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Automatic Production and Integration of Knowledge to the Support of the Decision and Planning Activities in Medical-Clinical Diagnosis, Treatment and Prognosis

John A. Bohada

UNIVERSITAT POLITÈCNICA DE CATALUNYA

Supervisor:

Dr. David Riaño Ramos
Universitat Rovira i Virgili

Tutor:

Dr. Ulises Cortés
Universitat Politècnica de Catalunya

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**Automatic Production and Integration of Knowledge to
the Support of the Decision and Planning Activities in
Medical-Clinical Diagnosis, Treatment and Prognosis**

John A. Bohada

Dedicated to

My wife and my family, for always being there.
A mi esposa y a mi familia, por estar siempre ahí.

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Abstract

The concept of medical procedure refers to the set of activities carried out by the health care professionals to solve or mitigate the health problems that affect a patient. Decision making within a medical procedure has been, for a long time, one of the most interesting research areas in medical informatics and the research context of this thesis. The motivation to develop this research work is based on three main aspects: Nowadays there are not knowledge models for all the medical-clinical activities that can be induced from medical data, there are not inductive learning solutions for all the medical-clinical activities, and there is not an integral model that formalizes the concept of medical procedure. Therefore, our main objective is to develop a computable model based in knowledge that integrates all the decision and planning activities for the medical-clinical diagnosis, treatment and prognosis.

To achieve this main objective: first, we explain the research problem. Second, we describe the background of the work from both the medical and the informatics contexts. Third, we explain the development of the research proposal based on four main contributions: a novel knowledge representation model, based in data, to the planning activity in medical-clinical diagnosis and treatment; a novel inductive learning methodology to the planning activity in diagnosis and medical-clinical treatment; a novel inductive learning methodology to the decision activity in medical-clinical prognosis, and finally, a novel computable model, based on data and knowledge, which integrates the decision and planning activities of medical-clinical diagnosis, treatment and prognosis.

Resumen

El concepto de procedimiento médico se refiere al conjunto de actividades seguidas por los profesionales de la salud para solucionar o mitigar el problema de salud que afecta a un paciente. La toma de decisiones dentro del procedimiento médico ha sido, por largo tiempo, uno de las áreas más interesantes de investigación en la informática médica y el contexto de investigación de esta tesis. La motivación para desarrollar este trabajo de investigación se basa en tres aspectos fundamentales: no hay modelos de conocimiento para todas las actividades médico-clínicas que puedan ser inducidas a partir de datos médicos, no hay soluciones de aprendizaje inductivo para todas las actividades de la asistencia médica y no hay un modelo integral que formalice el concepto de procedimiento médico. Por tanto, nuestro objetivo principal es desarrollar un modelo computable basado en conocimiento que integre todas las actividades de decisión y planificación para el diagnóstico, tratamiento y pronóstico médico-clínicos.

Para alcanzar el objetivo principal, en primer lugar, explicamos el problema de investigación. En segundo lugar, describimos los antecedentes del problema de investigación desde los contextos médico e informático. En tercer lugar, explicamos el desarrollo de la propuesta de investigación, basada en cuatro contribuciones principales: un nuevo modelo, basado en datos y conocimiento, para la actividad de planificación en el diagnóstico y tratamiento médico-clínicos; una novedosa metodología de aprendizaje inductivo para la actividad de planificación en el diagnóstico y tratamiento médico-clínico; una novedosa metodología de aprendizaje inductivo para la actividad de decisión en el pronóstico médico-clínico, y finalmente, un nuevo modelo computable, basado en datos y conocimiento, que integra las actividades de decisión y planificación para el diagnóstico, tratamiento y pronóstico médico-clínicos.

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Part I

Introduction

Chapter 1

Introduction

The concept of medical procedure refers to the set of activities carried out by the health care professionals to solve or mitigate the health problem that affects a patient. For a long time, decision making within medical procedures has been one of the most interesting research areas in medical informatics and the research context of this thesis. The motivation behind this research is centred in the modelling and the integration of the decision and planning activities in medical-clinical diagnosis, treatment and prognosis for decision making support in medicine.

1.1 Research Context

The health care professionals who attend a patient affected by one or more diseases must decide about the best medical-clinical attention that helps to improve, stabilize or delay the worsening of patient health. This attention begins with the application of diagnostic techniques and continues with the selection and adaptation of a concrete treatment. Likewise, the realization of a prognostic to determine the patient's evolution according to the followed treatment allow us, if it is required, to make the appropriate adjustments for giving the best medical-clinical attention. Through the last decades, multiple computer based tools have been developed with the purpose of improving these activities. These tools are developed to give the health care professionals an alternative focus in the process of decisions making in medical assistance, particularly in the decision and planning activities in diagnosis, treatment and prognosis. This is the case of the medical decision support systems (MDSS) [Coi03, MamS06, LW06, Gre07, Har09], where advances resulting from disciplines such as decision theory, mathematics, statistics and artificial intelligence, have allowed its development during the last decades. An example of these advances in artificial intelligence is inductive learning. *Inductive learning* consists in inferring general descriptions (knowledge) from a

set of observed instances (data). So, the inductive learning algorithms are based in a data model to be processed and in a model of knowledge to be generated. The use of learning algorithms in medicine must therefore be based in models capable of representing data and knowledge about medical-clinical diagnosis, treatment and prognosis. These models can be different depending on whether the activity made by the health care professionals is of the kind decision or planning.

