspond to actions under the direct control of the decision maker. Utility nodes (drawn as diamonds) represent the expected benefit or loss, or more generally, the preferences of the decision maker. Utility nodes can not be parents of chance or decision nodes.

(Tatman and Shachter, 1990) proposed an extended framework of IDs with SVNs[1]. They distinguished two types of utility nodes: *ordinary utility nodes*, whose parents are decision and/or chance nodes, and *super value nodes* (SVNs), whose parents are utility nodes. We assume that there is a utility node U_0 that is a descendant of all the other utility nodes, and therefore has no children[2].

There are three types of arcs in an ID, corresponding to the type of node they go into. Arcs into chance nodes represent probabilistic dependency. Arcs into decision nodes, named *informational arcs*, represent availability of information; i.e., if there is an arc from a node X to a decision node D then the state of X is known when the decision D is made. Arcs into utility nodes represent functional dependency: arcs into ordinary utility nodes indicate the domain of the associated utility function; arcs into an SVN U indicate that the associated utility function is a combination (generally a sum or a product) of the utility functions of the parents of U.

We assume that there is a path in the ID that includes all the decision nodes, which induces a total order among the n decisions $\{D_1, ..., D_n\}$ and indicates the order in which the decisions are made. Such order originates a partitioning of $\mathbf{V_C}$ into a collection of disjoint subsets, $\mathbf{C_0}, \mathbf{C_1}, ..., \mathbf{C_n}$, where $\mathbf{C_i}$ contains every chance variable C such that there is an arc $C \longrightarrow D_i$ but there is not an arc

[1] Super Value Nodes

[2] Clearly, an ID having only one utility node satisfies this condition by identifying such a node with U_0. An ID having several utility nodes assumes that the global utility is their sum, and can be modified to fulfill that condition by adding a new node U_0, of type sum, whose parents are the original utility nodes. Therefore, this assumption does not restrict the types of IDs that we can represent.

$C \longrightarrow D_j, j < i$; i.e., $\mathbf{C_i}$ is the subset of chance variables known for D_i but unknown for any previous decision. This induces a *partial order* $\prec$ in $\mathbf{V_C} \cup \mathbf{V_D}$:

$$\mathbf{C_0} \prec D_0 \prec \mathbf{C_1} \prec ... \prec D_n \prec \mathbf{C_n} \tag{2.1}$$

The set of variables known to the decision maker when deciding on D_j is termed the *informational predecessors* of D_j and is denoted $iPred(D_j)$. By assuming the *no-forgetting* hypothesis, which states that the decision maker remembers all previous decisions and observations, we have $iPred(D_i) \subseteq iPred(D_j)$ (for $i \leq j$). In particular, $iPred(D_j)$ is the set of chance variables that occurs before D_j under $\prec$, i.e., $iPred(D_j) = \mathbf{C_0} \cup \{D_0\} \cup \mathbf{C_1} \cup ... \cup \{D_{i?1}\} \cup \mathbf{C_i}$. If we have a chance or decision variable X, two decisions D_i and D_j such that $i < j$, and two arcs $X \longrightarrow D_i$ and $X \longrightarrow D_j$, then the latter is said to be a *no-forgetting arc*.

The quantitative information that defines an ID is given by (1) assigning to each chance node C a conditional probability potential $p(C|pa(C))$ for each configuration of its parents, $pa(C)$[3]; (2) assigning to each ordinary utility node U a potential $\psi_U(pa(U))$ that maps each configuration of its parents onto a real number, and (3) assigning a utility-combination function to each SVN. Every utility function ψ_U of a utility node U can finally be expressed as a function of chance and decision nodes, termed the *functional predecessors* of U and denoted by $fPred(U)$. Thus, the functional predecessors of an ordinary utility node are its parents, $fPred(U) = Pa(U)$, and the functional predecessors of an SVN are all the functional predecessors of its parents: $fPred(U) = \cup\{fPred(U')|U' \in Pa(U)\}$. In analogy with the terms of variable and node, we will use the terms utility function and utility node interchangeably.

For example, in the ID in Figure 2.1 we have $fPred(U_1) = \{X, D\}$, $fPred(U_2) = \{T\}$ and $fPred(U_0) = \{X, D, T\}$. Similarly, considering that U_0 is a sum node, we have $\psi_{U_0}(T, X, D) = \psi_{U_1}(T) + \psi_{U_2}(X, D)$.

In order to simplify the notation, we shall sometimes assume without loss of generality that $fPred(U) = \mathbf{V_C} \cup \mathbf{V_D}$ for every utility node U, i.e., U depends on all the chance variables and decisions.

For each configuration $\mathbf{v_D}$ of the decision variables in $\mathbf{V_D}$ we have a joint probability distribution defined over the set of random variables $\mathbf{V_C}$:

[3]We denote by $Pa(X)$ the set of parents of X, and by $pa(X)$ a configuration of the parents of X.

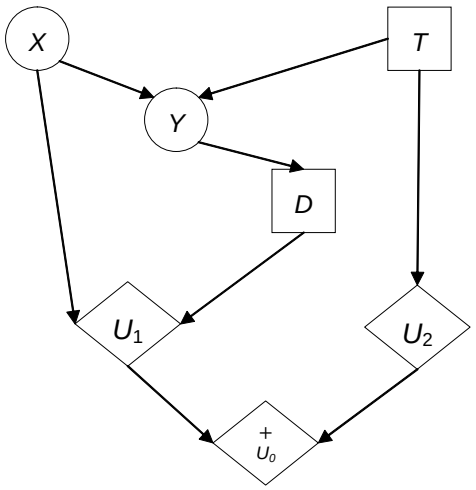

Figure 2.1: An ID of the test problem (Example 2.2.1).

$$P(\mathbf{v_C} : \mathbf{v_D}) = \prod_{X \in \mathbf{V_C}} P(x|pa_C(X) : pa_D(X)) = \prod_{X \in \mathbf{V_C}} P(x|pa(X)), \tag{2.2}$$

where $Pa_C(X)$ and $Pa_D(X)$ denote the parents of X that are chance and decision variables respectively, i.e., $Pa_C(X) = Pa(X) \cap \mathbf{V_C}$, and $Pa_D(X) = Pa(X) \cap \mathbf{V_D}$. Equation 2.2 represents the probability of configuration $\mathbf{v_C}$ when the decision variables are externally set to the values given by $\mathbf{v_D}$. This notation, introduced by (Cowell et al., 1999), is equivalent to the notation used by (Pearl, 1994); (Pearl, 2000), $P(\mathbf{v_C}|do(\mathbf{v_D}))$[4].

A very simple example of ID is the **test problem**.

Example - Test problem *A physician has to decide whether to treat or not a patient, who may suffer from a disease (X). Before making this decision (D), the physician can decide to perform a test (T). This test will produce the test result (Y), which would help to determine whether the patient suffers from the disease.*

An ID for this decision problem is given in Figure 2.1. The decision node T designates the decision about whether or not to perform the test. The chance

[4] $P(\mathbf{v_C} : \mathbf{v_D})$ should not be confused with $P_\Delta(\mathbf{v_C}|\mathbf{v_D})$, which we will present further and that is directly derived from the joint probability distribution $P_\Delta(\mathbf{v_C}, \mathbf{v_D})$ by using equation 2.3 and which only makes sense after selecting a strategy Δ. On the contrary, $P(\mathbf{v_C} : \mathbf{v_D})$ represents the probability of $\mathbf{v_C}$ if the actions given by $\mathbf{v_D}$ are externally set, independently of the values of the variables observed when making each decision.

node Y represents the result of the test (if the test is performed). The utility function associated with the utility node U_1 encodes the cost of performing the test. The decision D is the decision whether or not to treat for the disease. The chance node X represents the presence of the disease. The utility function associated with the utility node U_2 specifies the health state of the patient as a function of the treatment and the disease. The SVN U_0 represents the health state as a sum of the cost of the test (U_2) and the health state of the patient after being treated (U_1).

The directed path from T to D indicates that the physician decides on T before deciding on D. The informational arc from Y to D specifies that the test result is known before deciding on D. On the other hand, as there is no informational arc from X to either of the decision nodes, the state of X is observed (sometimes) after deciding on D. The parents of U_1 and U_2 are the variables in the domains of their respective utility functions. Thus, the parents of U_0 are both the parents of U_1 and U_2. The utility function of U_0 can therefore be expressed in terms of $pa(U_1) \cup pa(U_2) = \{T, X, D\}$.

Finally, with respect to the states of the variables in the ID in Figure 2.1, decision T has two states, $+t$ and $\neg t$, and the result of the test (Y) has three states: $+y$, $\neg y$ and *no-result*. Thus, the probability distribution of Y has to reflect that the result of the test is only available if the physician decides to perform it.

Policies and strategies

A *stochastic policy* for a decision D is a probability distribution defined over D and conditioned on the set of its informational predecessors, $P_D(d|iPred(D))$. If P_D is degenerate (consisting of ones and zeros only) then we say that the policy is *deterministic*.

A strategy Δ for an ID is a set of policies, one for each decision, $\{P_D|D \in \mathbf{V_D}\}$. If every policy in the strategy Δ is deterministic, then Δ is said to be *deterministic*; otherwise Δ is *stochastic*. A strategy Δ *induces* a joint probability distribution over $\mathbf{V_C} \cup \mathbf{V_D}$ defined as follows:

$$\begin{aligned} P_\Delta(\mathbf{v_C}, \mathbf{v_D}) &= P(\mathbf{v_C} : \mathbf{v_D}) \prod_{D \in \mathbf{V_D}} P_D(d|iPred(D)) \\ &= \prod_{C \in \mathbf{V_C}} P(c|pa(C)) \prod_{D \in \mathbf{V_D}} P_D(d|iPred(D)). \end{aligned} \tag{2.3}$$

Let I be an ID, Δ a strategy for I and $\mathbf{r}$ a configuration defined over a set of variables $\mathbf{R} \subseteq \mathbf{V_C} \cup \mathbf{V_D}$ such that $P_\Delta(\mathbf{r}) \neq 0$. The conditional probability distribution *induced by the strategy* Δ *given the configuration* $\mathbf{r}$, defined over $\mathbf{R}' = (\mathbf{V_C} \cup \mathbf{V_D}) \backslash \mathbf{R}$, is given by:

$$P_\Delta(\mathbf{r}'|\mathbf{r}) = \frac{P_\Delta(\mathbf{r}, \mathbf{r}')}{P_\Delta(\mathbf{r})}. \tag{2.4}$$

For example, in the ID in Figure 2.1 we have:

$$P_\Delta(\mathbf{v_C}, \mathbf{v_D}) = P(x) \cdot P(y|t, x) \cdot P_T(t) \cdot P_D(d|t, y), \tag{2.5}$$

where P_T and P_D are the policies contained in strategy Δ. If we have $\mathbf{R} = \{T, Y\}$, then the conditional probability distribution induced $P_\Delta(\mathbf{r}'|\mathbf{r})$ is:

$$P_\Delta(\mathbf{r}'|\mathbf{r}) = P_\Delta(x, d|t, y) = \frac{P_\Delta(x, d, t, y)}{P_\Delta(t, y)}. \tag{2.6}$$

Thus, the conditional probability distribution $P_\Delta(x, d|t, y)$ in Equation 2.6 represents the posterior probability of x and d, given the values t and y.

Using the distribution $P_\Delta(\mathbf{r}'|\mathbf{r})$ defined in Equation 2.4 we can compute the *expected utility of* U *under the strategy* Δ *given the configuration* $\mathbf{r}$ as:

$$EU_U(\Delta, \mathbf{r}) = \sum_{\mathbf{r}'} P_\Delta(\mathbf{r}'|\mathbf{r}) \psi_U(\mathbf{r}, \mathbf{r}'). \tag{2.7}$$

For the terminal utility node U_0, $EU_{U_0}(\Delta, \mathbf{r})$ is said to be the *expected utility of the strategy* Δ *given the configuration* $\mathbf{r}$, and denoted by $EU(\Delta, \mathbf{r})$. For example, in the ID in Figure 2.1, if we have $\mathbf{R} = \{T, Y\}$, then the expected utility of the strategy Δ given the configuration $\mathbf{r} = \{t, y\}$ is as follows:

$$\begin{aligned} EU_U(\Delta, \mathbf{r}) &= \sum_x \sum_d P_\Delta(x, d|t, y) \cdot \psi_{U_0}(x, y, d, t) = \\ &= \sum_x \sum_d \frac{P_\Delta(x, d, t, y)}{P_\Delta(t, y)} (U_1(x, d) + U_2(t)). \end{aligned} \tag{2.8}$$

We define the *expected utility of* U *under the strategy* Δ as $EU_U(\Delta) = EU_U(\Delta, \blacklozenge)$, where $\blacklozenge$ is the empty configuration. We have that

$$EU_U(\Delta) = \sum_{\mathbf{v_C}} \sum_{\mathbf{v_D}} P(\mathbf{v_C}, \mathbf{v_D}) \psi_U(\mathbf{v_C}, \mathbf{v_D}). \tag{2.9}$$

We also define the expected utility of the strategy Δ as $EU(\Delta) = EU_{U_0}(\Delta)$.

An *optimal strategy* is a strategy Δ_{opt} that maximizes the expected utility:

$$\Delta_{opt} = \arg\max_{\Delta \in \Delta*} EU(\Delta), \tag{2.10}$$

where $\Delta*$ is the set of all the strategies for I. Each policy in an optimal strategy is said to be an *optimal policy*. The *maximum expected utility (MEU)* is

$$MEU = EU(\Delta_{opt}) = \max_{\Delta \in \Delta*} EU(\Delta). \tag{2.11}$$

The evaluation of an ID consists of finding the MEU and an optimal strategy, composed by an optimal policy for each decision. It can be proved (Cowell et al., 1999) that

$$MEU = \sum_{\mathbf{c_0}} \max_{d_0} ... \sum_{\mathbf{c_{n-1}}} \max_{d_{n-1}} \sum_{\mathbf{c_n}} P(\mathbf{v_C} : \mathbf{v_D}) \psi_{U_0}(\mathbf{v_C}, \mathbf{v_D}). \tag{2.12}$$

An *optimal policy* δ_{D_i} is therefore a function that maps each configuration of the variables in $iPred(D_{i-1})$, i.e., those at the left of $\max_{D_i}$ in the above expression, onto the value d_i of D_i that maximizes the expression at the right of D_i (in the case of a tie, any of the values of D_i that maximize that expression can be chosen arbitrarily):

$$\delta_{D_i}(iPred(D_i)) = \arg\max_{d_i \in D_i} \sum_{\mathbf{c_i}} \max_{d_{i+1}} ... \sum_{\mathbf{c_{n-1}}} \max_{d_n} \sum_{\mathbf{c_n}} P(\mathbf{v_C} : \mathbf{v_D}) \psi_{U_0}(\mathbf{v_C}, \mathbf{v_D}). \tag{2.13}$$

For instance, the MEU for the ID in Figure 2.1 is

$$MEU = \max_t \sum_y \max_d \sum_x P(x) \cdot P(y|t,x) \cdot (U_1(x,d) + U_2(t)), \tag{2.14}$$

and an optimal policy δ_D is

$$\delta_D(b) = \arg\max_{d \in D} \sum_x P(x) \cdot P(y|t,x) \cdot (U_1(x,d) + U_2(t)). \tag{2.15}$$

There can be more than one optimal strategy for an ID. However, we can always find a deterministic optimal strategy. The literature about IDs usually assumes that the strategies in IDs are deterministic. We will also assume in this memory that the strategies are deterministic, except when we point out that they can also be stochastic.

2.2.2 Applications

In this section we describe several clinical decision support systems, all of them based on influence diagrams. In contrast with the small number of decision support systems for orthopaedic surgery mentioned in the previous section, there are many based on influence diagrams systems used in many other clinical specialities.

We highlight the work (Luque Gallego, 2009), whose objectives were (1) to develop a variable-elimination algorithm for influence diagrams with super-value nodes, and to compare it with the arc-reversal algorithm by (Tatman and Shachter, 1990), (2) to have explanation capabilities and sensitivity analysis tools for influence diagrams with super value nodes, (3) to develop an anytime algorithm for unconstrained influence diagrams, and (4) to build and evaluate a decision support system for the mediastinal staging of non-small cell lung cancer. The latter objective was satisfied by an influence diagram built using Elvira (Elvira consortium, 2002), a free-software package developed as a joint project of several Spanish universities[5].

Going back to the first medical influence diagrams, we must mention (Provan and Clarke, 1993), where the authors addressed the problem of diagnosis in domains with continuously changing data. To address that task, a dynamic influence diagram was built, as well as an updating system. Later, these were used to construct a decision-theoretic model to diagnose acute abdominal pain, a domain in which the findings evolve during the diagnostic process. The system constructs a parsimonious influence diagram, and then dynamically updates it, rather than building a new network from scratch for every time interval. In addition, the system contains algorithms for testing the sensitivity of the constructed networks system parameters.

(Quaglini et al., 1994) built an influence diagram for assessing GVHD (Graft-

[5]http://www.ia.uned.es/~elvira/

versus-host disease) prophylaxis after bone marrow transplantation in children. The qualitative structure of the model and the conditional probabilities were first derived by combining literature results with a medical expert's judgement. More specifically, probabilities were initially assigned as ranges rather than as point values; then, they were updated, by using a learning algorithm, as new cases became available.

Several researches from the Artificial Intelligence Department of the Polytechnic University of Madrid made an influence diagram to treat the neonatal jaundice (Ríos-Insua et al., 1998). Aside from the inherent difficulties of constructing the diagram (structure, conditional probabilities and utility functions), the large size of the net (the last version contains 59 nodes) increased the computation to obtain the treatment policy.

(Sanders et al., 2000) describes a system that enables developers and users to create, disseminate and tailor clinical practice guidelines using normative decision models. The system, called ALCHEMIST, analyses a decision model, creates a clinical practice guideline in the form of an annotated algorithm, and displays the optimal strategy. In the pilot evaluation, the ALCHEMIST guidelines met established criteria for quality and compared favorably with United States clinical practice guidelines.

In (Sharma et al., 2001), the authors created cost-utility Markov models to determine the cost-effectiveness of photodynamic therapy under two different scenarios. The analysis was performed from the perspective of a for-profit third-party insurer. Decision analyses were performed by incorporating data from the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study, expected longevity data, and patient-based utilities. Cost-effective models were then created by incorporating incremental medical costs. Various sensitivity analyses were carried out to determine the robustness of the models. A Monte Carlo simulation was also used to determine whether there was a significant difference in quality-of-life adjusted years gained between photodynamic therapy and the placebo.

Another interesting influence diagram is that used as a basis in (Garside et al., 2004) in order to assess the cost-effectiveness of the second-generation surgical treatments for heavy menstrual bleeding (microwave and thermal balloon endometrial ablation) compared with existing endometrial ablation techniques (transcervical resection and rollerball, alone or in combination) and hysterec-

tomy. It was performed through a Markov cost-utility model, developed using spreadsheet software. Transition probabilities, costs and quality of life data were obtained from a systematic review of effectiveness undertaken by the authors, from published sources, and expert opinion. Cost data were obtained from the literature and from a National Health Service trust hospital. All methods comparisons were carried out from the perspective of health service payers. The effects of uncertainty were explored through extensive one-way sensitivity analyses and Monte Carlo simulation.

Later, (Meyer et al., 2004) tried to incorporate clinically relevant factors such as patient-specific and dosimetric information as well as data from clinical trials in the decision-making process for the selection of prostate intensity-modulated radiation therapy plans. Their approach was to incorporate the decision theoretic concept of an influence diagram into the solution of the multiobjective optimization inverse planning problem. An influence diagram based on a Bayesian network with 18 nodes was designed to model the decision process for plan selection. The model possessed nodes for clinical laboratory results, tumour grading, staging information, patient-specific information, dosimetric information, complications and survival statistics from clinical studies. A utility node was utilized for the decision-making process. At the end of the research, the authors established the influence diagram successfully ranked the plans based on the available information. Sensitivity analyses were used to judge the reasonableness of the diagram and the results.

(Uber, 2006) made a study to improve the efficacy of Ventricular Assisted Devices (VAD) therapy. The study focused on the specific decision of whether a Left Ventricular Assist Device (LVAD) or Biventricular Assist Device (BiVAD) is appropriate. A hierarchical decision model was constructed using an influence diagram of clinical risk factors derived through interviews with expert cardiologists and cardiac surgeons. Most of the variables were summarized by two independent criteria: risk of surgery and risk of right ventricular failure. These risks were computed from various patient demographics, tests, and hemodynamics using expert physician-selected weighted linear and weighted non-linear relationships. The model was validated with retrospective data from patient records at University of Pittsburgh Medical Center for patients implanted after 1990 and explanted before 2006. A nonlinear numerical optimizer was used to improve the model parameters to optimize the agreement with eventual outcomes. In conclusion, the

decision model provided a more aggressive use of biventricular assistance, which retrospectively would have benefited patients who required a Right Ventricular Assist Device (RVAD) at a later date, but would have unnecessarily implanted RVADs in some patients that survived with an LVAD alone.

In the same year (Duriseti et al., 2006) examined the cost-effectiveness of a quantitative D-dimer assay for the evaluation of patients with suspected pulmonary embolism in an urban emergency department by a sequential decision model, modelled on the basis of an influence diagram.

(Tung et al., 2008) examined whether screening for diabetic retinopathy among Chinese people with type 2 diabetes was economically feasible and clinically effective. In this study, a decision analysis using a Markov decision model was constructed to compare different screening regimes for diabetic retinopathy with a no-screening group. Finally, one-way sensitive analyses were conducted on the individual estimates to assess the impact on costs, effectiveness, and utility of screening for diabetic retinopathy.

Subsequently, (Coon et al., 2008) demonstrated how to evaluate the effectiveness and cost-effectiveness of surveillance for hepatocellular carcinoma using a decision-analytic model. To conclude the list, we must cite (Kongnakorn et al., 2009), a study where an influence diagram was used to evaluate the economic implications of results obtained by the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial.

We could not finish this section without naming the most important groups dedicated to researching on Bayesian networks, those from the Aalborg University in Denmark and Pavía University, Italy. Some studies from the first are (Olesen et al., 2009), (Murley et al., 2005) and (Ege et al., 2000). The latter has developed several Bayesian networks and influence diagrams to optimize the uremic anemia therapy, monitoring, childhood leukemia, hemodialysis, diabetes, AIDS, treatment of bone marrow transplanted children, nephritis, primary gastric lymphoma, idiopathic deep vein thrombosis and splenectomy inter alia; as shown in (Consonni et al., 2004), (Arcaini et al., 2009), (Bergamaschi et al., 2000) and (Berzuini and Allemani, 2004), inter alia.

Part III

Medical Application

Chapter 3

Application: Perioperative infection of a total knee arthroplasty

3.1 Introduction

The most common reason for knee arthroplasty failure is a non–infectious origin aseptic loosening. The second cause is a loosening of septic origin. The hip, unlike the knee, has a better blood supply and better protection of the soft tissues (Ayers et al., 1997), (Segawa et al., 1999), so the infection is more common in knee prostheses than in the hip. The factors that influence their appearance are different, grouped into those due to the patient and those due to the operating room environment and the surgeon. The number of infections has declined in recent years, in global terms, but the specific mechanism for why some patients are infected, and the cause of infection in a given situation, are in most cases unknown (Hanssen et al., 1996).

The occurrence of infection after total knee replacement should be minimized, because it is a very serious complication. Knowledge of risk factors is essential for prevention and early diagnosis is the key to effective treatment.

Because of this uncertainty and the variety (and costs) of tests to diagnose the perioperative prosthesis infection, we have developed a decision support system for total knee arthroplasty. The system basically consists of an influence diagram. We have relied on the expert advice of Dr. Rubén García Fraile, orthopedic

surgeon at the Hospital Clínico Universitario, in Valladolid (Spain).