The *decision activities* are made when a health care professional issues a definitive judgement on the health of a patient and they are based in the available information of that patient. So, the medical-clinical data about a patient allow the health care professional to conclude what particular disease that patient has (i.e, diagnosis), what specific therapy that patient should follow (i.e., treatment), and whether a therapy is applied, what the expected evolution is (i.e., prognosis). Otherwise, when there is not enough information available about the patient or about his/her disease to reach a conclusion about the patient diagnosis or treatment, the health care professional should start some *planning activities* which allow to organize the action sequences to be adopted in order to end in a diagnostic or a treatment decision.

Both activities (decision and planning) for diagnosis, treatment and prognosis are mutually related and they are part of the medical procedure. In medical assistance, the concept of *medical procedure* consists in a set of medical-clinical activities carried out for the care of a specific patient. The ways in which these activities are structured define the medical procedure applied to that patient. So, the medical procedure is defined as the model used by health care professionals to solve or mitigate the health problem that the patient has. The formalization of the medical procedure in terms of the activities previously mentioned allows us to gradually increase the automation of medical assistance through inductive learning algorithms. This medical procedure automation through the use of intelligent computer systems can be used by the health care professionals as an integral tool of medical decision support.

1.2 Research Motivations

The motivation of this doctoral thesis is based in the following issues:

- Nowadays there are not knowledge models for all the medical-clinical activities that can be induced from medical data.
- So far, there are not inductive learning solutions for all the medical-clinical activities.

- In the medical informatics context, there is not an integral model that formalizes the concept of medical procedure.

The resolution of these three deficiencies redounds in a clear contribution to formalize and automate the medical assistance.

1.3 Research Objectives

The main objective of this PhD thesis is to develop a computable model based in knowledge that integrates all the decision and planning activities for medical-clinical diagnosis, treatment and prognosis.

For achieving this general objective, the following specific objectives are proposed:

1. Propose a knowledge-based model for the planning activity in the medical assistance
2. Develop and integrate inductive learning methods that allow solving planning problems in medical-clinical diagnostic and treatment.
3. Develop and integrate inductive learning methods that allow solving decision problems in medical-clinical diagnosis, treatment and prognosis.
4. Propose a formal model to represent medical procedures that integrates the decision and planning activities to medical-clinical diagnosis, treatment and prognosis.
5. Propose a functional model based in knowledge that automates the formal model of medical procedures previously proposed.

1.4 Research Contributions

The main contributions of this PhD thesis are:

- Proposal of a knowledge representation model for the planning activity in medical assistance.
- Development of a method to automatically generate knowledge for the planning activity in medical-clinical diagnosis and treatment.
- Development of a method to automatically generate knowledge for the decision activity in medical-clinical prognosis.

- Proposal of an integral, computable and knowledge based model that helps in the automation of medical procedures for the decision and planning activities in medical-clinical diagnosis, treatment and prognosis. This model integrates different learning methods that support decision making in medical assistance from two different situations:
 1. When the available information of the patient is sufficient for decision making. In this case, the model proposes a value or a label indicating the disease (i.e., diagnosis), the therapy (i.e., treatment), or the patient evolution if the therapy has been applied (i.e., prognosis).
 2. When the available information of the patient is not sufficient for decision making. In this case, the model is able to automatically build action plans to find the patient's diagnosis, and after the patient has been diagnosed, obtain or adjust his/her treatment. In this sense, these action plans can be used to support the health care professionals to program the actions that are aimed at achieving a correct diagnosis and an adequate treatment.

1.5 Document Organization

This document has three main parts. The first part (Introduction) explains the research problem. The second part (State of Art) describes the background of the problem in two chapters: chapter 2 and 3. Chapter 2 describes the medical context of this document. The medical context description begins with the introduction of main activities that medical assistance has and how they are used in a medical procedure for decision making in medicine. Then, the features, limitations and problems related to the decision making process in medical assistance are specified. After that, the main technologies for decision making support in medical assistance are introduced. Finally, the conclusions of this chapter are presented. Chapter 3 explains the formalization of knowledge in medical assistance. This formalization begins with an introduction to the main categories of knowledge in medical assistance. After that, the main formalisms of knowledge representation in medical assistance are detailed. Next, a description of the main machine learning methods used in the process of inducing useful knowledge for decision making support in medical assistance are described. Finally, the conclusions of this chapter are presented.

Part three (Modelling of a Holistic Architecture for the Diagnosis, Treatment and Prognosis in Medicine) describes the development of the research proposal of this thesis, this description is

detailed in four chapters: Chapter 4, 5, 6 and 7. Chapter 4 introduces a novel model, based in data, to represent know-how knowledge in the medical assistance. This model called the SDA (State Decision and Action) model is presented as an alternative to the current representation models of this sort of knowledge. Chapter 5 presents a novel methodology for the know-how knowledge automatically generation in the medical assistance. This learning methodology is based in the SDA representation model, introduced in the previous chapter. Chapter 6 presents a novel methodology for the automatic generation of know-what knowledge for medical-clinical prognosis. This learning methodology is based in partial orders that together with state-transition diagrams, allows predicting several medical events simultaneously (improve, worsen, cure, death and survival). Chapter 7 presents the proposal of a knowledge based model which integrate the decision and planning activities for medical-clinical diagnosis, treatment and prognosis.

Finally, part four (Conclusions) composed by chapter 8, the conclusions of this thesis are described. These conclusions are organized as limitations and future work, main contributions and final conclusion.

Part II

State of the Art

Chapter 2

The Medical Assistance

This chapter presents a general description about what is medical assistance. The description is structured in three sections. The first section introduces the concept of medical assistance, defines its three principal activities: medical-clinical diagnosis, treatment and prognosis, and explains how these activities are integrated in the medical procedure nowadays. The second section describes the aspects used for medical assistance decision making: medical skills, medical knowledge and medical reasoning. It also includes medical reasoning limitations and the problems derived from the uncertainty and the variability in medicine. Finally, it presents a classification of the principal techniques developed to offer support to decision making in medical assistance. The classification is based on the following aspects: techniques based in protocols and clinical practice guidelines, classification and encoding systems of medical data, decision making support systems based in decision theory, maths and statistics, and decision making support systems based in artificial intelligence.

2.1 Introduction

Medical assistance is the process of medical intervention which is related to provide some attention to the patient health care. Its components are data and medical information, perceptions, reasoning, judgments and decisions of the health care professionals, the procedures used and the interventions applied. This process begins when a patient suffering from an ailment is attended by a health care professional, or, when the patient is submitted to a control or monitoring routine visit. The process continues until the patient is discharged from the hospital, because the procedures have led either to a total or partial cure or stabilization that do not involve high risks for his/her health [Gre07, Har09]. Also, there are too many situations in which, due to the complexity or seriousness of illness, the procedures realized do not determine a good expectation in the patient health evolution,

forcing in some cases to incorporate new procedures that improve his/her quality of life.

Medical assistance depends on whether the activity made by the health care professional is about decision or planning. *Decision activities* are realized when a health care professional issues a definitive judgment about a patient's health based on the available information about that patient. For that reason, the medical-clinical data of a patient allows the health care professional to conclude what particular disease that patient has (i.e., diagnosis), what specific therapy he must follow (i.e., treatment), and if a therapy is applied, what is the expected outcome (i.e., prognosis). Otherwise, when there is a lack of information about the patient or his/her disease to reach a definitive decision, the health care professional needs to realize *planning activities* that will allow him to organize a sequence of actions which will lead to a diagnostic or treatment decision.

The integration of medical activities considering decision and planning for the diagnostic, treatment and prognostic in medical assistance is structured following a medical procedure which represents how the health care professionals act in the process of medical-clinical decisions making.

2.1.1 Medical-Clinical Diagnosis

Medical-clinical diagnosis is the central act of medicine. The word diagnosis is used in two senses: on the one hand, it's the process by which the health care professional begins when he wants to know the state of a particular patient and, on the other hand, it's the result of the knowledge acquired by the health care professional as consequence of the above process [Roz06]. So, in order to make a medical-clinical diagnosis, the health care professionals observe the data provided by three main resources [Har09]: information elicitation (or anamnesis), physical examination and diagnostic tests. *Information elicitation* is the inquiry by the health care professional of the available patient's medical information. This information includes the patient's perception of their *symptoms*, the medical history, the family history and other aspects that the health care professional thinks are important. *Physical examination* allows through senses: sight-inspection, touch-palpation, hear-auscultation, smell-olfaction, to determine the *signs* or objective data, which include pathological and normal data of the patient. Finally, the *diagnostic tests* allow improving the available information of the patient with laboratory data. These diagnostic tests usually confirm or discard a specific disease before beginning a treatment.

Given the way of making a diagnostic procedure or diagnostic test, the medical-clinical diagnostic can be classified in: differential diagnostic, clinical diagnostic and histological diagnostic. *Differential diagnostic* is based in a set of diseases which can cause a syndrome, discarding one by

one the possible diseases by taking into account the proposed hypothesis and the complementary explorations, until only the most feasible disease that can cause the patient symptoms remains. *Clinical diagnostic* is established through the anamnesis, the physical and complementary examinations (except those of pathological anatomy) to determine the patient disease. Finally, *histological diagnostic* is obtained through non-routine diagnostic tests (e.g., a biopsy¹), being it, the definitive diagnostic in complex diseases as cancer.