3.2 Statement of the problem

3.2.1 Epidemiological importance

The frequency of deep infection after total knee replacement varies from 0.5% to 5%, mainly due to several risk factors. Infection depends mainly on the amount and virulence of the bacteria that contaminate the surgical wound, and the patient's immune capacity to eliminate them. It is estimated that the cost of treatment of prosthetic infection, either hip or knee, is more than €50,000 (Hanssen et al., 1996). The knowledge of the factors that contribute to the infection onset is essential to develop a preventive school discipline, intraoperative and postoperative; such discipline should cover all the surgical team, and must be very important to educate all of them. Prosthetic infection is not only an economic issue, there is also the health cost of the patient because of his suffering, the limb function and even the risk of death must be considered. Therefore the prophylaxis, early diagnosis and adequate treatment are the priorities of all the equipment engaged in surgical knee replacement.

3.2.2 Impact

Although infection rates have dropped significantly since the first knee implants were made, it seems to be a handicap to overcome, because the rate of deep infection remains constant between 1% and 2% (Hanssen et al., 1996). The frequency of infection after total knee arthroplasty published in a set of 18,794 cases from the Mayo Clinic, collected between 1969 and 1996, was 2.5%. In this set, the infection rate reached 5.6%, and 2% for primary prosthesis (Rand, 1993). The lowest infection rate known is 0.5% (Insall, 1986).

3.2.3 Risk factors

There are many studies relating a higher rate of periprosthetic infection with rheumatoid arthritis. In a series of 4,240 replacements, the number of infection episodes was 2.6 times higher in patients with rheumatoid arthritis than in those with osteoarthritis (Hanssen et al., 1996). In another series of 4,171 cases,

0.9% of patients diagnosed with deep periprosthetic infection evolved into knee osteoarthritis, compared with 2.2% of patients with rheumatoid arthritis (Wilson et al., 1990).

In another study of 425 male patients with polyarticular rheumatoid arthritis, 17 (4%) had deep infection after total knee arthroplasty (Wilson et al., 1990). Another review made in Sweden, with 12,118 knee replacements followed for six years, the number of infection was 1.7% for knee osteoarthritis and 4.4% for rheumatoid arthritis (Gristina, 1994). These studies have also found a greater infection incidence in patients with diabetes mellitus, being more predisposed than those with rheumatoid arthritis (Bengtson et al., 1989), (England et al., 1990).

Patients with diabetes mellitus have up to 7% risk of infection and complications in wound healing (England et al., 1990). Poor nutrition is another factor that predisposes to infection: both undernutrition and obesity are considered important. Urinary tract infections, oral corticosteroid therapy and psoriasis have been also described as risk factors, among others. Patients with psoriasis evolve up to 7% of infections after knee arthroplasty (Stern et al., 1989).

It is often impossible to know the cause of infection in a given situation, because the intimate mechanisms of bacterial colonization are unknown. The development of an infection depends on three main factors: the quantity and virulence of the organism, the type of wound and the patient's response capability (Poss et al., 1984). The origin of the infection may be in the preoperative period, in the surgical procedure itself or in the postoperative period.

The operations carried out previously in the area are also important. (Wilson et al., 1990), in a review of patients with knee osteoarthritis, compared knees with no previous surgery (which had an infection in 0.3% of cases) with those operated before (which had an infection in 1.4% of cases). These numbers increased if the previous surgery had been a knee replacement, and even more if there was a history of previous infection. The size and type of implant is also important, as well as the use of structural bone.

Advanced age, wear particles and extended preoperative admission are also risk factors for infection. In a set of 23,649 interventions, the rate of infections was 1.1% in patients admitted the day of surgery, while in those admitted two weeks before the surgery was 4.3% (Hanssen et al., 1996). The environment and the discipline of surgery are also important, the number of people who are in

it, the preparation of the surgical field, laminar flow, the surgical team gowns, gloves, masks, air exchange and ultraviolet light are factors to consider. The greatest source of bacteria in the operating room comes from people who are inside. Compared with an empty operating room, the number of colonies is thirty times greater in a busy one.

Shaving the surgical field should be performed immediately before the beginning of the intervention (Garner, 1986), because otherwise small skin lesions may serve as a gateway to the bacteria. Prolonged use of the vacuum cleaner can be a source of infection (Mangram et al., 1999); probably attracting airborne particles contaminated the instruments's tip. The role of laminar airflow is controversial. The flow can be vertical or horizontal; it seems logical that the horizontal system is not effective in knee arthroplasty, because of the allocation of the surgical team in, and the particles detached from the surgeon and assistants. Laminar airflow seems to decrease the pollution of the instruments of the operating table (Ritter et al., 1973). Another factor that serves to control the antiseptic atmosphere surgery is ultraviolet light. However (Salvati et al., 1982) found an increased incidence of periprosthetic infection in relation to the horizontal laminar air flow, but subsequent studies (Rand, 1993) comparing series of arthroplasties performed with and without laminar flow found no differences in the infection rate.

The strongest impact factor as a source of deep infection is the surgical technique and the professional preparation of the surgical team (Kolmos et al., 1997). The treatment of soft tissue, hemostasis, time of exposure, careful closure plans, the use of road appropriate approach and incision, and the prevention of tissue necrosis areas positively influence risk reduction. The implant type to use decision is also important; the old large hinge type prosthesis with metal-metal friction torque favored the infections, probably due to the wear of metal particles that cause metalosis and particulate synovitis.

Several experimental studies evaluate the susceptibility to infection, linking it to different materials (Steckelberg and Osmon, 1994): polyethylene, steel, cobalt chromium, polymethylmethacrylate, which have been mentioned as inhibiting factors on in vitro chemotaxis, phagocytosis and have the ability to destroy bacteria in polymorphonuclear leukocytes. Biomaterials create an area of immune incompetence (Carbonell et al., 2005), probably due to lack of vascularization; the higher risk of immune incompetence comes from the stainless steel and chromium-cobalt alloys (Ampuero et al., 2000).

3.2.4 Infectious complications prophylaxis

The reduction of risk factors is the main way to prevent periprosthetic infection in knee arthroplasty. Adequate preoperative antibiotic therapy is the most effective way to reduce postoperative infection (Hanssen et al., 1996), (Lotke, 1992). Currently there is consensus on the systematic use of preoperative antibiotics before tourniquet inflation in knee arthroplasty. However, controversy exists with respect to the antibiotic to be used (Steckelberg and Osmon, 1994), and length of administration (van Kasteren et al., 2007).

The perfect antibiotic prophylaxis must be that one that uses an antibiotic which has excellent in vitro activity against staphylococci and streptococci, possess a large tissue penetration, has a long plasma half-life, is no toxic and has an affordable price (Fitzgerald and Thompson, 1983). The first-generation cephalosporins have been studied extensively and have proven their efficacy. Compared with other antimicrobial agents, they have a long plasma half-life, low toxicity and a moderate price. For patients with hypersensitivity to cephalosporins, vancomycin is the best alternative. The administration of antibiotic prophylaxis should be before tourniquet inflation and the skin incision. It should be performed by intravenous infusion 30 to 60 minutes before the surgery, to allow the antibiotic to get a right tissue penetration. In long procedures, another dose should be given if the operating time exceeds twice the plasma half-life of the antibiotic or when there is large blood loss during surgery (Martin, 1994).

There are protocols (Windsor et al., 1990) that recommend a single preoperative dose followed by two or three post-operative doses, in order to reduce the risk of selection of resistant organisms and toxicity. The proven efficacy is the same as long length protocols. The use of cement with antibiotics, particularly gentamicin, has proven effective in experimental models and has been used widely as prophylaxis. Its use in revision surgery is commonly accepted. However, its use in primary implants continues to cause controversy today. Also among the disadvantages of using antibiotic cement the possible allergy reactions and the selection of resistant bacterial strains.

Frequently intraoperative irrigation prevents the tissue drying and reduces bacterial colonization (Moran et al., 2007). Copious washing without excessive pressure that can damage tissue, is a good way to decontaminate the wound. Chlorhexidine is not disabled in the wound and applied in 0.05% solution via washing syringe washing is a proven antiseptic effectiveness (Blom et al., 2004).

Many successful procedures end in failure during the postoperative period due to the lack of control over the patient. The patient's position in bed should avoid the appearance of scars. Possible hematomas, draining systems, the pressure bandage and the administration of antibiotic protection to prevent bacterial colonization must be monitored. Blood stream infection should be considered: the use of catheters can be a source of bacterial contamination, as well as the use of urinary catheters. Both should be removed as soon as possible. In patients with knee arthroplasty to be subjected to dental or endoscopic manipulation or interventions in the genitourinary tract, antimicrobial prophylaxis is recommended in the postoperative period, but unlike the current antibiotic prophylaxis protocols for exogenous implants in other areas surgery (prosthetic heart valves, endovascular devices etc.) it is still a controversial issue in orthopedic surgery, although it is widely documented (Poss et al., 1984).

In order to reduce the possibility of deep periprosthetic infection, it is important to carefully apply the principles of infection control, such as optimizing the wound environment (please see Table 3.1). This way the patient response can be improved, minimizing bacterial contamination in the preoperative, intraoperative and postoperative periods.

3.2.5 Microbiology

The most frequently isolated pathogenic bacteria in deep periprosthetic infections are gram positive. (Wilson et al., 1990) have identified gram-positive cocci Staphylococcus aureus in 63% of infections. (Schoifet and Morrey, 1990) have reported that these germs are responsible for 58% of infections. Staphylococcus epidermidis is responsible for a large number of cases. (Rand, 1993), collecting data from 16 sets, has shown that 57% of knee prosthesis infections are caused by gram-positive cocci Staphylococcus aureus type and 30% by gram-positive cocci Staphylococcus epidermidis type. (Rand, 1993) determined that 13% of cases were due to gram-negative and streptococci were the cause of 8% of infections. Anaerobes represent only 4%, as shown in Table 3.2.

Staphylococcus epidermidis has a great ability to grip to polyethylene (Gristina, 1994). There is a close relationship between bacterial resistance to antibiotics and the ability of bacteria to produce an adhesion to and colonization of the implant surface. The bacteria adhere forming a very persistent and difficult to eradicate

	Preoperative	**Intraoperative**	**Postoperative**
Bacteria	Skin ulcers Prolonged hospitalization Antibiotic prophylaxis Shaving of the field	Surgical staff Right sterilization Masks and suits Washing Surgery time Aspirator Gloves and cloths Laminar flow	Dental or urological procedures Intraurethral catheter Catheters and bloodstream infections
Patients	Diabetes mellitus Rheumatoid Arthritis Psoriasis Corticotherapy Obesity or malnutrition Systemic disease Advanced age		Systemic diseases Alcoholism Smoking
Wound	Previous surgery Previous infection Poor wound healing Vascular deficit	Duration Technique Correct sutures Antibiotics in cement Bone graft Haemostasis Drains	Skin necrosis Hematoma Suture dehiscence Wear particles Loosening of prosthesis

Table 3.1: Factors influencing the development of periprosthetic infection

Single germ	
Staphylococcus epidermidis	18
Staphylococcus aureus	9
Other coagulase-negative staphylococci	1
Escherichia coli	1
Peptostreptococcus spp.	1
Streptococcus spp.	1

Mixed flora	
Actinomyces and mycobacteria	1
Coliforms and Staphylococcus epidermidis	1
Enterococci and Staphylococcus epidermidis	1
Staphylococcus epidermidis and other coagulase-negative staphylococci	1
Staphylococcus epidermidis and mycobacteria	1
Staphylococcus epidermidis and Serratia spp.	1

Table 3.2: Bacteria found in 37 infected knee prosthesis

glycoproteins layer. This layer is called slime, and makes the dissemination of the antibiotic extraordinarily difficult. The most virulent pathogens are methicillin-resistant staphylococci, gram-negative, group D streptococci, enterococci and glycocalyx-producing microorganisms. The least virulent are methicillin sensitive staphylococci, generally anaerobic cocci and streptococci not group D (Hanssen et al., 1996). The assessment of virulence and antibiotic sensitivity will be very important to ask ourselves about the proper treatment.

Patients with active chronic fistulas develop mainly mixed infections caused by bacteria association. The emergence of resistant bacteria is associated with rescue attempts using antibiotics indiscriminately.

3.2.6 Diagnosis

Infection after knee arthroplasty can be divided into three types according to the time of appearance: type I include infections in the first two months post surgery, the type II presentation occurs somewhere between 2 and 24 months after surgery, and type III infection occurs after 24 months (Rand, 1993). From a practical standpoint, they can be divided into early and late (Insall, 1986). Early infections appear during the three months after surgery and acutely. Late infections appear over three months after the surgery and chronically. The main causes of early appearance of infection is intraoperative contamination (Morrey et al.,

1987), problems in wound healing (Johnson and Bannister, 1986), hematoma (Saleh et al., 2002), prolonged maintenance of drainage systems (Weiss et al., 1993), and the presence of superficial inflammation (Johnson and Bannister, 1986) of the surgical wound (sometimes difficult to distinguish from deep infection).

Symptoms are pain, fever and joint swelling with local inflammation, often accompanied by laboratory abnormalities during the acute phase, with high sedimentation rate, leukocytosis and neutrophilia (not usually seen neither leukocytosis nor neutrophilia when the infection becomes chronic). Early administration of antibiotics may mask the syndrome, making diagnosis difficult and the isolation and identification of the germ, usually done by puncture aspiration. C-reactive protein, although rises because of surgery, is also a good indicator of infection, if it remains high over than three weeks after surgery (Greidanus et al., 2007).

In this period oral antibiotics should not be given. In case of persistent abnormal serous drainage from the wound is indicated to take shots for bacteriological analysis, to identify the germ, perform antibiograms, intravenous antibiotic treatment establishment and maintaining regular physical measures of rest, tip elevation and delay the rehabilitation treatment.

If drainage persists for over eight or ten days, debridement surgery or recovery can be evaluated (Esler et al., 2003), consisting of abundant washing of the joint replacement polyethylene implants with sterile cleaning brush and chlorhexidine. This option requires a prolonged use of postoperative selective antibiotics administered intravenously.

There is consensus in the international literature about the importance of avoiding early postoperative empirical antibiotics that are not conducive to solve the problem, but to postpone it and make it worse, as well as making the diagnosis difficult. A persistent fever of unclear origin during the postoperative knee replacement should always be investigated by blood-screening formula, count, sedimentation rate, C reactive protein, biochemical tests and urinalysis with urine cultures, chest X-ray study and blood cultures obtained during the acute febrile phase.

Following the first three months late chronic infection can be caused by intraoperative contamination by bacteria of low virulence or blood stream infection due to a distant focus. Dental manipulations and interventions on the genitourinary tract are the most common causes of bacterial bloodstream (Berbari et al., 2010), (LaPorte et al., 1999). There are many possibilities and exceptional cases

have been reported about hematogenous periprosthetic knee infection caused by Brucella mellitensis (Malizos et al., 1997). Faced with a knee replacement that evolves satisfactory and begins to manifest painful symptoms without previous trauma should be ruled out as the first possibility of septic loosening. Early diagnosis in these situations is the best guarantee to minimize complications.

The exploration and clinical history provide initial information on the diagnosis of infectious complications in knee replacement. The review of the graphs of temperature, drainage notes, observations on the development of scar appearance, personal history and predisposing factors identification, knee mobility, type and timing of pain, inflammation and fistulae must be reviewed by the surgeon during the postoperative period.

Additional tests are sometimes an essential aid, but do not replace careful study of the history and proper physical examination.

The final diagnosis is made during the intervention, using the shots for biopsy and bacteriology (culture deferred). Sometimes in a knee replacement, the diagnosis of prosthetic mobility due to low aggressiveness germs must be done after several days of culture with appropriate technics at the microbiology department.

Laboratory diagnostic tests

The most commonly used laboratory tests in patients with suspected infection of total knee prostheses are blood count, sedimentation rate and C reactive protein. The rise in the number of leukocytes or neutrophils rarely appears in an infected arthroplasty in a chronic phase. When the formula is already altered, the infection is evident and the diagnosis is facilitated by the clinic.

Acute phase reactants are a type of positively charged macromolecules, which are synthesized in the liver in response to inflammatory states, on more acute phase reactants, higher agglutination of erythrocytes and higher sedimentation rate. The sedimentation rate is higher in the infected cases than in non-infected, but can produce false positives and negatives. The sedimentation rate may remain elevated for three months or more after surgery. If the sedimentation rate is elevated after six months and in the absence of another outbreak, its positive predictive value is 80%.

C-reactive protein is an acute phase reactant, synthesized in the liver. In normal situations, there are only negligible traces. An increase of this protein is a nonspecific way to detect tumors or acute inflammatory processes. After

surgery, its number remains elevated and returns to normal after two or three weeks. A persistent elevation beyond that time, at least 10 mg / l, can make us think about infection. Serial blood cultures may be helpful to identify the pathogen in cases of bacteremia.

Scintigraphy

Scintigraphy has been widely used for the diagnosis of periprosthetic infection, although its precise value remains controversial. Technetium-99m methylene diphosphonate was first used in the 70s as a marker of bone activity. The infection can accelerate bone activity, but this activity is also accelerated in aseptic loosening. The specificity of this test is not good, especially in the tibia during the first year because the bone metabolism could be increased even in the absence of infection (Lotke, 1992). It can also give a false negative if there is insufficient blood supply (Wegener and Alavi, 1991). The gallium-67 citrate is a radioisotope which accumulates in areas of inflammation. Using sequential technetium-gallium is safer for the diagnosis of infection. The Indium-111 leukocyte marker is used for diagnosis in terms of increased vascularity and accumulation of blood cells, but its role is not well defined. Other radionuclides have been used, such as immunoglobulin-G labeled with radioisotopes, its role similar is to that of Indium-111 (see Figure 3.1).

Scintigraphic studies are currently over-utilized in the study of prosthetic knee pain. They provide by themselves enough data to help us make decisions about the treatment to choose. In those cases where the components are properly engaged it would be best to use sequential technetium-99m (see Figure 3.2) labeled leukocytes with indium-111. Sequential method sensitivity is 33% and specificity is 86% (Levitsky et al., 1991).

Radiological study

Radiography is routinely done for any knee pain after prosthetic replacement, although in the early phase of infection it is rare to get information from them. The appearance of a complete radiolucency is suspicious for infection (see Figure 3.3). Many radiological findings, such as loosening, osteolysis and endosteal scalloping are common in septic loosening. The quick changes with respect to previous X-ray control, with periostitis and periosteal new bone formation, with or without loosening, are almost pathognomonic of infection.

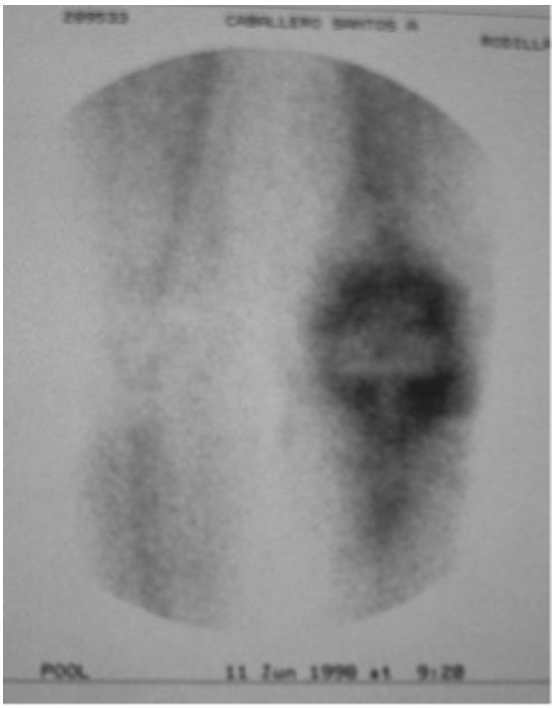

Figure 3.1: Scintigraphic image (Gallium 67) of an infected knee arthroplasty.

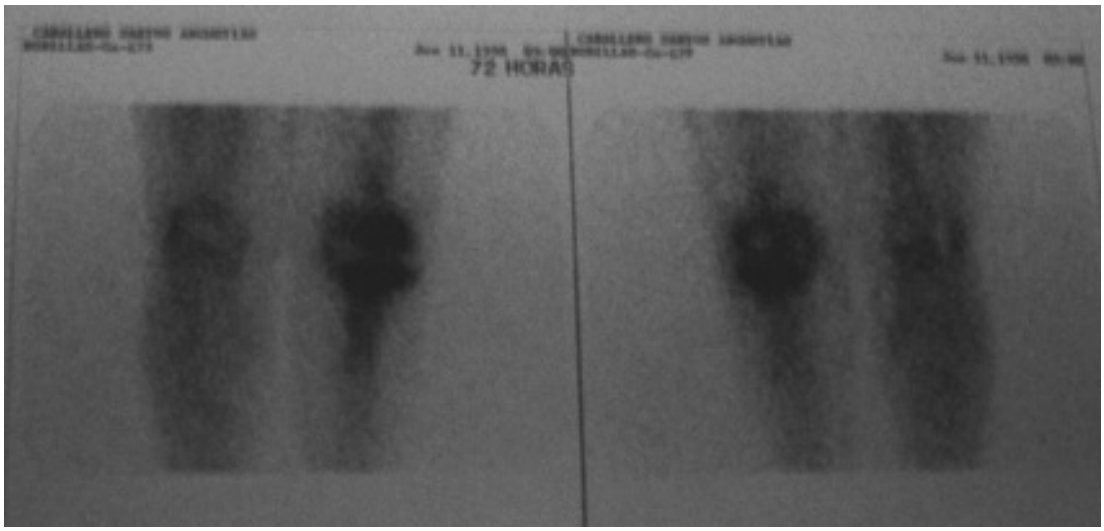

Figure 3.2: Scintigraphic image (Technetium 99) of an infected knee arthroplasty.

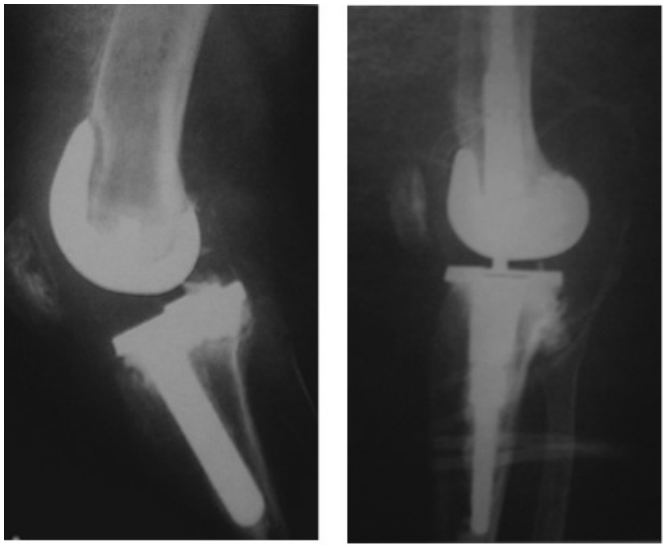

Figure 3.3: Radiographic images of an infected knee arthroplasty. Image on the left shows femoral periprosthetic radiolucency and periosteal growth, indirect signs of infection; while the right image shows the postoperative control after the replacement.

Joint aspiration

The aspiration of the joint and its cultivation is the most simple, important and standard to determine the existence of a deep infection. It provides information about the sensitivity of germs to antibiotics. It is also possible to perform a cell count: a cell count higher than 25,000 cells/ml. is suggestive of infection. Performing a gram stain type, only 25% of infected knee aspirations offer a positive result.

Glucose and synovial fluid proteins can also be measured (Insall, 1986). Infectious processes decreases glucose and increase protein, both contained in the synovial fluid; if this happens, we should suspect the existence of infection. The specificity of synovial aspiration is 97% and the sensitivity is 67% (Levitsky et al., 1991).

A negative result could not exclude the diagnosis because the infection may be located at a point that is not in contact with the synovial fluid (false negative).

The use of local anesthetics, which can be bacteriostatic, or even the use of intraarticular saline wash, may promote the occurrence of false negatives. However, the most common cause of false negatives is the administration of oral antibiotics. When the result is negative, the re-aspiration, without antibiotics, saline and no local anesthetic, could provide a sensitivity of 75% and a specificity

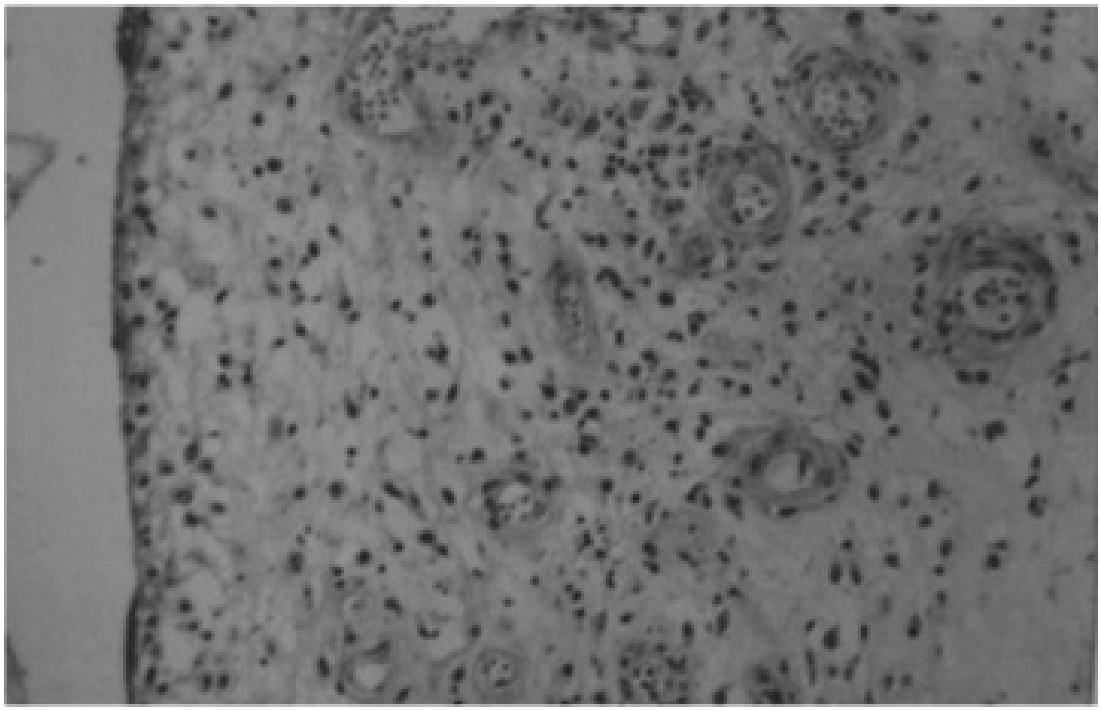

Figure 3.4: Microscopic image of frozen section. Numerous polymorphonuclear in periprosthetic infection.

of 96% (Barrack et al., 1997).

Intraoperative diagnosis

The leukocyte count, obtained from the synovial fluid by opening the joint capsule using a needle and syringe is important; if the percentage of neutrophils is greater than 80%, the liquid is considered to be septic (septic arthritis) (Spangehl et al., 1999). The gram stain and culture during the intervention is very important. The shots taken in the pseudocapsule, in the bone-prosthesis and in parts with more inflammatory appearance, should be sent to the laboratory. If there is only growth in a sample of three, the result is negative; if there is growth in more than one third of the samples, the diagnosis of infection is considered positive. Gram stain produces a high percentage of positive results. The presence of microorganisms on gram stain is evidence of infection. However the absence of microorganisms does not exclude the possibility of infection.

In the intraoperative analysis, a sample of tissue from the synovial surface is taken (see Figure 3.4), from an area that seems more inflamed. The result is considered suggestive of bacterial infection when in a field there are at least five

polymorphonuclears (Fehring and McAlister Jr, 1994). The study of intraoperative samples by freezing has a sensitivity of 84% and a specificity of 95%. If the number of polymorphonuclears per field is ten, the specificity increases to 99%, positive predictive value being 89%.

Polymerase chain reaction

It is a technology that investigates the presence of bacterial remains by specific DNA copies. These findings take about six hours to complete (Levine et al., 1995). The presence of traces of bacteria is demonstrated by the fact that the bacteria infecting the knee have a specific DNA polymorphism. Its sensitivity, specificity and predictive value have been reported as 100% (Levine et al., 1995). Additional advantages of this technology are that: (1) previous taking of antibiotics does not alter the results and (2) its running time is lower (cultures take five to six days). Its main disadvantage is that it does not provide information on in vitro sensitivity to antibiotics.

The sample may be contaminated, thus producing false positives. There may be remains of bacterial DNA and absence of infection, a situation described as defeated infection, producing a false positive. The technique is complex and requires a highly qualified research team, not always available.

3.2.7 Treatment

The frequency of knee deep infection has decreased over the past decade in relative terms. It has increased in absolute numbers, because many more patients have access to the arthroplasty, and the population at risk has grown exponentially. It is important to distinguish between deep and superficial infection, because the former one has a bad prognosis and requires aggressive surgical and specific antibiotic treatment, while the latter is usually benign and restricted in time.

Gustilo classification (Segawa et al., 1999), see Table 3.3, provides a guideline for therapeutic action to follow in the presence of an infectious complication in total knee arthroplasty, relating chronology, clinical laboratory tests and therapeutic options.

Removal and replacement of the prosthesis offers several alternatives. The replacement could be performed immediately in a single surgical time, in a two-

	TYPE 1	**TYPE 2**	**TYPE 3**	**TYPE 4**
Time of onset	Positive intraoperative culture	Early postoperative infection	Acute hematogenous infection	Late chronic infection
Definition	Two or more positive cultures during the intervention	The infection appears in the first month after the surgery	Arthroplasty previously well, which is infected by hematogenous spread	Indolent chronic clinical. Infection which takes more than a month
Treatment	Specific antibiotics	Debridement and prosthesis retention	Debridement. Retention or removal of prosthesis	Removal of prosthesis

Table 3.3: Gustilo classification of chronology, clinical appearance and treatment of infection in knee arthroplasty

stage intermediate way or delayed in two stages.

The extraction and rescue is the only choice when the failure of the surgery is absolute. Other alternatives are the resection arthroplasty, the arthrodesis and the amputation.

The conservation of the prosthesis is rarely indicated in deep infection. It is a reasonable option in the early diagnosed infected arthroplasty, produced by a low pathogenic microorganism, for example staphylococci, whose antibiograms show sensitivity to penicillin. This conservation requires selective antibiotic, closely monitored with serial punctures, joint aspirations until the disappearance of the general syndromic manifestations, inflammatory local clinic, the negativization of direct diagnostic microbiological tests and blood tests. The results of these alternatives are often disappointing: it is effective in only 15% of cases (Ayers et al., 1997). The lack of response to this treatment requires a more aggressive surgical option.

With the rise of endoscopic techniques, intraarticular arthroscopic lavage has proven to be a better choice than traditional cleaning performed by puncture, since itis done in a way more plentiful and aggressive. However, synovectomy and endoscopic debridement is always less complete than the one made open. The replacement of the polyethylene is another option.

The surgical debridement with retention of the cemented materials and extraction of polyethylene requires that the femoral and tibial components are closely

bonded. Later the stability of the joint and the absence of osteolysis or loosening must be checked. The presence of periosteal reaction or positive cultures for aggressive bacteria contraindicates the retention of the components when they are firmly attached.

The results of debridement with prosthesis retention published in the international literature vary. In a study of 43 months follow-up is described a 45% failure rate, the microorganism Staphylococcus aureus is the one having the worst prognosis (Thornhill, 1995). Some publications have found a rate of recurrent infection of 77% in 8 years of follow up in 31 infected arthroplasties treated through prosthetic retention with positive cultures for Staphylococcus aureus. The maximum success rate for prosthetic retention is 26% (Ayers et al., 1997).

These numbers are directly related to bacterial adhesion and glycocalyx layer (Ampuero et al., 2000), (Gristina, 1994). There are encouraging results in novel sets that publish the use of rifampicin in combination with oral fluorinated quinolones (England et al., 1990). The high tissue penetration of these antibiotics eliminated intracellular inclusions of staphylococci (Ampuero et al., 2000), (Drancourt et al., 1993).

Replacement at one-time or two-stage intermediate way are therapeutic options that leverage the use of cement as a dispenser of local antibiotics by dilution through the porosity of the polymer. This property was described in (Buchholz et al., 1981). It also allows to extend the prophylaxis in primary surgery, to treat deep periprosthetic infection its use is fundamental for the one-time replacement.

(Fitzgerald and Thompson, 1983), (Salvati et al., 1986) and other authors have published their experience with one-time replaced infected arthroplasty, also using cement with gentamicin. Their results contraindicate the replacement at one-time when there is an active fistula, a gram negative, mixed flora presence or intraarticular pus during surgery. A correct immune status of the patient is also essential for the prosthetic replacement at one-time.

The advantages of one-time replacement are: a single surgical procedure, shorter hospitalization, better soft tissue status and availability of a wider range of alternatives in case of treatment failure.

The technique requires: aggressive and thorough debridement, wide synovectomy, resection of inflamed or necrotic tissue, removal of prosthesis and cement diaphysis with great care, abounding cleaning, reimplantation of prosthetic material with cement and antibiotics, specific intravenous antibiotics for 4 to 6 weeks,

that should be continued orally for months. Regarding the technical details of the cement with antibiotic, a polymer that provides strength and porosity must be chosen, combined with gentamicin. Some studies (Hanssen et al., 1996) recommend to add 0.6 to 1.2 grams of tobramycin and 0.5 to 1 gram of vancomycin to the cement. Excessive amounts of antibiotics alter the chemical properties of the polymer and a few orthopedic surgeons accept the handling of commercial cement to add antibiotics, fearing to cause an alteration in the response of the re-polymerization and the subsequent aseptic loosening.

It has been demonstrated through scanning electron microscopy and cultures that bacteria are unable to adhere to tobramycin impregnated polymethylmethacrylate materials (Lyons et al., 1992).

The comparative results between one and two-times replacements vary. There are sets with 75% of cases in which there is no difference between one-time and two-time techniques (Thornhill, 1995). The immediate reimplantation of prosthesis after a previously infected joint replacement is a very complex and controversial issue. Multitude of variables and peculiarities in each case prevent and objective comparison of the the two procedures objectively, since patients selected for one-time replacement usually have the best prognoses. Meticulous surgical technique and wide debridement have an important role in these situations. At present, there seems to be consensus that two-time replacements produce better infection eradication rates (Westrich et al., 2010).

The two-time replacement is technically similar to the above case; without implanting a new prosthesis. Instead, pre-formed spacers impregnated with antibiotics are used. The disadvantage of these devices is that they are not biomechanically suited for the support, and could produce dislocations, fractures and loss of bone stock, because they are usually implanted for 4 or 6 weeks, when the patient should not bear weight on the limb. (McPherson et al., 1995) described a spacer model that allows the support, and certain mechanical stresses as the solution to this problem. The reimplantation is performed after the removal of the spacer as described previously. After reimplantation intravenous antibiotics should be given for at least seven days (Ayers et al., 1997).

Sets with 97% of success in the replacement in two-times have been described (Ayers et al., 1997), (Calton et al., 1997).

3.3 Construction of ArthroNET

In this section, we describe the construction of ArthroNET, a decision support system for the diagnosis of perioperative infection in total knee arthroplasty. The system basically consists of an influence diagram. It has been built using Elvira[1] and DPL 7 Standard[2] software. We have used these both tools because the former could not display the results of the decision analysis.

3.3.1 Construction of the structure of the graph

A graph is basically a set of nodes (or variables) and a set of arcs relating them. We describe in this section how we have built the graph of the model (see Figure 3.5 – In order to better appreciate the details of the diagram, the image has been exported from Elvira software). The process of identifying the variables of the problem, their domains and their relations in ArthroNET has been performed with the expert's help.

Identification of variables

We have identified three types of variables, which correspond to the three types of nodes that can appear in an influence diagram: chance, decision and utility.

Chance variables

In medical diagnosis, chance variables usually correspond to possible causes and risk factors of a disease, as well as the symptoms, signs and laboratory tests that may confirm or discard the presence of the disease. Given that our objective is the early diagnosis of deep infection in the total knee arthroplasty, we have included a variable representing the presence or absence of infection. This variable, probably the most important in the network, has been named *Knee deep infection*, and its domain is {present, absent}.

The variables that represent risk factors are the following:

[1] Elvira, a free-software package developed as a joint project of several Spanish universities (Elvira consortium, 2002).

[2] A commercial software developed by Syncopation software, a leading provider of decision support software tools including decision analysis software, risk analysis software and decision tree-based valuation software - http://www.syncopation.com.

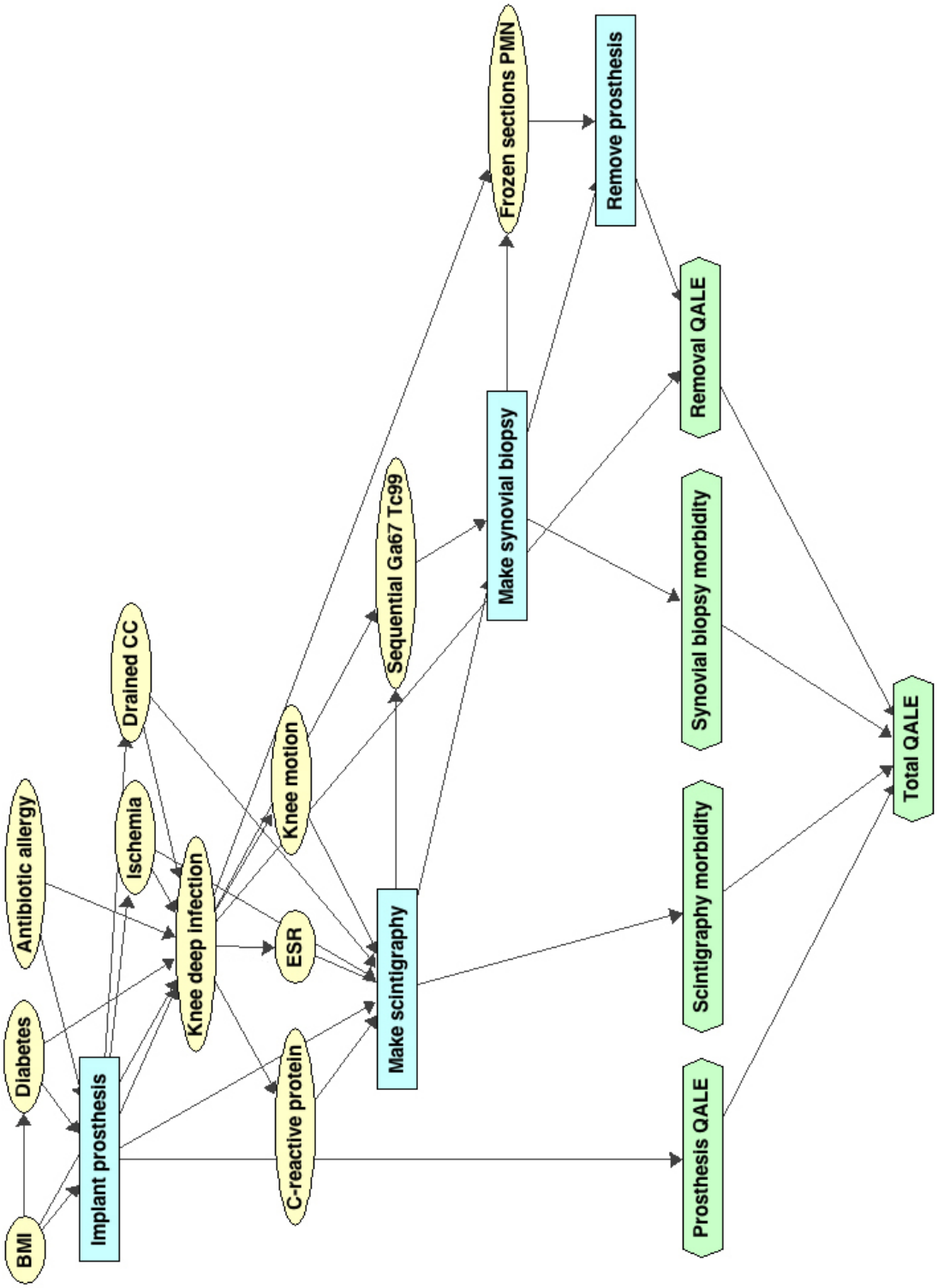

Figure 3.5: Influence diagram of ArthroNET.

- *BMI* (Body Mass Index), which indicate whether the patient is obese. This variable has been discretized into two values, {yes, no}, where the former means that BMI ≥ 35.

- *Diabetes*: a random node that represents the presence of diabetes mellitus; its domain is {present, absent}.

- *Antibiotic allergy*: it determines whether the patient is allergic to antibiotics or not. Its domain is {yes, no}.

When the arthroplasty is made, the surgeon can verify some postoperative signs, which are:

- *Ischemia*: time in minutes after applying the pressure inflated tourniquet in the tight until the air is released. Its accurately measured via the built-in clock of the air pump. This variable has been discretized into two values, {> 90 minutes, ≤ 90 minutes}.

- *Drained CC*: cubic centimeters of fluid drained through the wound. Discretized into two values, {≥ 800 cc and ≤ 1000 cc, < 800 cc or > 1000 cc}.

- *Knee motion*: variable that represents the range of motion of knee after the surgical procedure. More information about this measure is detailed in (Ounpuu et al., 1993). It has been discretized into the following two values: {≥ 65, < 65}.

Aditionaly the surgeon may also order some laboratory tests, represented by the following variables:

- *C-reactive protein*: is a plasma protein that increases their levels in response to inflammation. The normal serum of healthy adults is usually lower than 10 mg/L, therefore this variable takes the following values: > 10 or ≤ 10 mg/L. We assume that it represents the value measured three weeks after surgery.

- *ESR* (Erythrocyte sedimentation rate): is the rate at which red blood cells sediment in a period of 1 hour. It is a common hematology test that is a non-specific measure of inflammation. Six months after the implant we consider values greater than 30 mm/h as abnormal, so the possible values that we have chosen for this variable are: > 30 or ≤ 30 mm/h.

- *Sequential Ga67 Tc99*: this node means a positive or negative deep infection finding detected by a sequential gallium-67 and technetium-99 scintigraphy.
- *Frozen sections PMN*: this node measures the number of polymorphonuclears founded in a frozen sample of tissue from the synovial surface. Its domain is $\{> 5$ PMN, ≤ 5 PMN$\}$.

Decision variables

The decisions to make are: (1) whether to implant the prosthesis or not, (2) whether to perform the scintigraphy or not, (3) whether to perform the synovial biopsy or not and (4) whether to treat or not a possible infection by the removal of the implant, represented by the following variables: *Implant prosthesis*, *Make scintigraphy*, *Make synovial biopsy* and *Remove prosthesis*, whose states are *yes* and *no*. The first three decisions force us to introduce a new state to some of the chance variables. Thus, the state *Implant not made* is added to the variables *Knee deep infection*, *C-reactive protein*, *ESR*, *Knee motion*, *Ischemia* and *Drained CC*, because the measurement of this variables depends on the performing of the implant; also, the state *Not performed* is added to the test variables *Sequential Ga67 Tc99* and *Frozen sections PMN*.

Ordinary utility nodes

The decision maker's preferences have been represented by a set of utility nodes. The improvement of QALE (quality-adjusted life expectancy) of those patients who have been implanted prosthesis is represented by the node *Prosthesis QALE*. The morbidities due to scintigraphy and synovial biopsy are depicted by *Scintigraphy morbidity* and *Synovial biopsy morbidity* respectively, and measured in QALYs (quality-adjusted life year) -see (Weinstein et al., 2009)-. *Removal QALE* indicates the QALE loss for patients that require a removal of their previously implanted prosthesis, either because they a knee deep infection or because of a different reason.

Super value nodes

The ordinary utility nodes presented above have been combined by using super-value nodes, as proposed by (Tatman and Shachter, 1990). The nodes *Prosthesis QALE*, *Scintigraphy morbidity*, *Synovial biopsy morbidity* and *Removal QALE*

have been combined into the sum node *Total QALE*. We have used a sum node because morbidities (and the removal of the prosthesis) decrease the QALE of patients, considering that the utilities of nodes that represent morbidities and the treatment will take non-positive values.

Arcs of the graph

The influence diagram in Figure 3.5 contains four kind of arcs:

1. Arcs into chance nodes. They represent probabilistic dependencies. In our diagram, an arc from a node representing the decision of a test, such as the arc *Make scintigraphy* $\longrightarrow$ *Sequential Ga67 Tc99*, indicates that the result is only available whether we perform the test (*Make scintigraphy* = *yes*).

2. Arcs into decision nodes. They imply availability of informational. For example, the arc *Antibiotic allergy* $\longrightarrow$ *Implant prosthesis* has been included in ArthroNET to indicate that the patient's allergy to antibiotics is known when the surgeon decides whether to implant the prosthesis or not. Based on the no-forgetting assumption, we have specified in our diagram the minimum set of informational arcs (Nielsen and Jensen, 1999). Thus, the arc *Antibiotic allergy* $\longrightarrow$ *Make scintigraphy* has not been specified because we are making the no-forgetting assumption.

3. Arcs into ordinary utility nodes. They represent functional dependencies. The parents of a utility node indicate the domain of the associated utility function. For instance, the arcs into the node *Removal QALE* mean that the domain of its utility function depends on the nodes *Knee deep infection* and *Remove prosthesis*.

4. Arcs into super value nodes. They indicate the set of utility nodes that are combined into the super value nodes. In ArthroNET, arcs into the node *Total QALE* indicate that is the combination of *Prosthesis QALE*, *Scintigraphy morbidity*, *Synovial biopsy morbidity* and *Removal QALE*.

Decision tree

As mentioned above, using the DPL 7 Standard software was needed in order to obtain the decision analysis results. In this software, the analysis is based on

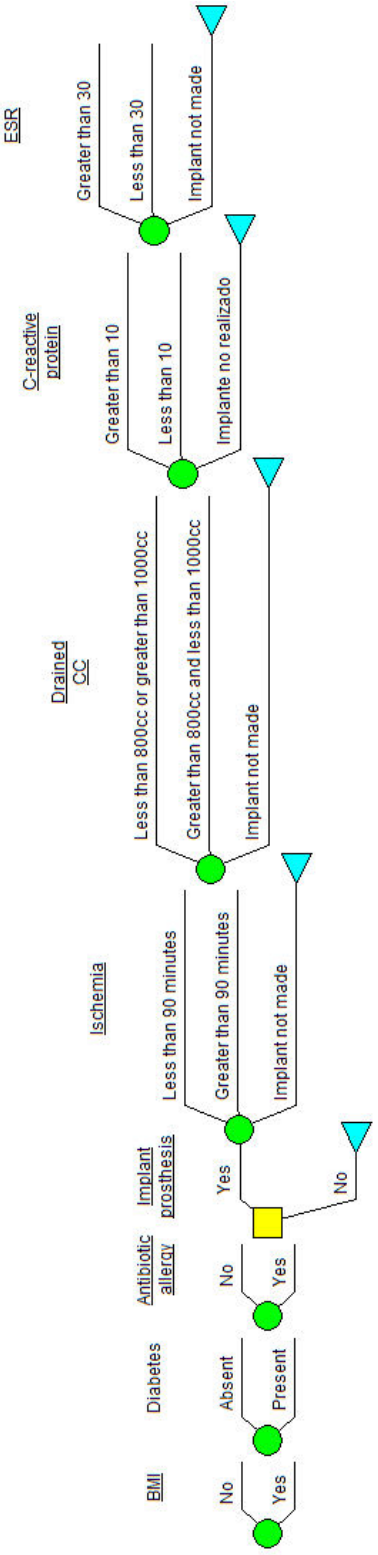

Figure 3.6: ArthroNET decision tree (first part).