2.1.2 Medical-Clinical Treatment

Medical-clinical treatment or therapy of a disease can be defined as a temporal sequence of medical actions, such as drugs prescription, lifestyles modifications, medical procedures application or other medical actions, that a health care professional can determine for a particular patient, generally as a continuation of a diagnostic activity.

Medical-clinical treatment can be classified in various guises. The first distinction considers the object of the treatment [Pee00]:causal or symptomatic treatment. *Causal treatment* aims to fight the causes of the disease, whereas the *symptomatic treatment* aims to suppress the symptoms. A second distinction is between curative or palliative treatment. *Curative treatment* intends to cure the patient completely from the disease and its underlying causes, and *palliative treatment* intends to alleviate the patient’s suffering or to prolong his duration of life. Palliative treatment is mostly symptomatic but can sometimes be classified as causal.

2.1.3 Medical-Clinical Prognosis

Medical-clinical prognosis refers to the prediction of the a disease evolution or the treatment outcomes. When the particular characteristics of a patient are being used to predict the outcomes of a disease, they are called *prognostic factors* [VH03]. A prognostic factor can be of different type: demographic (e.g., age and sex), specific about the disease (e.g., tumour size, involvement of lymph nodes or not), or comorbidities (e.g., diabetic patient). Health care professionals find out these prognostic factors in a patient through the symptomatology and some diagnostic tests.

The prognosis can be expressed both qualitatively or quantitatively. In *qualitative prognosis*, the health care professionals value these prognostics using terms as “good”, “bad” or “intermediate”, or “mild”, “moderate” or “severe”. The term *reserved prognostic* refers to an unknown or uncertain prognostic that can result in severe problems or even the patient death. In *quantitative prognosis*,

¹A biopsy is the removal of a sample of tissue from the body with diagnostic purposes.

the prognostic is made according to morbidity and mortality percentages and rates.

2.1.4 The Medical-Clinical Procedure

Medical procedure (MP) is the frame where the medical assistance activities of decisions and planning are integrated to deal with medical-clinical diagnosis, treatment and prognosis. This integration must consider and solve all the problems referred to how the medical diagnosis introduced in section 2.1.1 (differential, clinical and histological diagnostic) are related with the sorts of medical treatment introduced in section 2.1.2 (causal, symptomatic, curative and palliative treatment), and to predict how these treatments are expected to affect the evolution of the patient

The standard MP used by the health care professionals is shown in figure 2.1 [Har09, Gre07, Roz06, Kuk03a, Pee00]. This MP begins when a patient realizes about some symptoms he has or manifestations of some disease and decides to visit a health care professional. The health care professional makes a set of actions to solve the ailments which affect the patient. First, the health care professional starts carefully collecting the clinical history of the patient or *anamnesis*, in which he will inquire about *symptoms* or subjective ailments that the patient manifests. Often, at the end of anamnesis, a *suspected diagnostic* (Sd) can be deduced [Roz06].

Immediately after, secondly, the health care professional makes the *physical examination* of the patient. This physical examination will permit to find causes not detected in the anamnesis. Once the two phases finish, the health care professional will recommend, in case of being necessary, to realize *routine diagnostic tests* to confirm or discard the initial Sd. The combination of the symptoms obtained in the anamnesis, the signs obtained after a physical exploration and the available laboratory data, the health care professionals can set the patient medical frame. When this process finishes, the suspected disease becomes in a *presumption diagnostic* or provisional diagnostic (Pd), even in the *definitive diagnostic* (Dd) of the disease.

If the Pd persists, the health care professional can suggest non-routine diagnostic tests (e.g., imaging diagnostic techniques as radiography, echography, computed tomography or magnetic resonance, and other instrumental techniques such as electrocardiograms, electroencephalography, spirometry, laparoscopy, etc.), which may help him to accept or to reject that Pd, and so to reach a Dd. However, and due to the complexity of the non-routine diagnostic tests (high costs, required time, a risk possibility to the patient, pain, etc.) [Pee00], the risks and benefits of these tests are compared with the advantages and disadvantages of the possible therapeutic alternatives. This comparative work ends with a set of suggestions to the patient [Kuk03a]. According to the patient