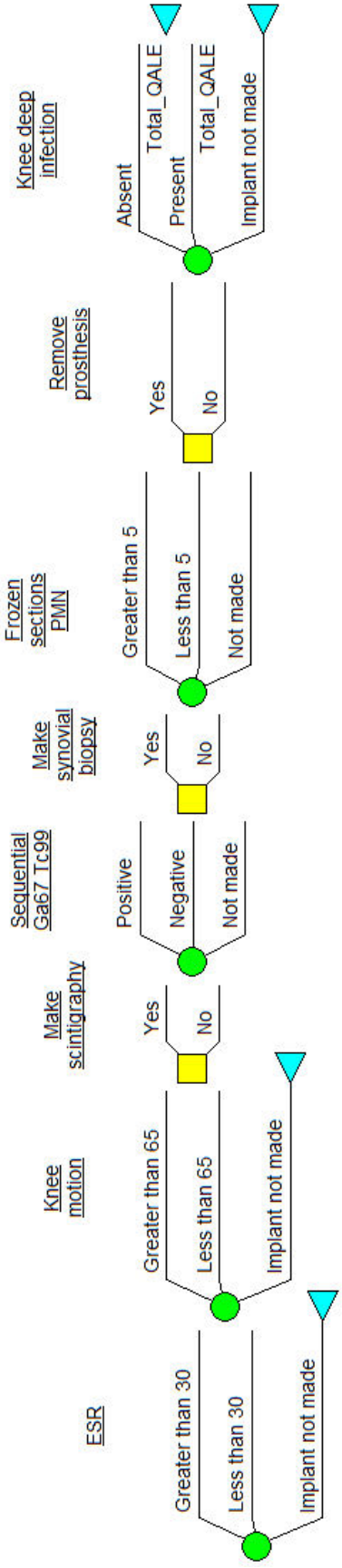

Figure 3.7: ArthroNET decision tree (second part).

decision trees. Fortunately, this software has capabilities to transform influence diagrams in decision trees automatically. Once the conversion was made, the *Knee deep infection* node was moved from its original position to the last one in the decision tree by the decision analysis process, as shown in Figure 3.6 and Figure 3.7.

3.3.2 Numerical values

When the graph of the influence diagram has been constructed, it is necessary to complete the quantitative part of the diagram, which consists of a set of probability and utility potentials. For instance, for each chance node C we must give a conditional probability potential $p(C|pa(C))$ for each configuration of its parents, $pa(C)$. Then, the table for $p(C|pa(C))$ requires $|dom(C)|\prod_{X\in pa(C)}|dom(X)|$ numbers, but given the restriction that

$$\sum_{c} p(C|pa(C)) = 1, \tag{3.1}$$

only some of them are independent. When eliciting the parameters of the model, we asked the expert to estimate only a certain number of independent parameters, mainly those relating to the conditional probability table for the node *Knee motion*. In our study we have chosen a set of 50 independent parameters for all the model (see Table 3.5). Two of them are the probability of the different states of *Ischemia* and *Drained CC* nodes, conditioned on the implantation of the prosthesis; 10 parameters are conditioned probabilities of the tests (sensitivity and specificity), given knee deep infection; 6 are utilities measured in QALYs; and 32 parameters are conditional probabilities of occurrence of a knee deep infection, obtained all of them from a binary logistic regression.

This regression was made on a database of 279 cases of a public health service hospital, which may have introduced an important bias in the study. For that purpose, the IBM's software SPSS PASW Statistics 18 -see (SPSS)- was used. The aim of this regression is to predict the dichotomous variable *Knee deep infection*. The following variables were included as control independent variables (also called covariables): *BMI*, *Diabetes*, *Antibiotic allergy*, *Ischemia* and *Drained CC*. Table 3.4 shows the adjustment constant and regression coefficients obtained from the analysis.

Table 3.4: *Knee deep infection* variable logistic regression equation parameters

Name of the variable	**Value**
BMI	1.443
Diabetes	0.945
Antibiotic allergy	1.595
Ischemia	3.519
Drained CC	1.603
Adjustment constant	-4.554

Applying the logistic regression equation:

$$P(+k|b,d,a,i,c) = \frac{1}{1+e^{-ac-1.443\cdot b-0.945\cdot d-1.595\cdot a-3{,}519\cdot i-1.603\cdot c}}, \tag{3.2}$$

where $+k$ means the knee deep infection appearance probability, b, d, a, i and c the covariables (*BMI*, *Diabetes*, *Antibiotic allergy*, *Ischemia* and *Drained CC*) binary codification and ac the adjustment constant; the *Knee deep infection* variable probability table could be obtained.

We have followed a convention for naming the parameters of ArthroNET, which basically consists in abbreviating each name of laboratory test, test result, risk factor, clinical sign and decision to their two or three first letters. For instance, the parameter *sen_ESR_KDI_pos* refers to the sensitivity of the Erythrocyte sedimentation rate test when the patient suffers a knee deep infection. In contrast, the parameter *prob_KDI_pos_DIA_neg_AAL_pos_BMI_neg_DCC_extrem_ISC_low* refers to the conditional probability of suffering a total knee arthroplasty perioperative infection if the patient is not diabetic, is allergic to antibiotics, is not obese, has drained too much or little fluid and the ischemia time was lower than ninety minutes. The Table 3.5 shows all those 50 parameters, and how they were obtained (binary logistic regression, medical literature or expert's subjective estimates). For the data collected from literature, other bibliographical sources were considered, but rejected because the expert considered that they do not represent accurately the clinical reality.

Table 3.5: ArthroNET independent parameters

Name of the parameter	Value assigned	Obtained from
prior_ISC_low	0.3728	Expert
prior_DCC_medium	0.8495	Expert
sen_ESR_KDI_pos	0.82	(Spangehl et al., 1999)
spe_ESR_KDI_neg	0.85	(Spangehl et al., 1999)
sen_CRP_KDI_pos	0.89	(Piper et al., 2010)
spe_CRP_KDI_neg	0.74	(Piper et al., 2010)
sen_KMO_KDI_pos	0.70	Expert
spe_KMO_KDI_neg	0.85	Expert
sen_SGT_KDI_pos	0.33	(Levitsky et al., 1991)
spe_SGT_KDI_neg	0.86	(Levitsky et al., 1991)
sen_PMN_KDI_pos	0.84	(Fehring and McAlister Jr, 1994)
spe_PMN_KDI_neg	0.95	(Fehring and McAlister Jr, 1994)
qale_prosthesis	4.64	(Espigares and Torres, 2008)
morbidity_SGT	0.00	Expert
morbidity_PMN	-9.205E-06	(Small, 1988)
qale_removal_KDI_pos_REM_pos	-4.64	(Espigares and Torres, 2008)
qale_removal_KDI_pos_REM_neg	-14.40	(Torrance, 1987)

Continued on next page...

Table 3.5 – Continued

Name of the parameter	Value assigned	Obtained from
qale_removal_KDI_neg_REM_pos	-4.6419	(Espigares and Torres, 2008)
prob_KDI_pos_DIA_neg_AAL_neg_BMI_neg_DCC_medium_ISC_low	0.0104	Logistic regression
prob_KDI_pos_DIA_neg_AAL_neg_BMI_neg_DCC_medium_ISC_high	0.2621	Logistic regression
prob_KDI_pos_DIA_neg_AAL_neg_BMI_neg_DCC_extrem_ISC_low	0.0497	Logistic regression
prob_KDI_pos_DIA_neg_AAL_neg_BMI_neg_DCC_extrem_ISC_high	0.6386	Logistic regression
prob_KDI_pos_DIA_neg_AAL_neg_BMI_pos_DCC_medium_ISC_low	0.0426	Logistic regression
prob_KDI_pos_DIA_neg_AAL_neg_BMI_pos_DCC_medium_ISC_high	0.6006	Logistic regression
prob_KDI_pos_DIA_neg_AAL_neg_BMI_pos_DCC_extrem_ISC_low	0.1812	Logistic regression
prob_KDI_pos_DIA_neg_AAL_neg_BMI_pos_DCC_extrem_ISC_high	0.8819	Logistic regression
prob_KDI_pos_DIA_neg_AAL_pos_BMI_neg_DCC_medium_ISC_low	0.0493	Logistic regression
prob_KDI_pos_DIA_neg_AAL_pos_BMI_neg_DCC_medium_ISC_high	0.6365	Logistic regression
prob_KDI_pos_DIA_neg_AAL_pos_BMI_neg_DCC_extrem_ISC_low	0.2049	Logistic regression
prob_KDI_pos_DIA_neg_AAL_pos_BMI_neg_DCC_extrem_ISC_high	0.8969	Logistic regression
prob_KDI_pos_DIA_neg_AAL_pos_BMI_pos_DCC_medium_ISC_low	0.18	Logistic regression
prob_KDI_pos_DIA_neg_AAL_pos_BMI_pos_DCC_medium_ISC_high	0.8811	Logistic regression
prob_KDI_pos_DIA_neg_AAL_pos_BMI_pos_DCC_extrem_ISC_low	0.5217	Logistic regression
prob_KDI_pos_DIA_neg_AAL_pos_BMI_pos_DCC_extrem_ISC_high	0.9736	Logistic regression
prob_KDI_pos_DIA_pos_AAL_neg_BMI_neg_DCC_medium_ISC_low	0.0264	Logistic regression

Continued on next page...

Table 3.5 – Continued

Name of the parameter	Value assigned	Obtained from
prob_KDI_pos_DIA_pos_AAL_neg_BMI_neg_DCC_medium_ISC_high	0.4775	Logistic regression
prob_KDI_pos_DIA_pos_AAL_neg_BMI_neg_DCC_extrem_ISC_low	0.1186	Logistic regression
prob_KDI_pos_DIA_pos_AAL_neg_BMI_neg_DCC_extrem_ISC_high	0.8195	Logistic regression
prob_KDI_pos_DIA_pos_AAL_neg_BMI_pos_DCC_medium_ISC_low	0.1028	Logistic regression
prob_KDI_pos_DIA_pos_AAL_neg_BMI_pos_DCC_medium_ISC_high	0.7946	Logistic regression
prob_KDI_pos_DIA_pos_AAL_neg_BMI_pos_DCC_extrem_ISC_low	0.3629	Logistic regression
prob_KDI_pos_DIA_pos_AAL_neg_BMI_pos_DCC_extrem_ISC_high	0.9505	Logistic regression
prob_KDI_pos_DIA_pos_AAL_pos_BMI_neg_DCC_medium_ISC_low	0.1177	Logistic regression
prob_KDI_pos_DIA_pos_AAL_pos_BMI_neg_DCC_medium_ISC_high	0.8183	Logistic regression
prob_KDI_pos_DIA_pos_AAL_pos_BMI_neg_DCC_extrem_ISC_low	0.3987	Logistic regression
prob_KDI_pos_DIA_pos_AAL_pos_BMI_neg_DCC_extrem_ISC_high	0.9572	Logistic regression
prob_KDI_pos_DIA_pos_AAL_pos_BMI_pos_DCC_medium_ISC_low	0.361	Logistic regression
prob_KDI_pos_DIA_pos_AAL_pos_BMI_pos_DCC_medium_ISC_high	0.9501	Logistic regression
prob_KDI_pos_DIA_pos_AAL_pos_BMI_pos_DCC_extrem_ISC_low	0.7373	Logistic regression
prob_KDI_pos_DIA_pos_AAL_pos_BMI_pos_DCC_extrem_ISC_high	0.9896	Logistic regression

3.3.3 Cost-effectiveness and net health benefit

The version of ArthroNET presented above does not include the economic costs of the diagnostic tests and the treatments. However, in medical decision making costs cannot be ignored. Including the economic cost turns our medical problem into a multi objective optimization (Steuer, 1986). Nevertheless, instead of basing cost-effectiveness analysis on the incremental cost-effectiveness ratios (ICERs), which is the standard method, we will apply a different perspective: the maximization of the net benefit, because it is easier to integrate with influence diagrams, and of course, both approaches are equivalent. Thus, the global utility can be identified with the *net monetary benefit* (NMB), and defined by:

$$NMB = \lambda \cdot E - C, \tag{3.3}$$

where E is the effectiveness, C is the cost, and λ, sometimes called *willingness to pay*, is used here to convert the effectiveness into a monetary scale. Its value depends on each decision maker. NMB is the net monetary benefit, and can be seen as the effectiveness (converted into monetary value) minus the associated economic costs. Similarly, we can define the *net health benefit (NHB)* by:

$$NHB = E - \lambda' \cdot C, \tag{3.4}$$

where $\lambda' = 1/\lambda$. The NHB can be interpreted as the health benefit minus the economic costs (converted into medical units). Therefore, in the analysis maximizing the NMB is equivalent to maximizing the NHB because they are proportional ($NMB = \lambda \cdot NHB$) and $\lambda > 0$. However, we have used the NHB because it allows us to do $\lambda' = 0$, which amounts to maximizing the effectiveness, regardless of the economic cost; if we had used the NMB, we would not have been able to perform this analysis, because making $\lambda = \infty$ prevents the maximization of the utilities. The integration of Equation 3.4 into ArthroNET is as follows (see Figure 3.8 – In order to better appreciate the details of the diagram, the image has been exported from Elvira software):

- The cost, C, is represented by a super value node, *Total cost*, whose parents are the utility nodes *Prosthesis cost*, *Scintigraphy cost*, *Synovial biopsy cost* and *Removal cost*.

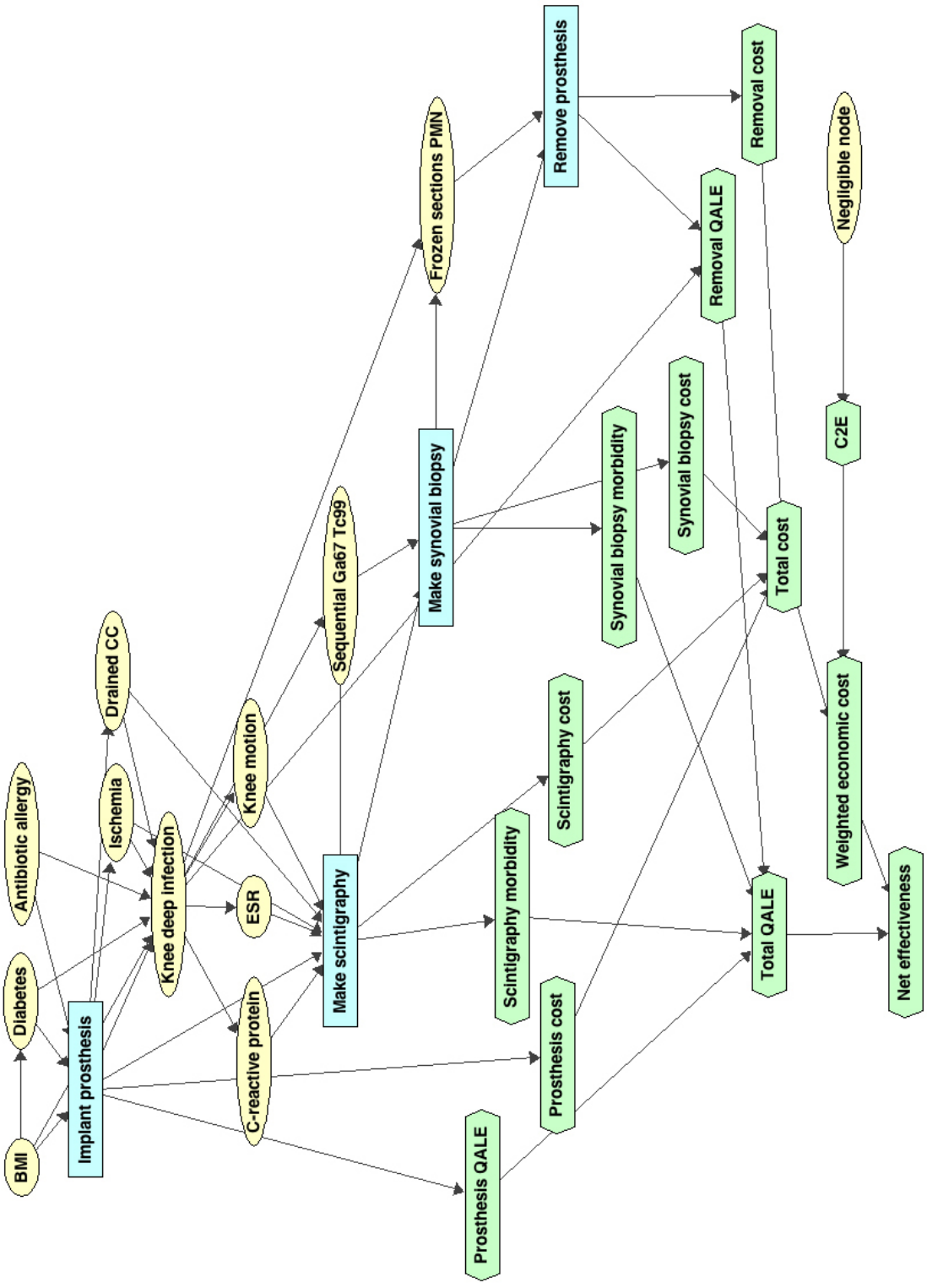

Figure 3.8: A new version of ArthroNET, including economic costs.

- The effectiveness, E, is represented by a structure of utility nodes explained in Section 3.3.1, having the *Total QALE* node at the bottom.
- The node *Weighted economic cost* is a super value node of type product, which represents $-\lambda' \cdot C$ ($-\lambda'$ is included in *C2E* node).
- *Net effectiveness* is a super value node of type sum, which represents the net health effectiveness (Equation 3.4).

Numerical values

Analogously to the case of Section 3.3.2, we have defined a set of minimal parameters for the new nodes added in the new version of ArthroNET (Figure 3.8). The new parameters are shown in Table 3.6, and the way they were collected is also described as in Table 3.5. The names of the parameters use a similar convention to those in Table 3.5. For instance, cost_SGT denotes the economic cost of making a sequential gallium-67 and technetium-99 scintigraphy. The last parameter in table, lambda, denotes the term λ in Equation 3.3, which is the inverse of λ'.

If we make $\lambda' = 0$, the evaluation of the influence diagram returns the strategy that maximizes the effectiveness, without taking into account the economic costs.

Table 3.6: Economic cost ArthroNET parameters

Name of the parameter	Value assigned	Obtained from
cost_prosthesis	€6,865.52	(Espigares and Torres, 2008)
cost_SGT	€335.08	(de Salud, 2007)
cost_PMN	€405.28	(de Salud, 2007)
cost_removal	$ 50,000	(Hanssen et al., 1996)
lambda	€30,000/QALY	(Sacristán et al., 2002)

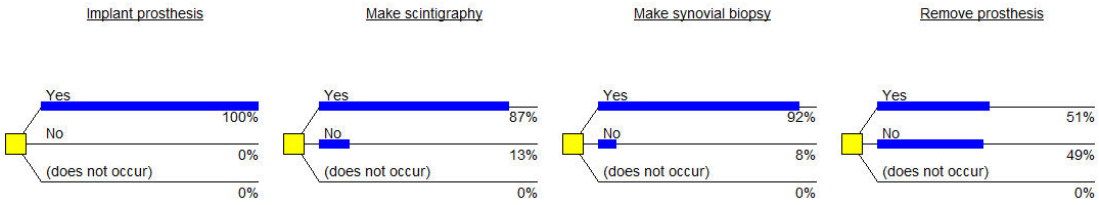

Figure 3.9: ArthroNET decision analysis policies summary.

3.4 Optimal strategies

In this section we show two strategies returned by ArthroNET with two different criteria: the maximization of the effectiveness (disregarding costs) and the maximization of the net health benefit -see (Luque Gallego, 2009)-.

3.4.1 Maximum-effectiveness strategy

The strategy that maximizes the effectiveness can be obtained from the version of ArthroNET that does not include economic costs (see Figure 3.5). However, instead of maintaining two versions of the influence diagram, with and without costs, we have only the one with costs (see Figure 3.8). As explained above, the maximum-effectiveness strategy can be obtained from this influence diagram by making $\lambda' = 0$ (see Equation 3.4). Below are the results of the decision analysis performed with the DPL software.

Due to the large number of branches of the policy tree, it is impossible to offer, for each of the more than 50,000 possibilities, an optimal policy. That is the reason why the Syncopation tool offers summaries of policies, as seen in Figure 3.9. For a particular patient, the specialist will choose those branches that suit to the diagnostic clinical reality in order to get the more useful policy. In our study, the policies summary indicates that the prosthesis implant is always made, regardless of the risk factors presented by the patient; in this case, the expected benefit of implanting the prosthesis is higher than when it is necessary to remove the prosthesis because of the appearance of a knee deep infection. This summary indicates a 51% failure of the implants, and suggests to carry out scintigraphies and synovial biopsies in 87% and 92% of the cases, respectively, in order to determine the presence of infection.

This means that if we have a patient per each possible combination of the

three risk factors (eight combinations)[3], 51% will need a removal of the prosthesis. Moreover, to obtain these summaries, the software uses all branches of the decision tree, including all the possible results of diagnostic tests. That is the reason why the analysis should be made pre or post-operatively on each specific sub-branch to reflect the clinical reality of the patient in terms of risk factors, among others.

The decision analysis was also carried out controlling those decision tree subbranches that contain information about the risk factors. Thus, it was necessary to perform 2^3 (8) analysis with the tool. Those analysis gave the policies summaries showed in Table 3.7, where *D1*, *D2*, *D3* and *D4* are the probabilities of making the decisions *Implant prosthesis*, *Make scintigraphy*, *Make synovial biopsy* and *Remove prosthesis* respectively.

Table 3.7: ArthroNET decision analysis policies summaries taking into account the risk factors

High BMI	**Diabetic**	**Antibiotic allergic**	***D1***	***D2***	***D3***	***D4***
No	No	No	1	0.72	0.95	0.22
No	No	Yes	1	0.93	0.84	0.47
No	Yes	No	1	0.91	0.74	0.36
No	Yes	Yes	1	0.94	1	0.60
Yes	No	No	1	0.89	0.87	0.45
Yes	No	Yes	1	0.80	0.99	0.66
Yes	Yes	No	1	0.77	0.98	0.58
Yes	Yes	Yes	1	0.98	1	0.78

3.4.2 Maximum-benefit strategy

In a second phase we have evaluated ArthroNET with economic costs. As shown in (Sacristán et al., 2002), all technologies with a cost-effectiveness ratio lower than €30,000 per QALY were recommended in the Spanish public health system,

[3]This classification does not take into account the prior probability of the risk factors.

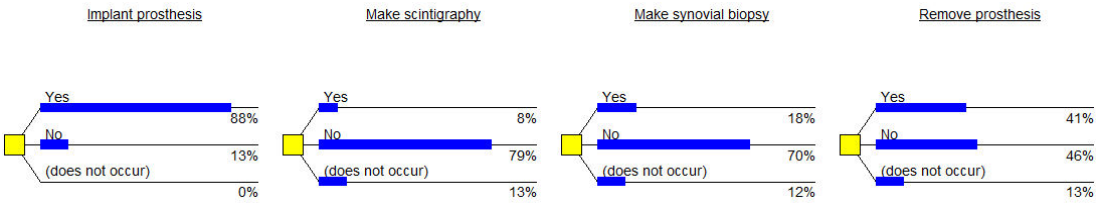

Figure 3.10: Policies summary of ArthroNET decision analysis including economic costs.

but up to that limit there was no a clear tendency. That is the reason why we have set the parameter lambda to a value of $\lambda = €30{,}000/\text{QALY}$. A different value of lambda could lead to a different strategy. Analogously as in section 3.4.1 below are the results of the decision analysis performed.

The summary of policies is presented in Figure 3.10. The introduction of economic costs to the model makes the optimal policies vary substantially:

1. Implant prosthesis: recommended for all patients, except for those with a high BMI, diabetes and allergy to antibiotics. The percentage of suggested implants shown has considered sets where there is a patient per each possible combination of the three risk factors. The calculation of a more abstract rate should take into account the prevalence of risk factors in the country where the diagnosis is made.

2. Make scintigraphy: only recommended in 8% of the cases, mainly due to the contrast low sensitivity - economic cost of this test.

3. Make synovial biopsy: recommended in 18% of cases.

4. Remove prosthesis: a policy that combines health and economic cost leads to cutting down cases of implant failure, although less implants are made.

As in the previous strategy, several decision analysis based on all possible risk factors casuistic have been performed, whose results are shown in Table 3.8[4].

[4]This table uses the same nomenclature as Table 3.7

Table 3.8: Economic version of ArthroNET decision analysis policies summaries taking into account the risk factors

High BMI	Diabetic	Antibiotic allergic	*D1*	*D2*	*D3*	*D4*
No	No	No	1	0.1	0.25	0.21
No	No	Yes	1	0.02	0.18	0.47
No	Yes	No	1	0.09	0.23	0.36
No	Yes	Yes	1	0.15	0.16	0.59
Yes	No	No	1	0.07	0.21	0.44
Yes	No	Yes	1	0.08	0.23	0.66
Yes	Yes	No	1	0.16	0.17	0.57
Yes	Yes	Yes	0	0	0	0

3.5 Sensitivity analysis

3.5.1 Introduction

The object of decision analysis on a probabilistic decision problem, represented for example in a decision tree, an influence diagram or an unconstrained influence diagram, is twofold: to determine an optimal strategy, consisting of an optimal policy for each decision, and on the other hand, to compute the maximum expected utility (MEU). In general it is usual to compute first the optimal policies and the MEU for a particular model, called the *reference* case, in which all the parameters are assumed to be known with certainty, and in a posterior phase, the decision analyst investigates whether these results depend on (are sensitive to) the uncertainty about the model. This post-hoc investigation is called *sensitivity analysis*. The optimal policies and the MEU are sensitive to variations in both the qualitative part of the influence diagram (arcs and nodes) and the quantitative part (the utilities and the probabilities).

Basic concepts

Sensitivity analysis (SA) consists in determining whether the conclusions obtained for the reference case (optimal strategy and MEU) hold in spite of the uncertainty about the accuracy of the model itself.

There exist several types of SA. Depending on the part of the model studied, SA can be:

1. **qualitative**, also referred to as **structural**, which examines how variations of the structure of the model can affect the conclusions;
2. **quantitative**, which explores the effect of the variations in the probabilities and utilities.

Depending on the types of conclusions studied, we can distinguish two types of SA:

1. **value sensitivity analysis**, which measures variations in the expected utility;
2. **decision sensitivity analysis**, which explores the changes in the optimal strategy.

Quantitative SA can furthermore be characterized as:

1. **interval-based SA**: each parameter to be within a certain interval;
2. **probabilistic SA**: it assigns a probability distribution to each parameter; (Doubilet et al., 1985) describes a practical method when uncertainties in all values are considered simultaneously, they used a parametric model that permits each distribution to be specified by two values: (1) the baseline estimate, and (2) a bound (upper or lower) of the 95 percent confidence interval;
3. **policy change thresholds SA**: it investigates the admissible values a parameter (or a set of parameters) can be assigned without changing the optimal strategy of the reference case.

The distributions commonly used in probabilistic SA when applied to medical decision making are shown in Table 3.9.

Table 3.9: Commonly used distributions in SA in medical decision making. Taken from http://www.york.ac.uk/inst/che/pdf/teehtacosteff04.pdf

Parameters	**Distribution**	**Details**
Probabilities	Beta	Between 0 and 1
Costs	Log-normal | Gamma	Ranging from 0 to ∞
Utilities	Beta | Gamma $(1 - U)$	$-\infty$ to 1
Relative risks	Log-normal	Ratios | Additive in log scale

Quantitative SA can be classified into three types (Díez, 2007):

1. **one-way**: it is concentrated on just one parameter; for instance, the prevalence;
2. ***n*-way independent analysis**, which consists in considering the consequences of individual variations of each of n parameters;
3. ***n*-way joint analysis**: it analyzes the joint variation of a set of n parameters.

There are three graphical representations very popular in SA of Bayesian decision problems (Díez, 2007), (Clemen and Reilly, 1999):

1. **Utility plots**: they can be used for finding treatment thresholds in different scenarios (van der Gaag and Coupé, 2000) and, in consequence, to explain the optimal policies. For instance, Figure 3.12 shows the results of one-way sensitivity analysis on the prevalence of X for the influence diagram given in Figure 3.11. This graph is obtained by evaluating several instances of the influence diagram, each having a different value of $P(+x)$. We can see that the treatment threshold is approximately 0.17, i.e., when $P(+x) < 0.17$ the best option is not to treat the patient, and when $P(+x) > 0.17$ it is better to treat. This way, utility plots show graphically the policy changes thresholds and why they emerge.

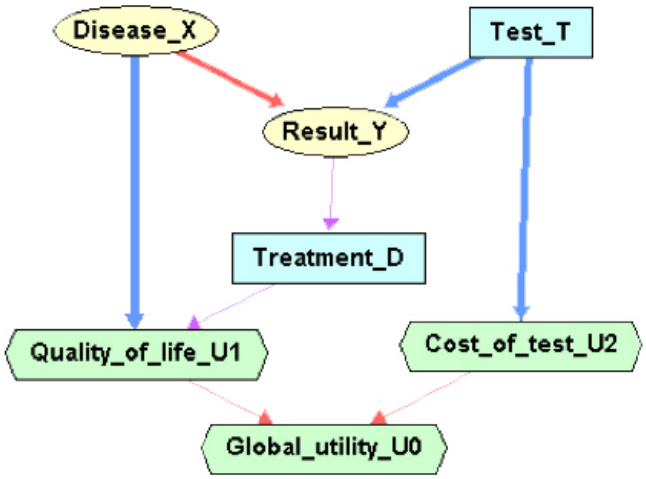

Figure 3.11: Influence diagram with two decisions, two chance nodes and three utility nodes. There is a directed path $T - Y - D - U_1 - U_0$ including all the decisions and the global utility node U_0.

2. **Tornado diagrams**: they are a form of interval-based n-way independent analysis. They show graphically which parameters in the model have the greatest influence on the expected utility. Each parameter is assigned to a bar whose length indicates the variation of the expected utility. The graph is laid out so that the most sensitive parameter (the one with the longest bar) is at the top, and the least sensitive is at the bottom, where the bars are arranged in this order. An example of tornado diagram is shown in Figure 3.13. The vertical bar represents the MEU for the reference case.

3. **Spider diagrams**: the analysis is identical to the tornado diagram. The only difference is how the results are presented. In a spider diagram, the utility is not represented on the horizontal axis but on the vertical one; the percentage variation of each parameter over its reference value is represented on the horizontal axis. An example of spider diagram is displayed in Figure 3.14.

Sensitivity analysis in influence diagrams

One of the first steps towards a framework for sensitivity analysis in influence diagrams was proposed in (Bielza et al., 1996). They consider influence diagrams in which only partial information is available about probabilities and utilities. Uncertain values are represented by parameters. The authors propose a method

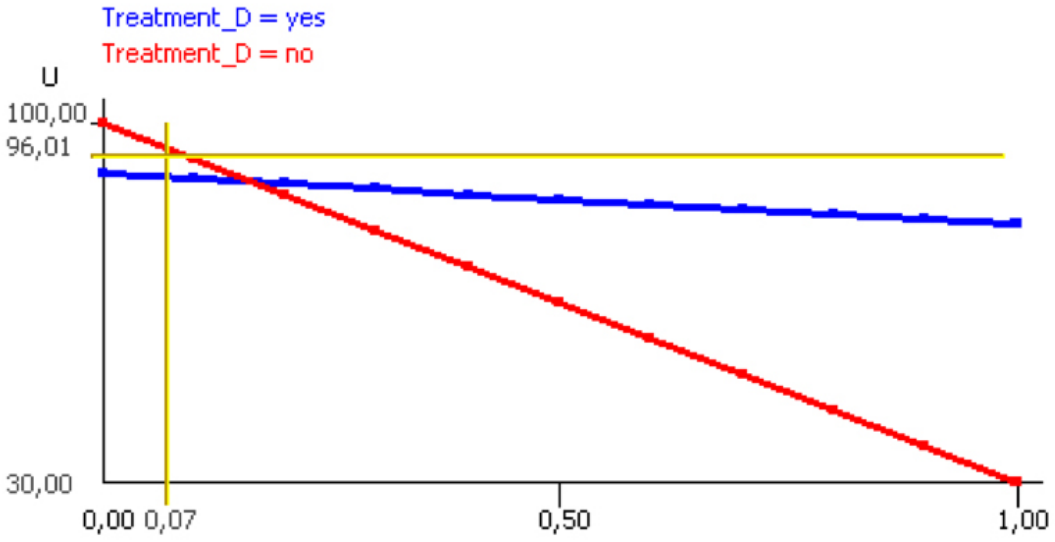

Figure 3.12: Utility plot of the prevalence of the disease, which is represented in the the x-axis. The y-axis represents the expected utility. The treatment threshold is 0.17.

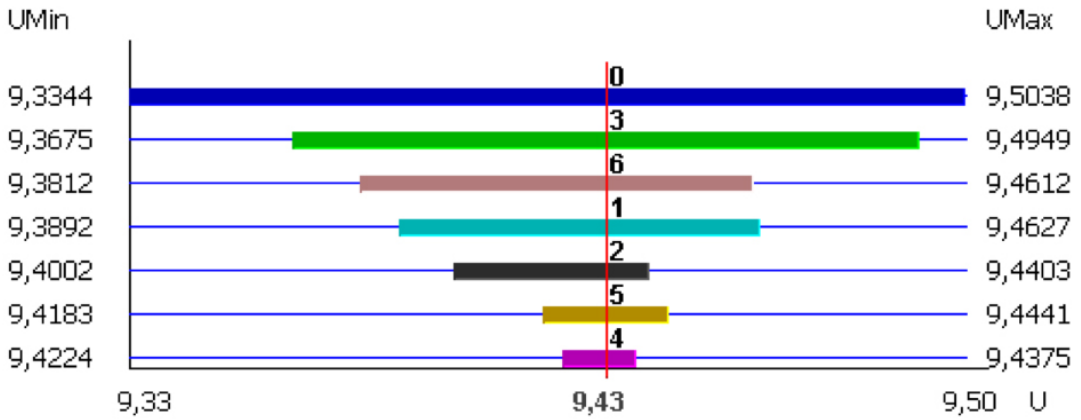

Figure 3.13: A tornado diagram. Taken from (Díez, 2007)

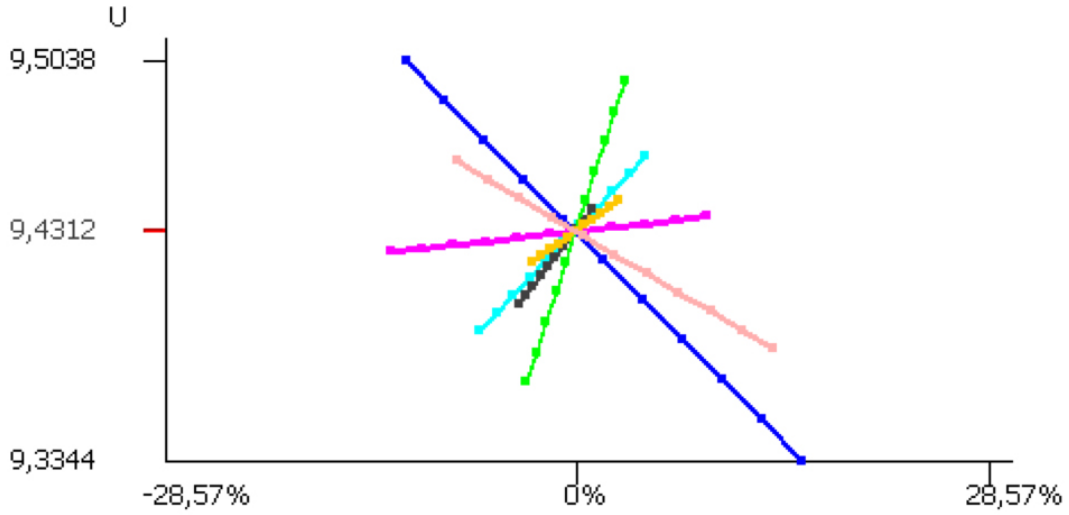

Figure 3.14: A spider diagram. Taken from (Díez, 2007)

for computing a set of non-dominated strategies based on that parametric model. Given that the set of non-dominated set may grow tremendously they introduce some additional criteria to limit the size of the sets, and eventually, select a non-dominated alternative.

A method based on value sensitivity was proposed in (Felli and Hazen, 1998). This method uses the expected value of perfect information, and it requires a probability distribution to be assigned to each parameter under investigation. Formally, let t be an uncertain parameter, and let $\mathbf{\Delta_0}$ be the optimal strategy found with the initial values of the parameters $\mathbf{t}$, denoted by $\mathbf{t_0}$. Let $EU(\mathbf{\Delta}, \mathbf{t})$ denote the expected utility of the influence diagram under strategy $\mathbf{\Delta}$ and values of parameters $\mathbf{t}$. Then, the *expected value of perfect information* (EVPI) is given by:

$$EVPI = E_t[(max_{\Delta} EU(\mathbf{\Delta}, \mathbf{t})) - EU(\mathbf{\Delta_0}, \mathbf{t})], \tag{3.5}$$

where E_t denotes the expected value with respect to the probability distribution of parameters $\mathbf{t}$. Monte Carlo methods are usually applied to sample values for the parameters in order to calculate *EVPI*. E_t in Equation 3.5 is then approximated by calculating the mean over the set of generated samples.

Ictneo, a decision support system to manage neonatal jaundice, is a good example of the application of sensitivity analysis techniques to a real influence diagram (Bielza et al., 2000). The authors deduced a relevant set of parameters

to analyze as a result of interviews with the doctors. They performed a one-way SA based on tornado diagrams and n-way SA through the EVPI calculated with Monte Carlo simulations.

(Nielsen and Jensen, 2003) proposed a method that performs decision SA in influence diagrams based on threshold-proximity. They developed very efficient algorithms for performing one-way and n-way SA. Their method is based on an explicit representation of the parameters in question, and the calculations are performed in the underlying junction tree representation of the influence diagram.

3.5.2 Sensitivity analysis in ArthroNET

We are interested in determining whether the conclusions obtained with ArthroNET hold in spite of the uncertainty relative to the construction of the model. The sensitivity analysis has been performed through the DPL software.

Expected value of perfect information

For both strategies, the expected value of perfect information charts (see Figure 3.15 and Figure 3.16) offer the same correlation between the model variables.

In these charts, a positive value of information means that knowing which state of the chance event will occur before making a decision changes the policy tree in some way to improve expected value. A zero value would mean that knowing the state has no impact on the policy tree. A negative value usually means that the objective was to minimize an utility, and that there is value to knowing the state of the event. In our study all values are positive, because decreasing the uncertainty of any variable in the model implies a better diagnosis, and subsequently a better treatment policy.

These graphs show that, as expected, the variable representing the presence of infection of the knee is the one with greater significance because it determines the success or failure of the implant, and therefore increase or decrease of the net health benefit. Additionally, the analysis of the C-reactive protein, and the time of ischemia are the variables more significant in the model.

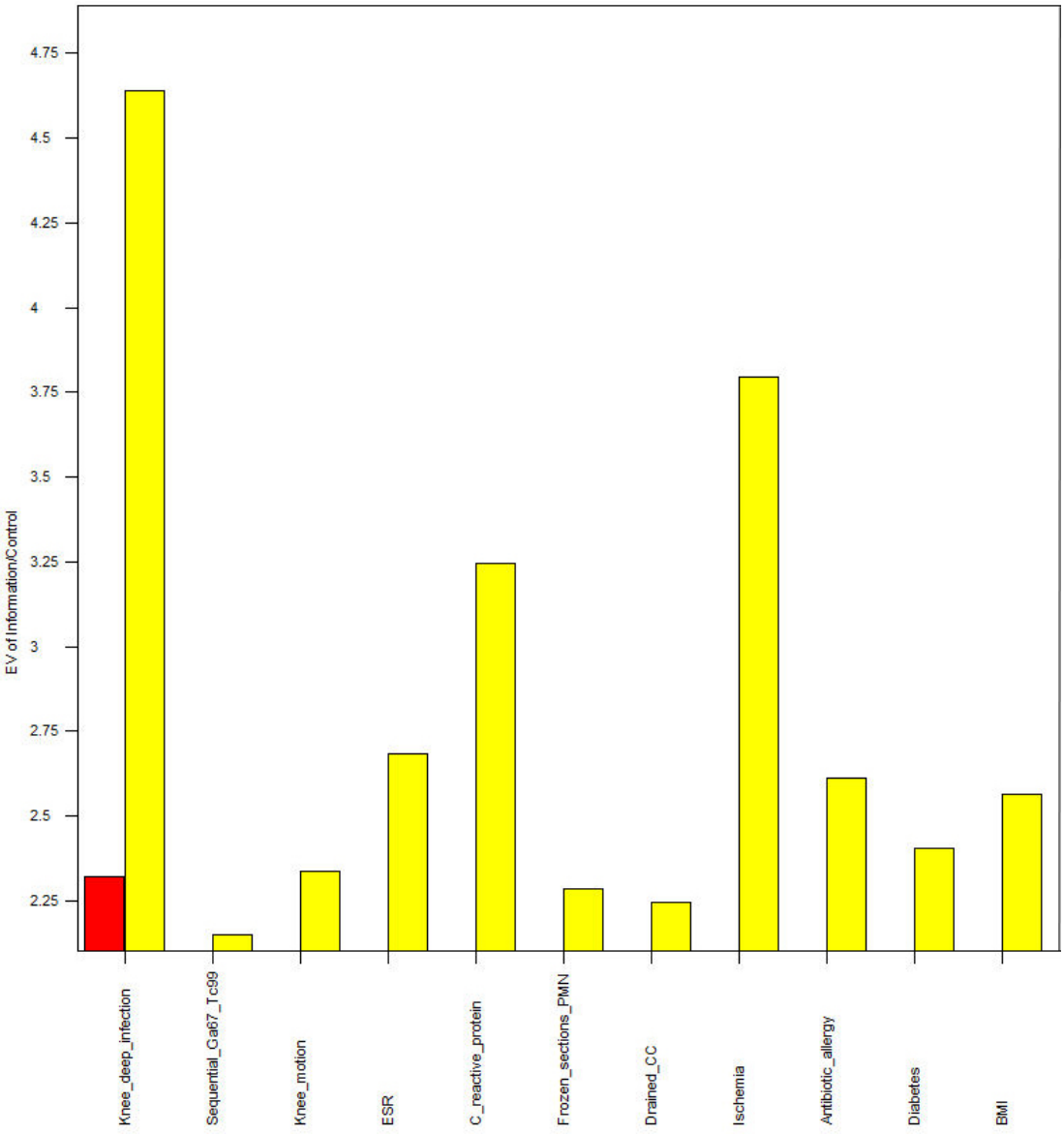

Figure 3.15: Expected value of perfect information - ArthroNET maximum-effectiveness strategy.

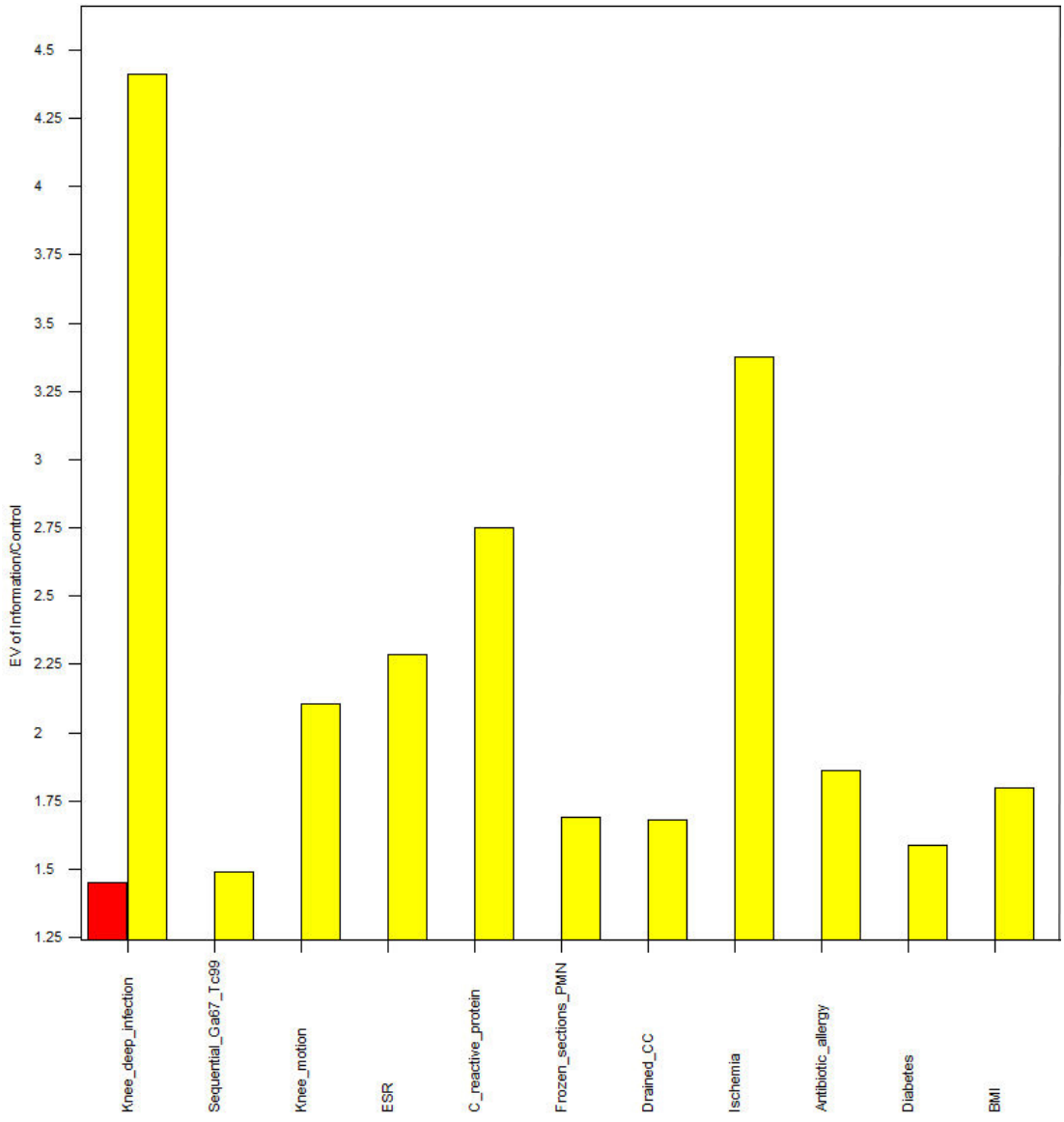

Figure 3.16: Expected value of perfect information - ArthroNET maximum-benefit strategy.

Rainbow diagrams

We present below (see Table 3.10) a series of one-way and two-way rainbow diagrams (Clemen and Reilly, 1999) to see the effects of varying a single variable on the optimal policy and the expected value. In these diagrams (obtained from the decision analysis performed with the DPL software), a region in which the optimal policy does not change is indicated with a single color. If there are more than one colored regions in the graph, then the optimal policy is different depending on the value of the sensitivity parameter. Because model outputs are determined at discrete values over a range of the sensitivity parameter, we cannot assume that the line between regions indicates the precise value at which the policy changes. Obtaining the precise points where the policy change is postulated as the subject of a future study. Analogously, in two-way rainbow diagrams, a region in which the optimal policy is the same is indicated with a single color, being displayed in a graph with the range of values for the first sensitivity variable along the horizontal axis and the range of values for the second sensitivity variable along the vertical axis.