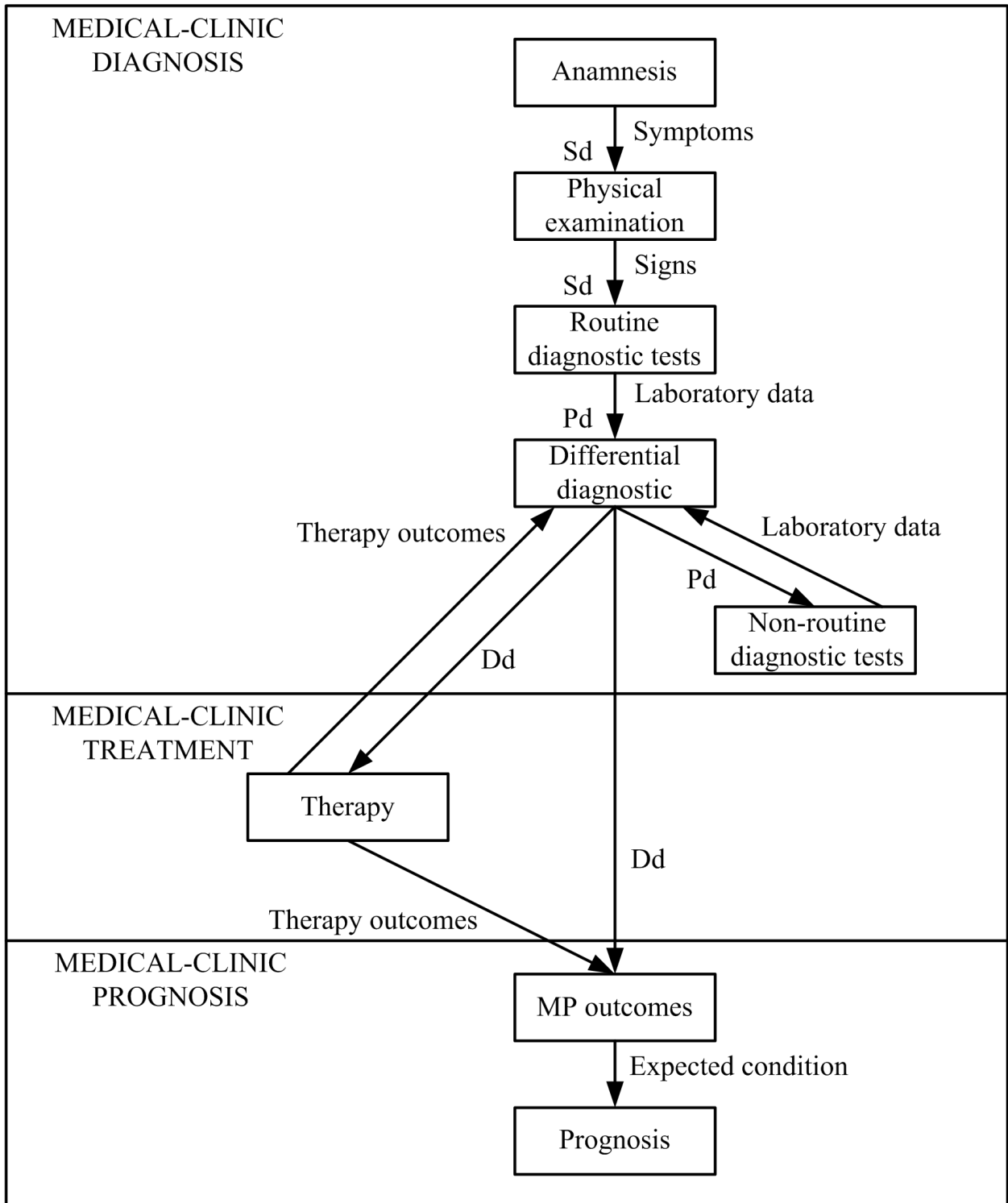


Figure 2.1: Medical procedure synthesis.

response to the proposed *therapy* and the obtained outcomes of non-routine diagnostic tests, the diagnostic process can require a reconsideration in which differential diagnosis is adjusted to the new information.

At the end of this step, the patient condition is called the *therapy outcome*, and the *expected condition* after a short or long time (typically ranging from days to a significant number of months or years) is the medical *prognosis* [Pee00]. It is common in many MP that the medical treatment has a follow-up with regular tests to monitor the patient's health. The therapy outcomes and prognoses are the most important criteria to evaluate and to determine whether the sequences of actions are right or not.

2.2 Decision Making in the Medical Assistance

Medical decisions are made during the diagnosis and medical-clinical treatment phases. These decisions involve the practice of more studies, request of consultations and decision making based on the prognostic. All of them force the health care professional to know all the pathophysiological and evolutive aspects of the disease.

Medical decisions are based in factual tests (i.e., based on evidences) so that the patients obtain the maximum benefit of the scientific knowledge available to the health care professionals [Mar07]. Planning the possibilities of a diagnostic, execution of a plan or suggesting a possible prognostic, requires not only to have a broad knowledge base, but also to consider the relative possibilities of evolution of some diseases and to know the importance of some symptoms and signs that arise less frequently. Confirmed all this, forces the health care professional to apply a *medical procedure* that allows the health care professional to collect data, to propose hypotheses and to reach objective conclusions as to whether to accept or reject a particular medical diagnostic hypothesis, to design and to execute a medical treatment plan or to determine the evolution of a disease through a medical prognostic. In this sense, the success of the decisions taken will depend of the aspects as *medical skill* against a particular situation, the *medical knowledge* available in that moment and the *medical reasoning* used against the available information.

2.2.1 Medical Skill

Skill of the health care professionals is defined as the ability to adequately address each of the decisions within the MP and it is closely related to other two aspects: medical knowledge and

reasoning. This is part of one's condition as health care professional and it is beyond the scope of this work.

2.2.2 Medical Knowledge

The meaning of medical knowledge is complex. Several studies have been developed to deepen in different aspects that influence in a better decision against to a determined medical situation [Mil94, Coc99, KF05, Har09]. These studies defend that, in case of a decision situation, an health care professional with *experience* reasons better than another one who does not have any experience, therefore they are able to realize a better selection of strategies against the decision that is going to be taken. This means that the experienced health care professionals have a better ability to combine of the different sorts of knowledge acquired from several external sources, or from their own professional formation and experience, allowing them to make wiser decisions. Examples of these sorts of knowledge are: scientific and experimental knowledge. These two sorts knowledge are the most used ones in the medical decisions making process [NS00].

In medicine, the *scientific knowledge* (or deep knowledge), includes the understanding of the scientific values and their relationship among the pathophysiological conditions and the disease symptoms. This knowledge is found in medical literature, and helps to understand and justify the empiric phenomena, explaining how these phenomena have sense in real situations. The *experimental knowledge* (or superficial knowledge), originates from the patient cases well documented and validated, allowing the evidence-based medicine. This type of knowledge helps the health care professionals to recognize a disease and proposes a medical treatment based only on their own or others experience [Coc99].

In a medical decisions making process, these two types of knowledge: scientific and experimental, can be intertwined. So, when a medical problem has to be solved, tests based on mathematics (e.g., diagnostic tests accuracy estimation [KBF⁺07]) can be based in experimental knowledge as alignments and approaches, whereas, the scientific knowledge shows, in this situation, to what extent these approximations and simplifications have sense.

Also, and not less important, explicit and tacit knowledge are used in medical decisions making [Nyk00, AKBP06]. *Explicit knowledge* is articulated in a formal language and is transmitted between the different components of the decision process. This type of knowledge corresponds to the results obtained from scientific researches and published in scientific articles, systematic reviews, protocols and clinical practice guidelines, that allow having a background knowledge necessary to decisions

making against to a particular patient. On the contrary, *tacit knowledge* describes the health care professional abilities against to a situation of decision making. This knowledge is personal, supported in the experience and based in intangible factors such as beliefs, perspectives and values. In this sense, this type of knowledge is formed by cognitive elements that refer to the mental models that the health care professional does in a particular situation of decisions making, and the technical elements that reference all the abilities and the concrete knowledge which can be applied in that particular situation.

2.2.3 Medical Reasoning

Medical reasoning is the last issue that influences the process of medical decisions making. Reasoning is the human ability to solve problems. In medicine, it's important to take into account that each health care professional may act and think different in each particular situation of decision making. For example, in medical diagnosis, a decision can be immediate whether the health care professional recognize a particular "pattern", whereas in other cases, it's necessary a complex procedure based on diagnostic tests, and even in *ex-juvantibus* treatments. In these treatments, with a medical suspicion and the seriousness of a disease, it begins a treatment, and if it's effective, the successful results can be part of the diagnostic criteria [Día04].

The types of reasoning that can be followed by health care professionals in the decision making are [SMAR97, Día04, Mar07]:

1. *Causal reasoning* or "model or pattern" recognition. This type of reasoning is based in the physiology or cause-effect relation between medical variables. The causal model can be defined as a description of anatomical, physiological and biochemical mechanisms which can be used for stimulating the normal function of the human body, according to the pathophysiological behaviour of the disease and the idiosyncrasies of each particular patient.
2. *Deterministic reasoning*. In this type of reasoning, the health care professional is limited to follow some predetermined and proposed steps, first, he is focusing on the recognition of some medical data and then, indicating certain medical tests. According to the results obtained, he will continue with the proposed steps.
3. *Heuristic reasoning*. This reasoning is based in the use of cognitive strategies which help the health care professional to make the best decision. These strategies or "empirical rules" are the usual way of reasoning which the health care professionals follow for medical assistance

decisions making, and are classified from two points of view: the representativeness heuristic and the availability heuristic. The *representativeness heuristic* allows, to study a patient, to weigh the similarity of his symptoms frame with the classes considered as the principal diagnostic hypotheses. That is, the health care professional researches the diagnostic (or diagnostics), which the patient is a representative example. The *availability heuristic* refers to medical judgements made in function of the remembrance ease of similar cases previously studied.

4. *Probabilistic Reasoning*. In this reasoning, the health care professional uses objective methods of probabilistic estimate in the decisions making, avoiding the systematic mistake associated with the clinical intuition or the personal inexperience. This reasoning requires having operative knowledge about diagnostic tests, and having access to statistical data about prevalence and frequency of diseases.
5. *Hypothetical-deductive Reasoning*. In this reasoning, once formulated the diagnostic initial hypotheses, the health care professional insists in the interrogatory areas with the purpose of refuting, gradually, some of the hypotheses and finally, to confirm one of the initial hypotheses.

As shown the table 2.1, all these types of reasoning have a formal foundation which has helped the development of several computer technologies to decision making support in the medical assistance.