For those cases where possible, and in order to make comparisons, diagrams for each one of the two strategies, maximum-effectiveness (ME) and maximum-benefit (MB), will be presented. The Table 3.10 contains the references to all the rainbow diagrams performed through the DPL software. The way the diagrams were obtained was specifying the value range that the parameter can take, and the steps to do it. For instance, a range [-10, 0] with 20 steps means that the model will be evaluated for the following parameter values: {-10, -9.47, -8.95, -8.42, -7.89, -7.37, -6,84, -6.32, -5,79, -5.26, -4.74, -4.21, -3.68, -3.16, -2.63, -2.11, -1.58, -1.05, -0.53, 0}.

Table 3.10: ArthroNET sensitivity analysis DPL outcome (rainbow diagrams)

Type	Variable	Reference	See also
One-way	*Prosthesis QALE*	A.1	
One-way	*Prosthesis QALE*	A.2	
One-way	*Removal QALE*	A.3	Table 3.11
Continued on next page...			

Table 3.10 – Continued

Type	Variable	Reference	See also
One-way	*Removal QALE*	A.4	Table 3.11
One-way	*Removal QALE*	A.5	Table 3.11
One-way	*Removal QALE*	A.6	Table 3.11
One-way	*Prosthesis cost*	A.7	Table 3.12
One-way	*Removal cost*	A.8	Table 3.12
One-way	*Scintigraphy cost*	A.9	Table 3.12
Oneway	*Synovial biopsy cost*	A.10	Table 3.12
Two-way	*Prosthesis* vs. *Removal QALE*	A.11	Table 3.13
Two-way	*Prosthesis* vs. *Removal QALE*	A.12	Table 3.13
Two-way	*Prosthesis* vs. *Removal QALE*	A.13	Table 3.13
Two-way	*Prosthesis* vs. *Removal QALE*	A.14	Table 3.13
Two-way	*Prosthesis* vs. *Removal QALE*	A.15	Table 3.13

As can be seen in figures A.1 and A.2, there is great variability of optimal policies due to the variation of the parameter *Prosthesis QALE* when the implant is made (evaluated range: [0,10], 20 steps), although in the case of maximum-benefit strategy, when it exceeds a value close to 5 QALEs, the optimal policy is maintained, being this to perform the implant on 100% of patients, because the economic cost of the implant does not affect the global net benefit (due to the high improvement of the quality of life).

The rainbow diagrams detailed in Table 3.11[5] show the expected value of the optimal policies when the *Removal QALE* parameter varies. To obtain those diagrams, the presence of infection has been considered, and the analysis has evaluate the model whether the implant was removed or not. This diagrams do not give too much information, but confirm the variability of policies depending on the parameter values.

As shown in Table 3.12[5], the economic costs rainbow diagrams are related to the four model decisions. In those diagrams only the *Removal cost* variable

[5]Each row of this table means one sensitivity analysis run. This table also specifies, for each run, the chance variables selected values and the decisions made. The last column of the table contains the reference to the graphical output of the analysis execution.

diagram (see Figure A.8) indicates a great variability of the policies, mainly due to the high economic cost of prosthesis removal. This parameter has been evaluated in a €60,000 range, whose real cost is much higher than the other arthroplasty procedures costs.

Finally, in Table 3.13[5], the sensitivity analysis conditions of the *Removal QALE*, *Prosthesis cost* and *Removal cost* two-way rainbow diagrams are presented. Their study will be made in a future work.

Table 3.11: Conditions used to perform the sensitivity analysis on the Removal QALE parameter

Strategy	Variable	Range	Steps	Knee deep infection	Remove prosthesis	Figure
ME	*Removal QALE*	[-20, -10]	20	Present	No	A.3
ME	*Removal QALE*	[-10, 0]	20	Present	Yes	A.4
MB	*Removal QALE*	[-20, -10]	20	Present	No	A.5
MB	*Removal QALE*	[-10, 0]	20	Present	Yes	A.6

Table 3.12: Conditions used to perform the sensitivity analysis on the economic costs parameters of the model

Strategy	Variable	Range	Steps	Implant	Remove	Scint.	Biopsy	Figure
MB	*Prosthesis cost*	[3,000, 10,000]	20	Yes				A.7
MB	*Removal cost*	[10,000, 30,000]	20		Yes			A.8
MB	*Scintigraphy cost*	[0, 600]	20			Yes		A.9
MB	*Synovial biopsy cost*	[0, 600]	20				Yes	A.10

Table 3.13: Conditions used to obtain the two-way rainbow diagrams in the sensitivity analysis

Strategy	**Variable 1**	**Range**	**Steps**	**Variable 2**	**Range**	**Steps**	**Implant**	**Remove**	**Figure**
ME	*Prosthesis QALE*	[0 ,10]	20	*Removal QALE*	[-20, -10]	20	Yes	No	A.11
ME	*Prosthesis QALE*	[0 ,10]	20	*Removal QALE*	[-20, -10]	20	Yes	Yes	A.12
MB	*Prosthesis QALE*	[0 ,10]	20	*Removal QALE*	[-20, -10]	20	Yes	No	A.13
MB	*Prosthesis QALE*	[0 ,10]	20	*Removal QALE*	[-20, -10]	20	Yes	Yes	A.14
MB	*Prosthesis QALE*	[0 ,10]	20	*Removal cost*	$[10^3, 7 \cdot 10^3]$	20	Yes	Yes	A.15

3.6 Discussion

In the daily clinical practice, indications of total knee arthroplasty are based mostly on clinical facts, like presence of pain, exploration, and results of image studies. However, after some time of practicing, each surgeon develops some kind of intuition that is mainly based on his/her experience. When the infection appears, the surgeons, usually ask themselves *What did I do wrong?* or *What should not I have done?* This afore mentioned intuition makes the surgeons suspect that some patients (over-weighted, diabetic, arthritic, immunodepressed, previously infected...) have a high probability of developing an infection after the arthroplasty.

Many studies have identificate some risk factors that increase the risk of infection in arthroplasties. However, the influence diagram presented in this memory (see Section 3.3.1) offers for the first time a tool based on a scientific, probabilistic, evidence-based algorithm for helping the surgeon decide whether to operate or not, when some risk factors are present, decide which methods are most suitable for the diagnosis of an infection, and decide what procedures and treatments are optimal when the infection has been diagnosed. Not only quality of life has been taken into consideration for this study, but also economic advantages and disadvantages.

Identifying pre-operative risk factors in total knee arthroplasty is a hard and painstaking task. Diversity of biological variables, correlations and dependence amongst them (i.e. age and overweight, age and diabetes, overweight and diabetes) and variability between individuals usually lead to invalid statistic models, and erroneous results. Therefore, for this model, we have considered two unquestionable risk factors for developing arthroplasty infections, both of them already extensively studied in literature (like obesity and diabetes) and a new risk factor (antibiotic-cephalosporin allergy) identified on our series, and based on the specialist's own experience.

Identifying risk factors is a hard task, but it is harder to determine whether a total knee arthroplasty is infected. Commonly used diagnostic tests are not 100% accurate, and their results should be interpreted as a probability of the presence of an infection. Scintigraphy, synovial biopsy, analytic results (C-reactive protein values), and clinical observation (stiffness, lowered range of motion) are taken into consideration into the model, as well as their morbidity and costs.

The proposed algorithm not only evaluates the probability of an infection, based on the presence of risk factors, combined with the results of diagnostic tests, but is capable of advising the surgeon of which diagnostic method is most suitable for each patient, i.e. this tool is capable of detecting if there is no need to make a synovial biopsy, when the probability of infection is already very high, thus lowering costs and morbidity.

ArthoNET is a decision support system for the diagnosis of perioperative infection in total knee arthroplasty and does not pretend to be an unquestionable method of election, but represents an advisor for the surgeon. The parameter λ, which in cost-effectiveness analyses represents the amount of money that the decision maker is willing to pay to obtain a unit of effectiveness, has been included in the influence diagram by introducing a utility node that represents $1/\lambda$ ($-\lambda'$ is included in the node *C2E* of the influence diagram in Figure 3.8).

We have evaluated the influence diagram with $\lambda' = 0$, which makes the net health benefit coincide with the effectiveness (see Equation 3.4), i.e., we have disregarded the economic costs. Then, we have evaluated it again with $\lambda =$ €30,000/QALY, which is accepted as the shadow cost-effectiveness equivalence in Spain (Sacristán et al., 2002).

3.7 Evaluation of ArthroNET

Previously guided by clinical common sense, by medical literature and by the specialist's empiric experience, ArthroNet has been used for three months in the clinical service where the specialist belongs to. The way it was used was through the influence diagram implemented in DPL software, leading to a maximum-benefit strategy.

Twenty-five (25) patients were included in the study. All of them eligible for a total knee arthroplasty. The Table 3.14 shows the patients' risk factors and the probability of outcome of infection for each of them before the surgical procedure (extracted from the decision analysis results). The software discouraged three (3) patients from making the implant. These three patients were obese and allergic to antibiotics (two of them were also diabetics), and are identified in Table 3.15 as patients *12*, *24* and *25*.

Table 3.14: Risk factors and prior probability of outcome of the infection of the 25 patients belonging to the sample under study

High BMI	**Diabetes**	**ATB allergy**	**Infection prob.**	**No. patients**
No	No	No	0.38	1
No	No	Yes	0.61	2
No	Yes	No	0.52	1
No	Yes	Yes	–	0
Yes	No	No	0.59	7
Yes	No	Yes	**1**	1
Yes	Yes	No	0.7	11
Yes	Yes	Yes	**1**	2

Regardless of the results offered by the tool, all the patients underwent total knee arthroplasty. The Table 3.15 shows, for each patient, his/her risk factors (*R1*, *R2* and *R3* are the risk factors *High BMI*, *Diabetes* and *Antibiotic allergy* severally), the variables observed during surgery (ischemia time and drained cubic centimeters), the probability of occurrence of infection, and the policies recommended by the tool (*D1*, *D2*, *D3* and *D4* are the decisions *Implant prosthesis*, *Make scintigraphy*, *Make synovial biopsy* and *Remove prosthesis* respectively.). The last column shows whether or not the infection appeared finally, so the success of the model can be checked.

Table 3.15: Patients' individual recommended policies and results

Patient	R1	R2	R3	Ischemia	Drained CC	Infection prob.	D1	D2	D3	D4	Inf. app.
1	No	No	No	85 min	950	0.01	Yes	No	No	No	No
2	No	No	Yes	75 min	775	0.2	Yes	No	No	No	No
3	No	No	Yes	87 min	800	0.05	Yes	No	No	No	No
4	No	Yes	No	98 min	850	0.48	Yes	No	No	No	No
5	Yes	No	No	126 min	700	0.88	Yes	No	No	Yes	Yes
6	Yes	No	No	101 min	600	0.88	Yes	No	No	Yes	Yes
7	Yes	No	No	80 min	750	0.18	Yes	No	No	No	No
8	Yes	No	No	83 min	800	0.04	Yes	No	No	No	No
9	Yes	No	No	75 min	900	0.04	Yes	No	No	No	No
10	Yes	No	No	85 min	950	0.04	Yes	No	No	No	No
11	Yes	No	No	119 min	800	0.6	Yes	No	No	Yes	Yes
12	Yes	No	Yes	95 min	1200	1	No	No	No	No	Yes
13	Yes	Yes	No	85 min	925	0.1	Yes	No	No	No	No
14	Yes	Yes	No	93 min	925	0.79	Yes	No	No	Yes	Yes
15	Yes	Yes	No	82 min	1125	0.36	Yes	No	No	No	No
16	Yes	Yes	No	81 min	850	0.1	Yes	No	No	No	No

Continued on next page...

Table 3.15 – Continued

Patient	R1	R2	R3	Ischemia	Drained CC	Infection prob.	D1	D2	D3	D4	Inf. app.
17	Yes	Yes	No	90 min	975	0.1	Yes	No	No	No	No
18	Yes	Yes	No	78 min	1000	0.1	Yes	No	No	No	No
19	Yes	Yes	No	82 min	900	0.1	Yes	No	No	No	No
20	Yes	Yes	No	85 min	925	0.1	Yes	No	No	No	No
21	Yes	Yes	No	79 min	1200	0.36	Yes	No	No	No	No
22	Yes	Yes	No	80 min	1250	0.36	Yes	No	No	No	No
23	Yes	Yes	No	122 min	675	0.95	Yes	No	No	Yes	Yes
24	Yes	Yes	Yes	103 min	700	1	No	No	No	No	Yes
25	Yes	Yes	Yes	112 min	1300	1	No	No	No	No	Yes

As can be seen in Table 3.15, the model has predicted accurately the outcome of infection in three (3) of twenty-five (25) patients before the surgical procedure. Despite of the recommendations of the software, and in order to evaluate its capabilities, the total knee arthroplasty was performed on all of the twenty-five (25) patients. After surgery, the model predicted the outcome of infection in another five (5) patients (total of eight -8-). Three months after all arthroplasties were made, the team was able to verify that the knees that became infected (eight -8-) were those the model predicted: 100% success.

Part IV

Conclusions

Chapter 4

Conclusions

We end this dissertation by summarizing the main contributions (Section 4.1) and proposing some lines open for future research (Section 4.2).

4.1 Main contributtions

Firstly, we have reviewed the state of the art of two kinds of decision support systems: (1) those related to knee arthroplasties and (2) those influence diagrams applied to medicine.

We have also built an influence diagram, ArthroNET, a decision support system for the diagnosis of perioperative infection of total knee arthroplasty. The parameter λ, which in cost-effectiveness analyses represents the amount of money that the decision maker is willing to pay to obtain a unit of effectiveness, has been included in the influence diagram by introducing an utility node that represents $-1/\lambda$ (*C2E* node - see Figure 3.8). We have evaluated the influence diagram with $\lambda' = 0$, which makes the net health benefit coincide with the effectiveness (see Equation 3.4), i.e., we have disregarded the economic costs. Then, we have evaluated it again with $\lambda =$ €30,000/QALY, which is accepted as the shadow cost-effectiveness equivalence in Spain (Sacristán et al., 2002).

For the eight infected patients mentioned in section 3.7 (out of a population of 25 candidates to total knee replacement), and in absolute terms of health and money, the software predicted pre-operatively a high risk of infection in three of them, based on the presence of obesity and/or diabetes and/or antibiotic allergy; and post-operatively a high probability of infection in the other five

patients, based on results of the tests. The eight infections were confirmed later in operating room, when the infected prostheses were extracted.

As it has already been said, this new tool does not pretend to exclude any patient from total knee arthroplasty, but to provide both the surgeon and the patient with an estimate of the risks for health and the probabilities of failure. The selection of the right patient includes other innumerable factors, most of them being not mathematically measurable, like personality or social features, self-sufficiency, mental health, personal care, capability of understanding the treatment and the care of the prosthesis, disposition to rehabilitation, etc.

In conclusion, our experience with ArthroNET showed a reasonable guideline to the alternatives in diagnosis and treatment, and a correct prediction of infectious disease outcome in 8 cases out of a 25 patients population (100% success).

4.2 Future work

There are some open lines for future research.

With respect to the explanation of the reasoning in influence diagrams, to find some method that could help to explain to the expert which variables are having more influence in the optimal strategy and in the maximum expected utility.

In relation to the application of ArthroNET we have three research lines suggested by the expert:

- To model the evolution of the implant through time.
- To add more risk factors to the model, such as the rheumatoid arthritis.
- To include in the model the bacterial organisms responsible for the infections.

Also, a more accurate sensitivity analysis is needed; it would be desirable to know the precise points where policies change. Besides, a sensitivity analysis must be performed on the model parameters that the DPL software does not allow to study.

In addition, the author intends to continue this study in a doctoral thesis, including the implementation of the model through OpenMarkov, a free software

tool for probabilistic graphical models, such as Bayesian networks, influence diagrams and Markov models, developed at the CISIAD[1], a Research Center on Intelligent Decision-Support Systems, UNED dependent center.

[1]http://www.cisiad.uned.es

Part V

Appendices and bibliography

Appendix A

Appendix of chapter 3

A.1 Figures

This section contains some of the figures mentioned in the sensitivity analysis of chapter 3.

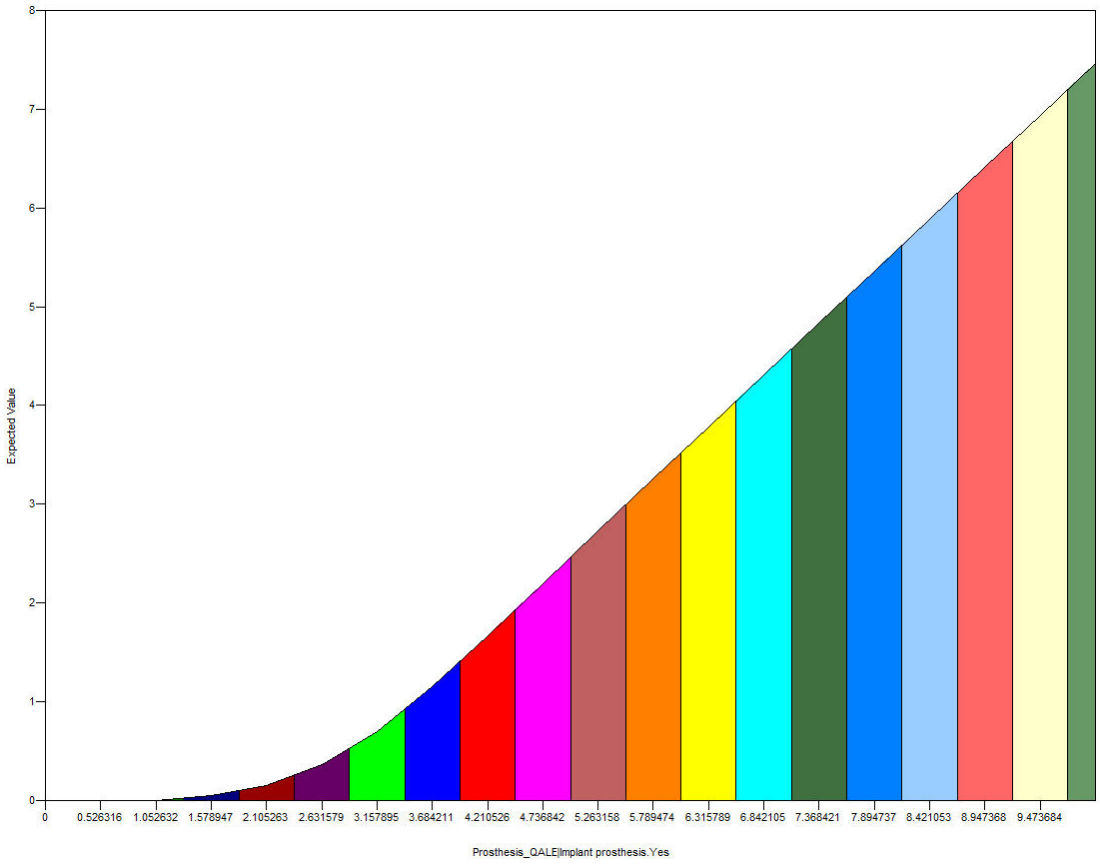

Figure A.1: Maximum-effectiveness - Rainbow diagram Prosthesis QALE — Implant prosthesis = Yes.

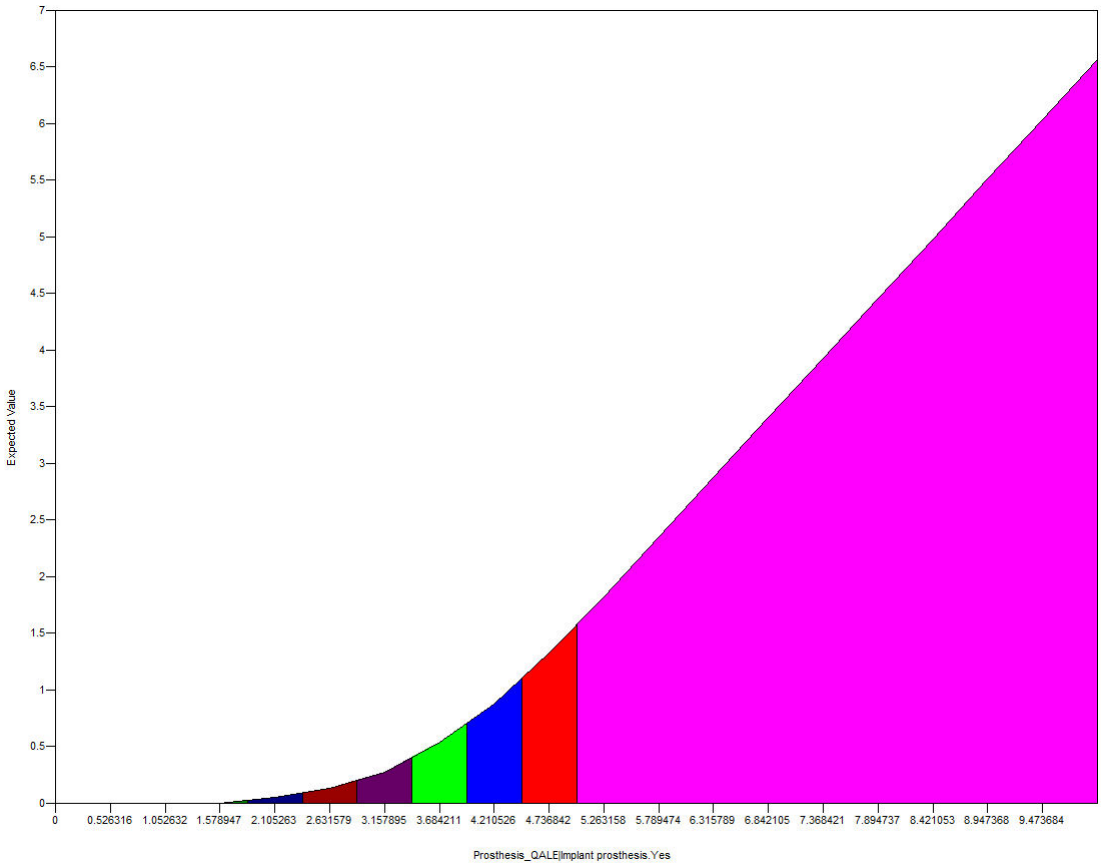

Figure A.2: Maximum-benefit - Rainbow diagram Prosthesis QALE — Implant prosthesis = Yes.