Medical Reasoning	Computer Technologies
Causal	Causal networks
Deterministic	Expert systems
Heuristic (representative)	Classification
Heuristic (availability)	Case-based reasoning
Hypothetic-deductive	Proof by contradiction

Table 2.1: Types of medical reasoning.

2.2.4 Medical Reasoning Limitations

The main *limitations* of medical reasoning can be summarized in a series of troubles or implicit biases on the types of reasoning which are previously mentioned [SMAR97, Día04]:

1. *Distortion of disease model in the personal experience of the health care professional*. This trouble is due to the discrepancy between the typical pattern of disease and the medical state

of a concrete patient, either by partial knowledge of the medical problem, or by an inadequate estimation of the probability of the occurrence of the disease in this environment.

2. *Excessive use of trails and non-specific signs* to decide a medical-clinical diagnostic, to predict the course of the disease, or to anticipate the outcome of the disease.
3. *Tendency to attribute changes on the disease course to factors or specific intervention* when these changes may have a random cause.
4. *Bias of memory* to favour some facts and unusual phenomena in front of others (the cases and most unusual events tend to be more accessible in the health care professional's mind).
5. *Bias of "anchor" or "hook", or the first impression is the true.* This bias is due to the omission of relevant data obtained after building the hypothesis because of the costs of modifying the hypothesis to host the new data.

2.2.5 Uncertainty and Variability in Medicine

In medical assistance, independently to the knowledge quality and medical reasoning used, there is a certain inevitable grade of uncertainty and variability in every medical decision, where the mistake and risk may be present. In this document, *uncertainty* is defined as equivalent to the lack of absolute certainty in a fact, for instance, a medical-clinical diagnostic. Uncertainty is observed on each medical procedure step, and it can arise for such dissimilar aspects as available information deficiency (e.g., incomplete, mistaken or imprecise information), deficiencies of the applied model when deciding (e.g. inaccurate or incomplete model), or because of the own non-determinism of the medical practice [Die03].

1. *Incomplete information.* Incompleteness is defined as a partial absence of elements which describe a fact. In many cases, the complete clinical history is not available, and the patient is incapable of remembering every symptom he/she has experienced and how the disease has developed itself. Besides, in other occasions, practical limitations prevent from counting with every resource which should be available, for which the health care professional must take decisions with partial information.
2. *Mistaken information.* A mistake is defined as a deviation regarding to a correct or precise fact. The information given by the patient, could contain incorrect descriptions of symptoms and even deliberate lies to the health care professional. It is also possible that the previous medical

diagnostic, registered in the medical record, has been mistaken. It is also not strange that laboratory tests outcomes are false positives or false negatives. For these reasons, the health care professional has always to keep a reasonable doubt against to all available information.

3. *Imprecise information.* Imprecision is defined as the lack of precision, the vagueness degree or poor affirmation or description of a fact. There are many medical data which are difficult of quantify and, then, susceptible of being intrinsically imprecise. It is the case, for instance, of certain symptoms like fatigue and pain.
4. *Incomplete model.* On the one hand, there are many medical phenomena in which the cause is still unknown; on the other hand, the lack of agreement or approval between experts from one specific field is frequent. These are the main reasons for not to have complete models for all the medical facts.
5. *Inaccurate model.* Any model to quantify uncertainty needs a high number of parameters. Great part of medical information is not usually available, for which it must be estimated subjectively. It is desirable, then, that the implemented reasoning method can take into account the model inaccuracy.
6. *Non-deterministic real world.* Non-determinism expresses which the willingness acts are spontaneous and non-determined. Health care professionals check every day that each patient is “a whole different world”, in which general laws are not always applicable. Many times, the same medical actions produce different effects in distinct patients, without any apparent explanation. Because of this, the decision must always be prepared to admit randomness and exceptions.

In front of uncertainty, *variability* in medical assistance is defined as the alternative of possibilities for a concrete fact like, for instance, the event which to a same medical-clinical diagnostic it is possible to provide diverse therapeutic alternatives. In the same way that uncertainty, the variability has been observed in, practically, each medical procedure step, either in anamnesis, in physical examination, in diagnostic tests interpretation or in therapeutic answer. The reasons that explain this variability may have their origin in the patient’s characteristics, in the health care system, in the health care professionals and in the population health state [Gál05]. In spite of these variability sources, there is a variability that relapses on the scientific evidence that underlies to medical decision making. This last variability, typical of *evidence-based medicine* and which it is

conceptually different to the first, is defined as the dispersion degree of a sample according to a determined medical model. This type of variability is conditioned by [Gom05]:

1. *Absence of evidence or scientific knowledge, inaccessibility to the evidence sources and lack of skill on information analysis.* When there is no available scientific evidence, health care professionals tend to base their decisions on their experience, in these cases, the possibility of variability increases. This is due to the fact that personal observations are insufficient and non-automatized, memory is selective, the appreciations are biased, and the mind does not elaborate random comparisons among patients.
2. *Presence of incorrect or tendentious information.* The non-valid and non-reliable information produces noise which confuses, disorientates and induces to the variability in the decision making.
3. *Not contrasted practices.* In medical assistance, there are modes, inertias or situations which are maintained or propagated successfully without any apparent reason. On the contrary, it is notorious the low spreading which have several procedures that are based on scientific information, such as protocols and clinical practice guidelines [WGH⁺99].
4. *Lost of scientific actualization.* Medical information is produced and renewed permanently, influencing the practice in an erratic or non validated way. Access and follow up to this scientific actualization is hard and this influence on the medical assistance variability.