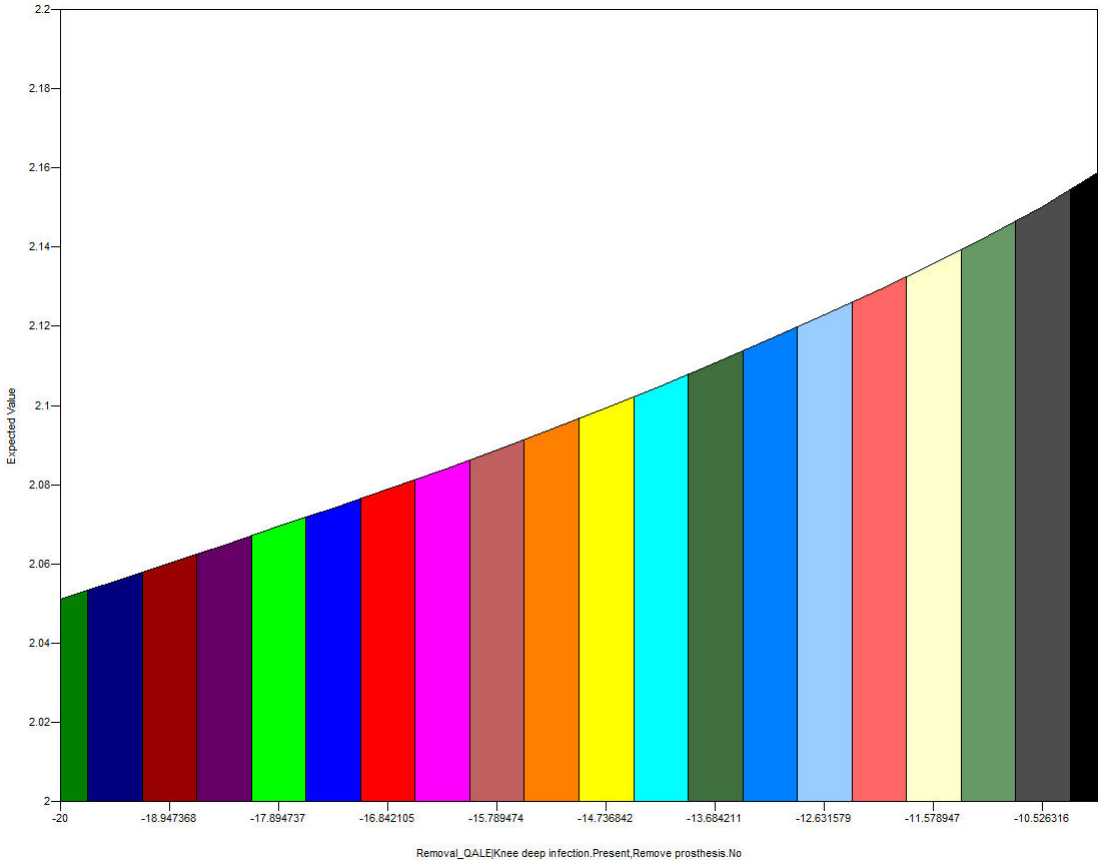

Figure A.3: Maximum-effectiveness - Rainbow diagram Removal QALE — Knee deep infection = Present, Remove prosthesis = No.

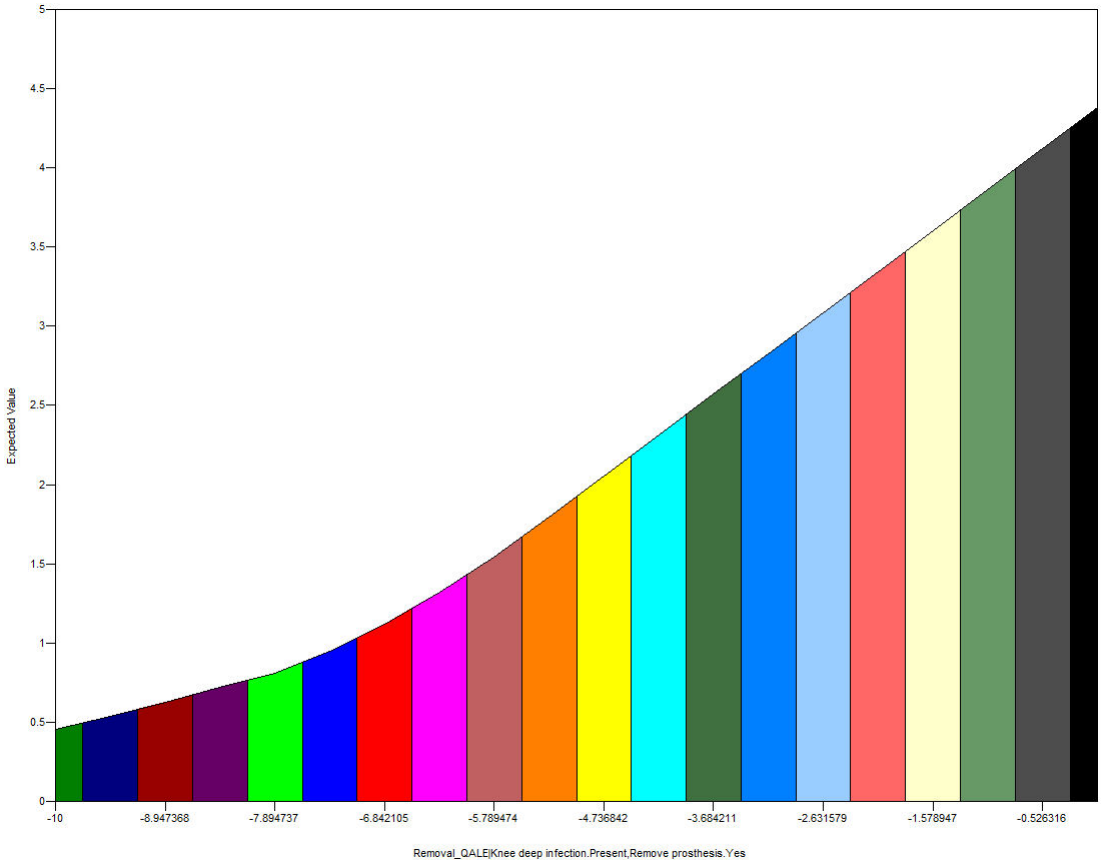

Figure A.4: Maximum-effectiveness - Rainbow diagram Removal QALE — Knee deep infection = Present, Remove prosthesis = Yes.

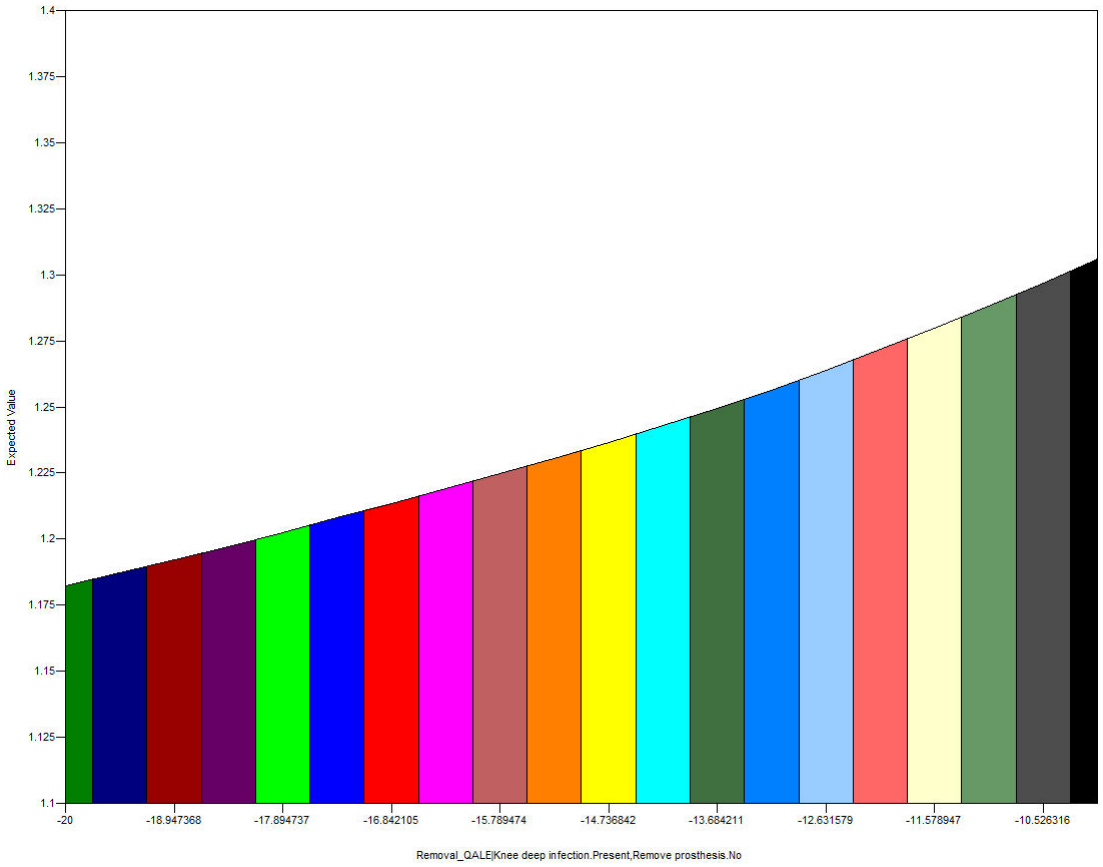

Figure A.5: Maximum-benefit - Rainbow diagram Removal QALE — Knee deep infection = Present, Remove prosthesis = No.

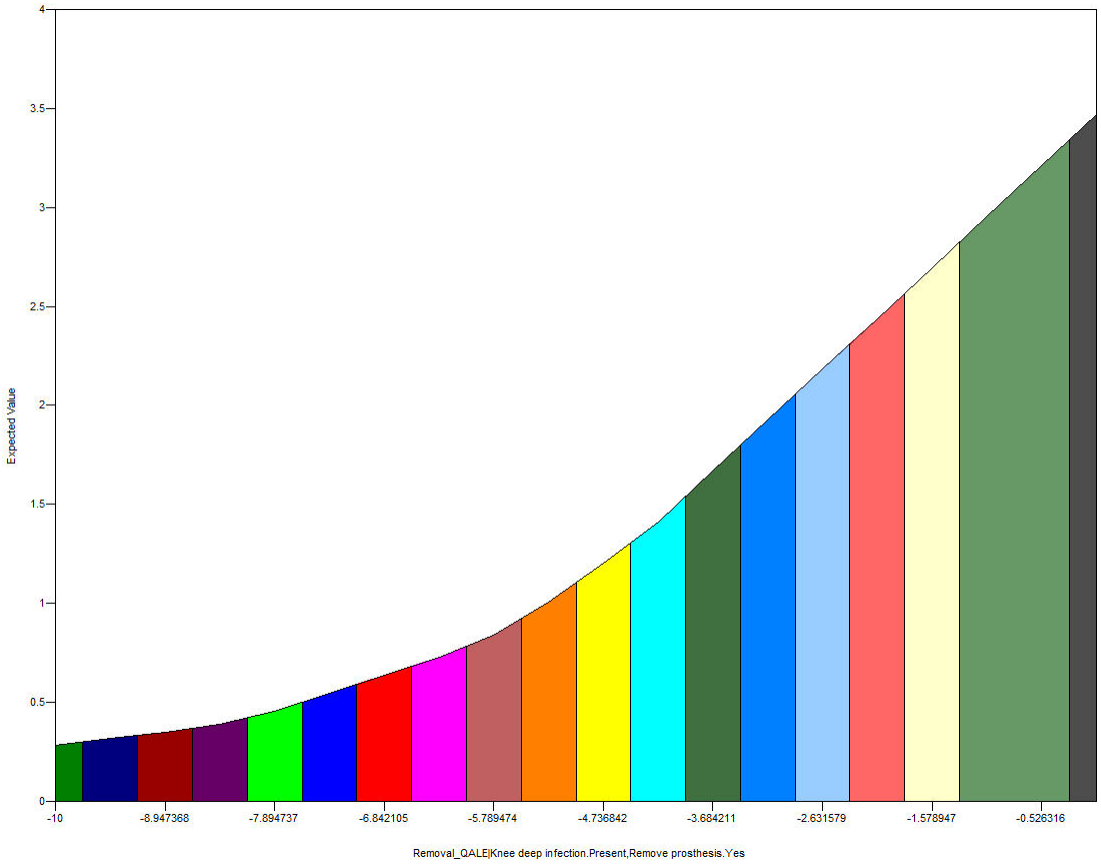

Figure A.6: Maximum-benefit - Rainbow diagram Removal QALE — Knee deep infection = Present, Remove prosthesis = Yes.

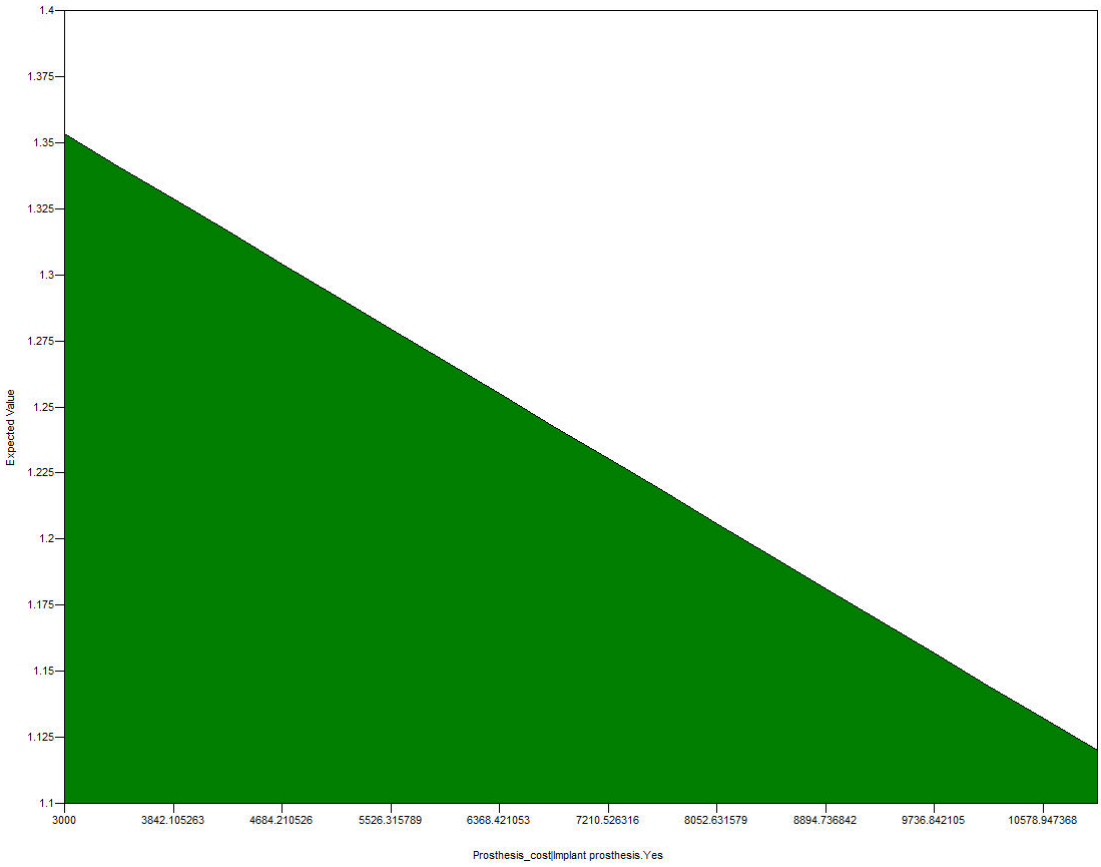

Figure A.7: Maximum-benefit - Rainbow diagram Prosthesis cost — Implant prosthesis = Yes.

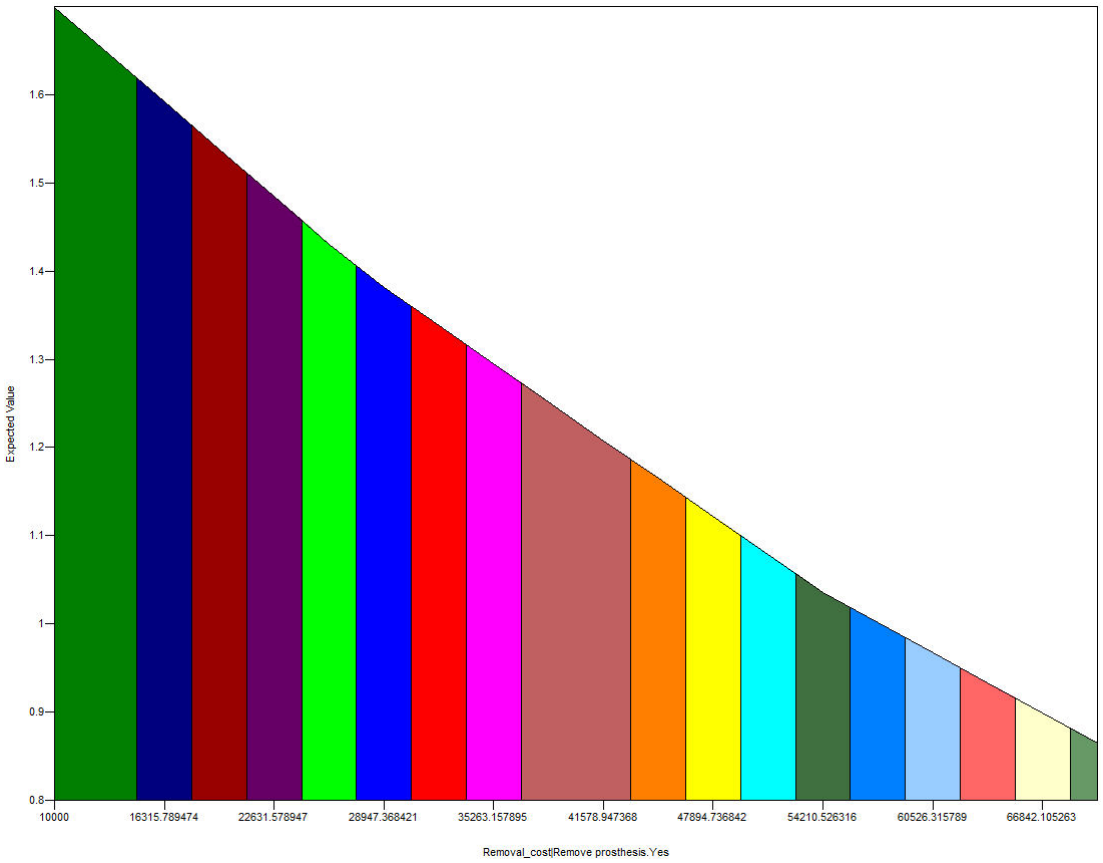

Figure A.8: Maximum-benefit - Rainbow diagram Removal cost — Remove prosthesis = Yes.

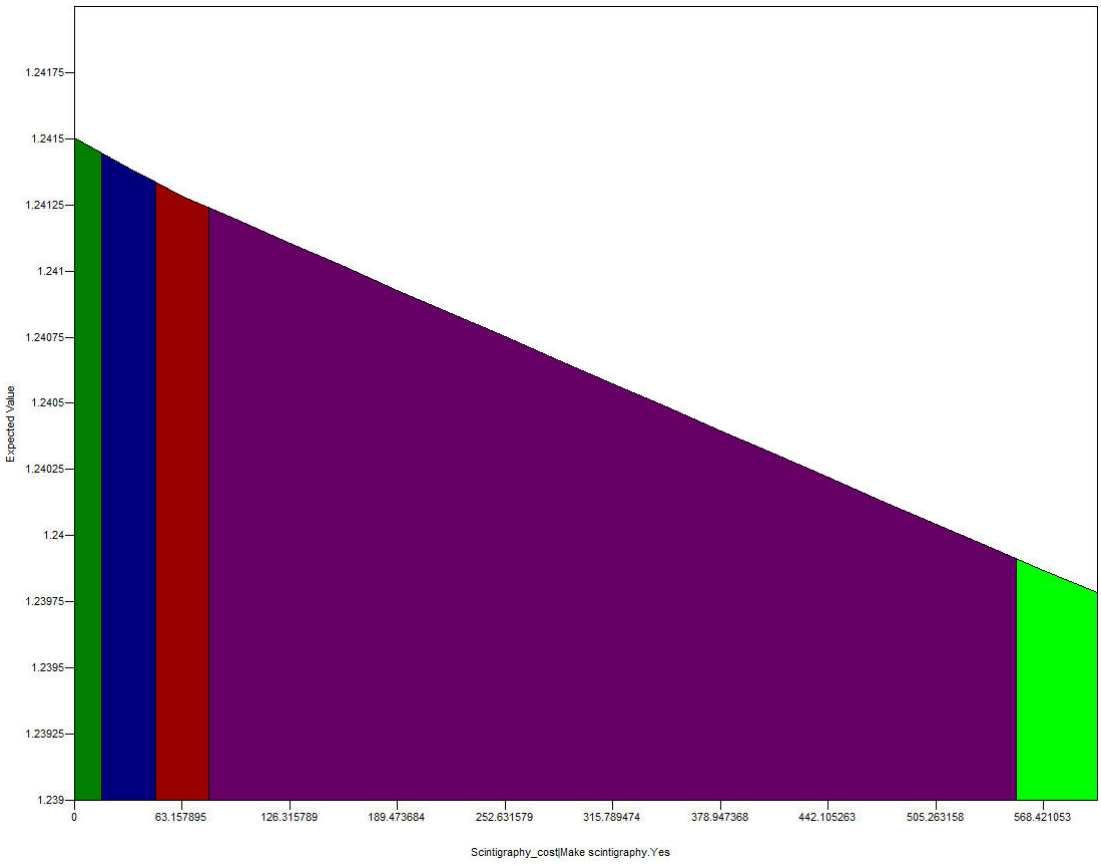

Figure A.9: Maximum-benefit - Rainbow diagram Scintigraphy cost — Make scintigraphy = Yes.

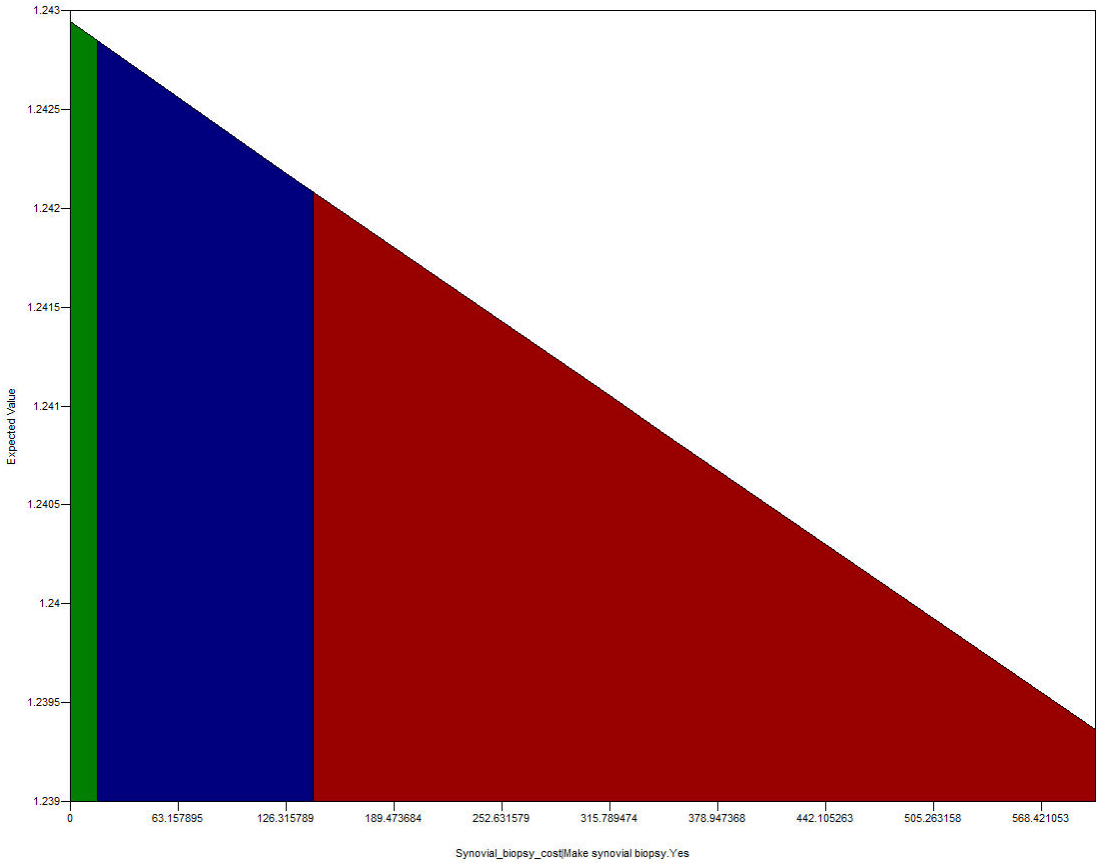

Figure A.10: Maximum-benefit - Rainbow diagram Synovial biopsy cost — Make synovial biopsy = Yes.

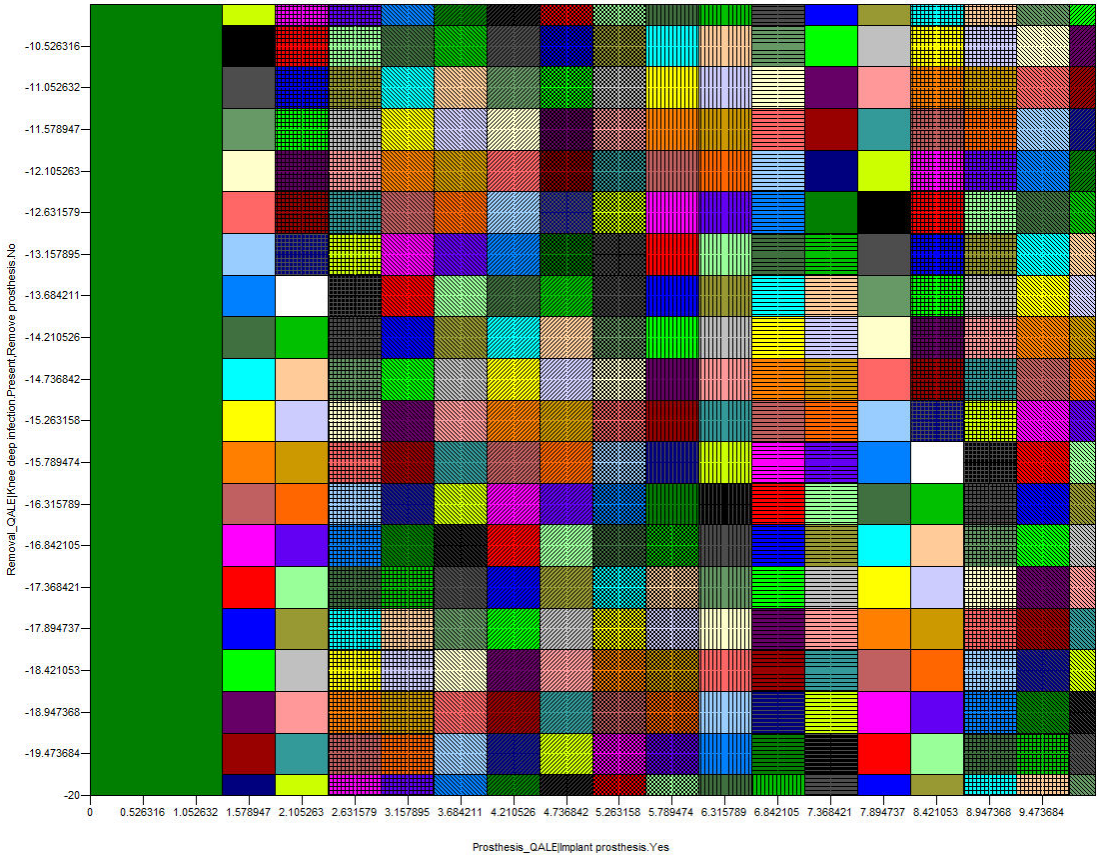

Figure A.11: Maximum-effectiveness Two-way rainbow diagram Prosthesis QALE — Implant prosthesis = Yes vs. Removal QALE — Remove prosthesis = No.

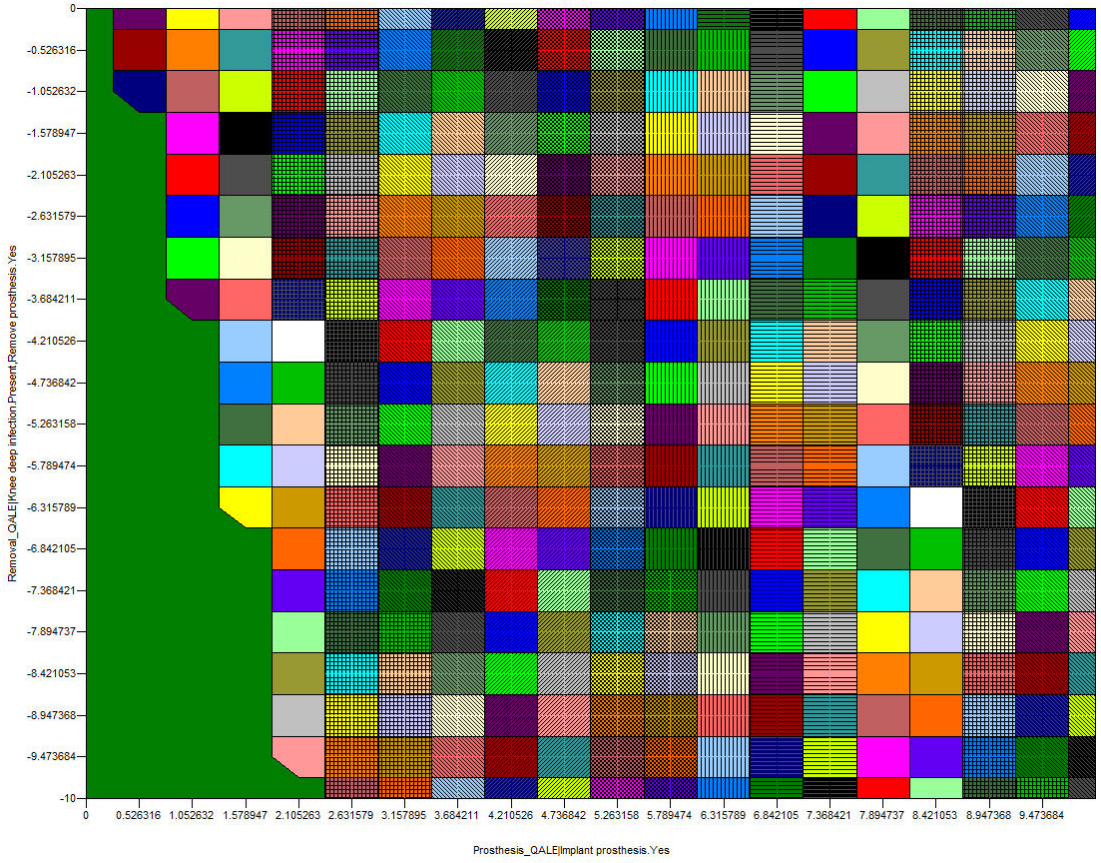

Figure A.12: Maximum-effectiveness Two-way rainbow diagram Prosthesis QALE — Implant prosthesis = Yes vs. Removal QALE — Remove prosthesis = Yes.

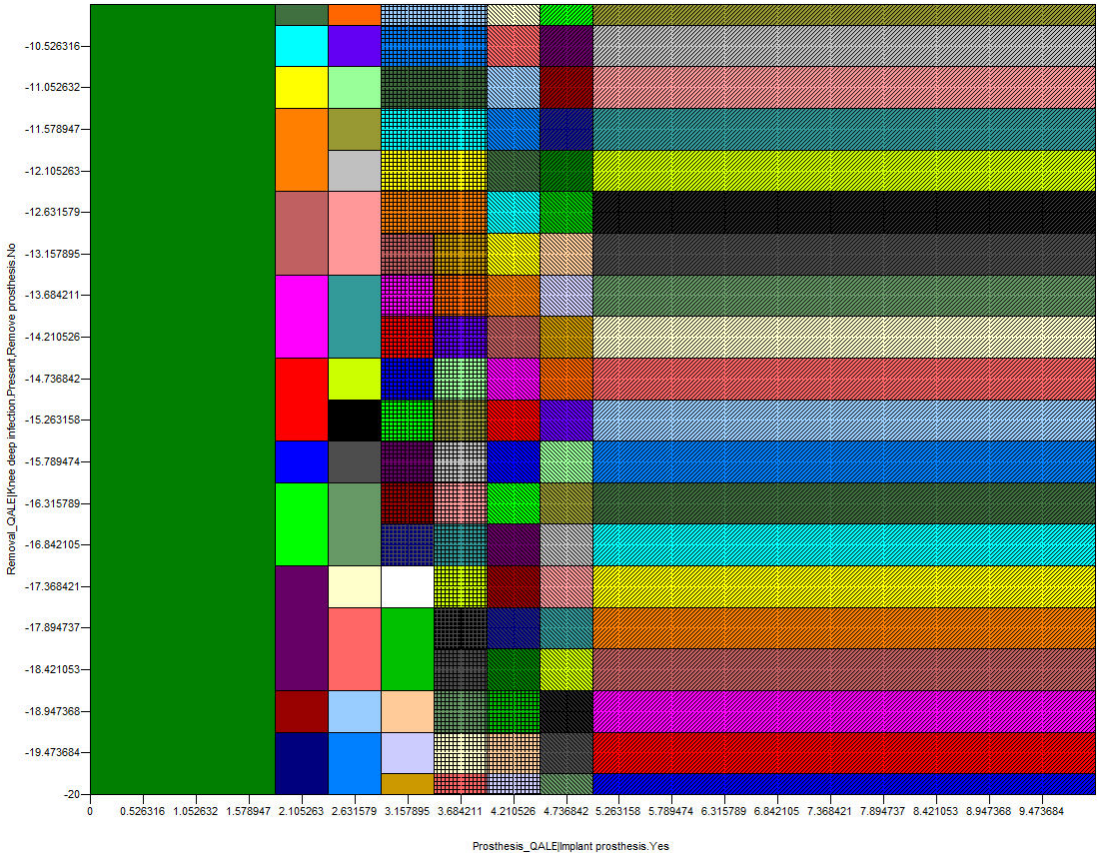

Figure A.13: Maximum-benefit Two-way rainbow diagram Prosthesis QALE — Implant prosthesis = Yes vs. Removal QALE — Remove prosthesis = No.

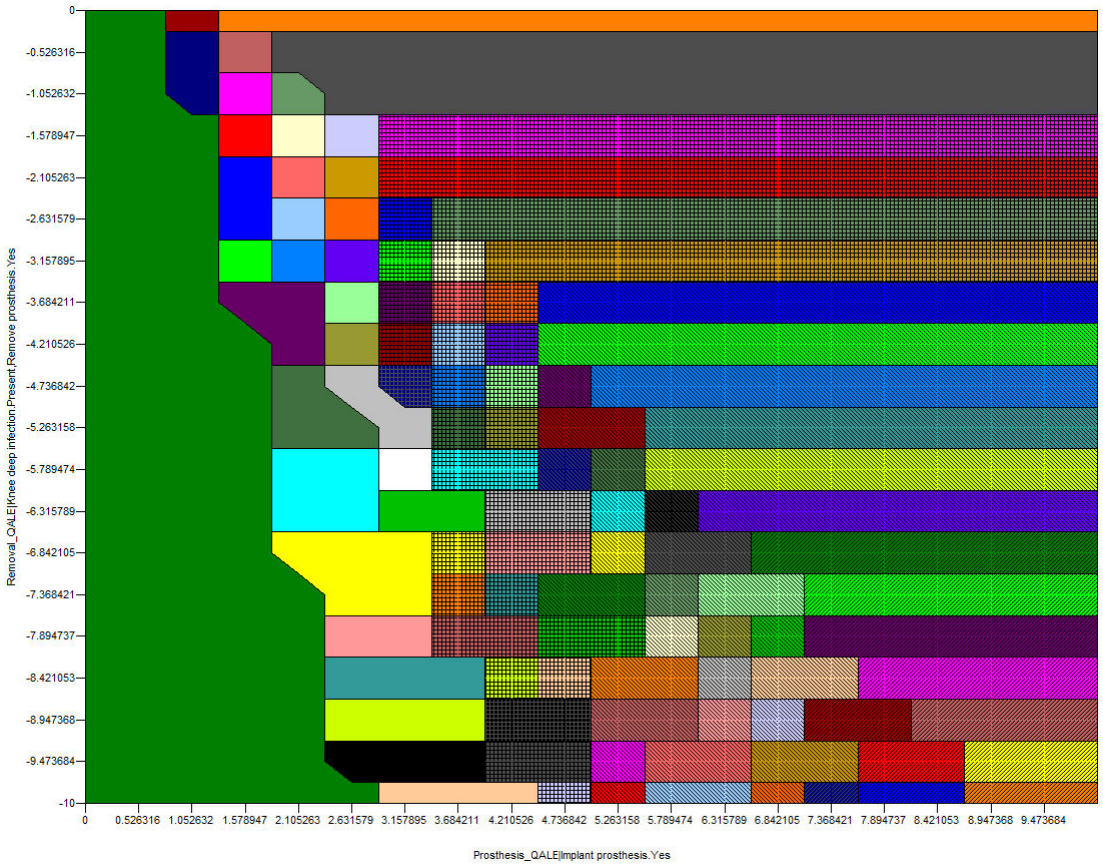

Figure A.14: Maximum-benefit Two-way rainbow diagram Prosthesis QALE — Implant prosthesis = Yes vs. Removal QALE — Remove prosthesis = Yes.

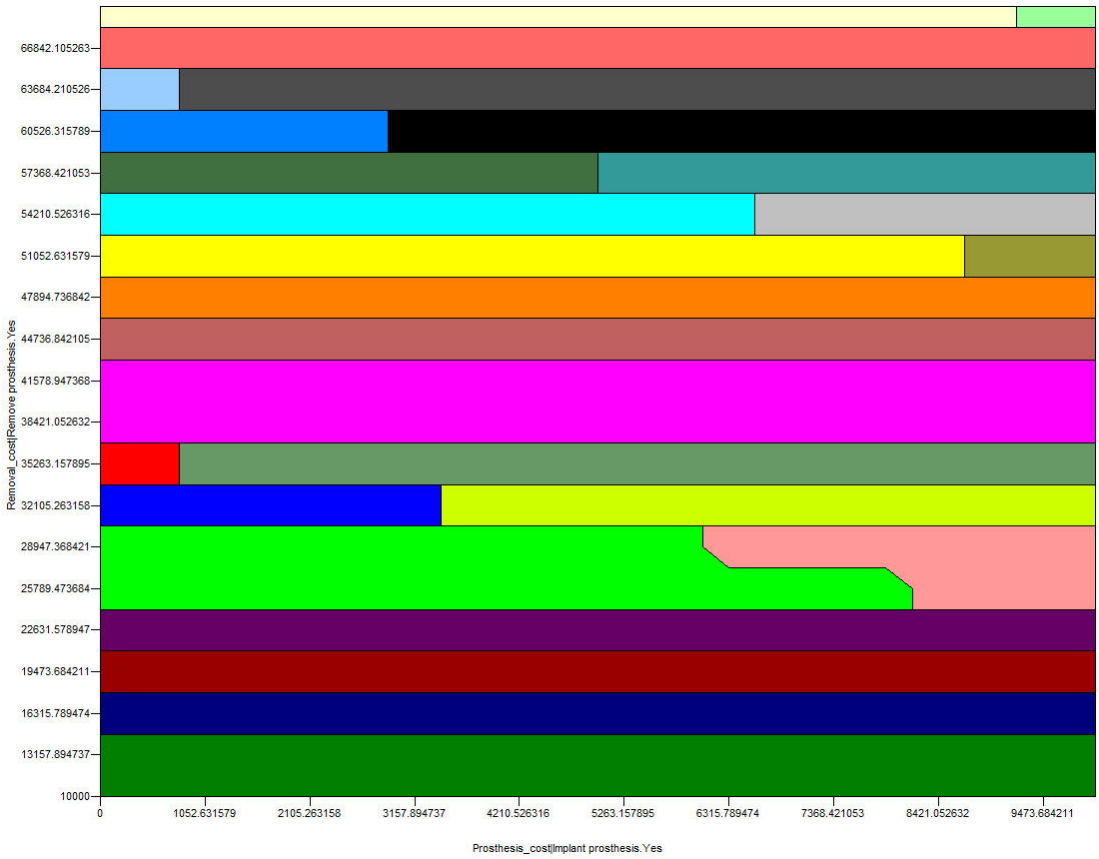

Figure A.15: Maximum-benefit Two-way rainbow diagram Prosthesis cost — Implant prosthesis = Yes vs. Removal cost — Remove prosthesis = Yes.

Appendix B

Resumen en español (Summary in spanish)

B.1 Motivación

Los modelos gráficos probabilísticos (MGP), en particular las redes bayesianas y los diagramas de influencia, fueron desarrollados en los años 80 por investigadores del campo de Inteligencia Artificial, Matemáticas y Economía con el propósito de resolver problemas cuya complejidad excede la capacidad de los métodos existentes hasta entonces. Hoy en día los MGP son aplicados a muchas áreas y existe un interés creciente en el campo académico y en el mundo empresarial. Los MGP permiten resolver problemas que no podrían ser abordados con los métodos probabilísticos tradicionales o con otras técnicas de Inteligencia Artificial.

Varios grupos de investigación españoles interesados en los MGP fueron surgiendo de forma independiente en diferentes universidades. El trabajo en MGP en la UNED comenzó en 1990 con la tesis doctoral de (Díez, 1994), que consistió en la construcción del sistema experto DIAVAL, una red bayesiana para el diagnóstico de enfermedades cardíacas por ecocardiografía.

La investigación del grupo CISIAD (Centro de Investigación sobre Sistemas Inteligentes de Ayuda a la Decisión)[1] siempre ha estado guiada por problemas médicos concretos: las necesidades surgidas al construirlos han motivado el desarrollo de nuevos modelos, algoritmos, y herramientas software, que posteriormente

[1]Centro dependiente de la UNED.

han sido aplicados a otros problemas, no solamente en medicina.

El principal objetivo de esta investigación fue la construcción de un diagrama de influencia para realizar un análisis coste-utilidad del proceso clínico de la artroplastia total de rodilla.

La principal motivación para construir este diagrama fue confirmar dos suposiciones del especialista que ha colaborado en esta investigación, el Dr. Rubén García Fraile, y que son las siguientes:

1. Los principales factores de riesgo a la hora de sufrir una infección peri-operatoria tras una artroplastia total de rodilla son: (1) un índice de masa corporal (IMC) elevado, (2) ser diabético (diabetes mellitus) y (3) ser alérgico a los antibióticos.

2. Para aquellos pacientes con los tres factores de riesgo anteriormente mencionados presentes, la artroplastia conducirá a una pérdida elevada de calidad de vida y de dinero, debido a que si la infección está presente la retirada de la prótesis es necesaria.

B.2 Objetivos

Debido a las necesidades planteadas en la sección previa, los objetivos de esta investigación pueden resumirse en:

1. Construir un diagrama de influencia con nodos super-valor representando el proceso clínico de la artroplastia total de rodilla y el diagnóstico de la infección peri-operatoria de la prótesis, que hemos llamado ArthroNET.

2. Evaluar este diagrama.

B.3 Metodología

La metodología seguida para alcanzar los objetivos se divide en tres fases, como se muestra en la Figura B.1.

La primera fase consiste en la construcción del diagrama de influencia ArthroNET, con la ayuda del cirujano especialista en traumatología y ortopedia citado en la Sección B.1. La segunda fase fue la validación del sistema, que condujo a la

Figure B.1: Fases del desarrollo de esta investigación.

modificación del diagrama con la ayuda del especialista en un proceso iterativo. Finalmente, pudimos evaluar el modelo y extraer algunas conclusiones.

B.4 Organización de la investigación

Esta memoria está estructurada en cuatro partes:

1. Parte I: se explica la motivación, objetivos y metodología de este trabajo.
2. Parte II: se revisa el estado del arte de dos tipos de sistemas de soporte a la toma de decisiones: (1) aquellos relacionados con las artroplastias totales de rodilla y (2) aquellos aplicados en el campo de la medicina que están basados en diagramas de influencia.
3. Parte III: se presenta el sistema de soporte a la toma de decisión para el diagnóstico de la infección peri-operatoria de la artroplastia total de rodilla.
4. Parte IV: se muestran las conclusiones y el trabajo futuro.

B.5 Principales contribuciones

Primeramente, hemos revisado el estado del arte de dos tipos de sistemas de soporte a la toma de decisiones: (1) aquellos relacionados con las artroplastias totales de rodilla y (2) aquellos aplicados en el campo de la medicina que están basados en diagramas de influencia.

También hemos construido un diagrama de influencia, ArthroNet, un sistema de soporte a la toma de decisión para el diagnóstico de la infección peri-operatoria de la artroplastia total de rodilla. El parámetro λ, que en análisis coste-efectividad representa la cantidad de dinero que el decisor está dispuesto a pagar para obtener una unidad de efectividad, ha sido incluido en el diagrama de influencia mediante

la introducción de un nodo de utilidad que representa $-1/\lambda$ (nodo *C2E* - ver Figura 3.8). Hemos evaluado el diagrama de influencia con $\lambda' = 0$, lo que hace que el beneficio de salud de la red coincida con la efectividad (ver Ecuación 3.4), omitiendo los costes económicos. Después, se ha evaluado de nuevo el diagrama con $\lambda = 30.000€/\text{QALY}$, que es aceptado como la equivalencia coste-efectividad en la "sombra" en España (Sacristán et al., 2002).

Para los ocho pacientes infectados mencionados en la sección 3.7 (de entre una población de 25 candidatos a la artroplastia total de rodilla), y en términos absolutos de salud y económicos, el modelo predijo de forma pre-operatoria un riesgo elevado de infección en tres de ellos, basándose en la presencia de obesidad y/o diabetes y/o alergia a antibióticos; y de forma post-operatoria una elevada probabilidad de infección en los otros cinco pacientes, basándose en los signos clínicos intra-operatorios. Las ocho infecciones se confirmaron posteriormente en quirófano, cuando fueron necesarias sus extracciones.

Esta herramienta no pretende excluir a ningún paciente de la artroplastia total de rodilla, pero sí dotar tanto al cirujano como al paciente de una estimación de los riesgos para la salud y las probabilidades de fallo del implante. La selección del paciente correcto incluye otros innumerables factores, la mayoría de ellos no cuantificables, como la personalidad o características sociales del paciente, su autosuficiencia, salud mental, cuidado personal, capacidad de comprender el tratamiento y el cuidado de la prótesis, disposición a la rehabilitación, etc.

En conclusión, nuestra experiencia demuestra que ArthroNET ha proporcionado: (1) una pauta razonable de las alternativas de diagnóstico y tratamiento en el proceso clínico, y (2) una predicción correcta de los procesos infecciosos en 8 casos de entre una población de 25 pacientes, con un acierto del 100%.

B.6 Trabajo futuro

A continuación se exponen algunas líneas futuras de trabajo.

Con respecto a la explicación del razonamiento en diagramas de influencia, encontrar algún método que pudiera ayudar a explicar al experto qué variables tienen más influencia en la estrategia óptima y en la máxima utilidad esperada.

En relación con la aplicación de ArthroNET tenemos tres líneas de investigación sugeridas por el especialista:

- Modelar la evolución del implante a lo largo del tiempo.
- Añadir más factores de riesgo al modelo, como la artritis reumatoide.
- Incluir en el modelo los organismos bacteriológicos responsables de las infecciones.

Además, se hace necesario un análisis de sensibilidad más preciso; sería deseable conocer los puntos precisos en los que las políticas óptimas cambian. Además, debería realizarse un análisis de sensibilidad sobre aquellos parámetros del modelo que el software DPL no permite evaluar.

Por otra parte, el autor pretende continuar este estudio en una tesis doctoral, incluyendo la implementación del modelo en OpenMarkov, una herramienta gratuita para modelos gráficos probabilistas, como redes bayesianas, diagramas de influencia y modelos de Markov, desarrollado por el CISIAD[2] (Centro de Investigación sobre Sistemas Inteligentes de Ayuda a la Decisión)[3].

[2]http://www.cisiad.uned.es
[3]Centro dependiente de la UNED.

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