After analysing, from a medical point of view, the concepts of knowledge and reasoning, just like different factors that influence the medical assistance decision making, we are able to consider the different tools that offer support to the medical decision making.

2.3 Decision Making Support in Medical Assistance

Decision making support in medical assistance (DMSMA) can be defined as the use of technologies which allow reducing problems derived from the limitations of human reasoning, uncertainty and medical practice variability, to obtain a better decision in a particular medical situation. As instances of these technologies we can cite, protocols and clinical practice guidelines, systems of medical data codification and classification, and different technologies and systems developed from disciplines like the decision theory, mathematics, statistics, and artificial intelligence.

2.3.1 Protocols and Clinical Practice Guidelines

A *medical protocol* can be defined as a sequence of behaviours which are applied to a patient in order to improve his/her medical course, or, as a set of procedures which can be used in patients with a determined medical frame. A medical protocol constitutes a precise and detailed plan for the diagnostic study and therapeutic manage of a specific medical problem [CCQS05]. *Clinical practice guidelines* (CPG) [FL90] are defined as a set of directives systematically made to assist health care professionals and patients in the decision making about adequate health-care attention to specific medical problems. In a more utilitarian sense, we can say that CPGs are tools to organize the best available scientific evidence at the moment of being used in the medical decision making [WGH⁺99]. Its main objective is to improve medical efficiency and the quality of the care delivered to the patient, promoting adequate actions and reducing uncertainty and unjustified variability in the selection of treatments.

According the problems listed in section 2.2.5, CPGs offer to the health care professionals directives based in the best results about the scientific research, and also provide references about good medical practice points to contrast their actions [GB01]. Nevertheless, the CPGs success depends on the conjunction of several factors such as the medical, social and health care context, the elaboration system, the means of dissemination and the implementation methods.

Tables 2.2 and 2.3 show a selection of institutions, whose main labour is the development, storage, and disclosure of the CPGs.

2.3.2 Systems of Encoding and Medical Data Classifications

The *encoding* and *classification* systems were developed in order to reduce the lack of specificity and structuring of medical data, making them more accessible in the decision making processes. The *encoding systems* are often structured lists of terms which, beside to its definitions, are designed to unequivocally describe the care and treatment of patients. Terms cover diseases, encounters, diagnostics, procedures, operations, prescriptions, etc., and they can be used to describe, on detail, the medical assistance realized to a patient, either textually or through electronic register. The *classification systems* systematically organize medical concepts (terms) in classes, for instance, a diseases classification can be defined as a category system which morbid entities are assigned according to established criteria [Ger95], as suggest the International Classification of Diseases system (ICD in its 10th version) [WHO07], where diseases like acute rheumatic fever (I00-I02), Chronic rheumatic heart diseases (I05-I09), hypertensive disease (I10-I15), ischaemic heart disease (I20-I25), etc., are

Centre	Country	Website
Health Service Technology Assessment Text (HSTAT)	United States	http://www.ncbi.nlm.nih.gov
New Zealand Guideline Group (NZGG)	New Zealand	http://www.nzgg.org.nz
Scottish Intercollegiate Guidelines Network (SIGN)	Scotland	http://www.sign.ac.uk

Table 2.2: Examples of CPGs development centres.

Centre	Country	Website
National Guideline Clearinghouse (NGC)	United States	http://www.guidelines.gov
Institute for Clinical Systems Improvement (ICSI)	United States	http://www.icsi.org/guidelines_and_more/
CMA Infobase	Canada	http://www.cma.ca/cpgs/index.htm
Sociedad Española de Cardiología	Spain	http://www.secardiologia.es
Fisterra	Spain	http://www.fisterra.com/index.asp

Table 2.3: Examples of storage and disclosure CPGs centres.

classified as diseases of the circulatory system.

Table 2.4 shows examples of systems used to classify and encode medical data [Bla00].

2.4 Formal Technologies for the DMSMA

The formal Technologies for DMSMA are defined as any computable program designed for helping the health care professionals to make decisions in the MP. In this sense, in the last decades a big variety of technologies for the design and implementation of systems for DMSMA have been developed [Sho87, Mil94, SCC00, Kul00, MSS06, Gre07, KXY08].

2.4.1 Classification of Formal Technologies for the DMSMA

Figure 2.2 shows a compendium of the main formal technologies which have been developed for DMSMA. These technologies are classified according to the disciplines in which the technologies were developed: decision theory, mathematics, statistic and artificial intelligence.

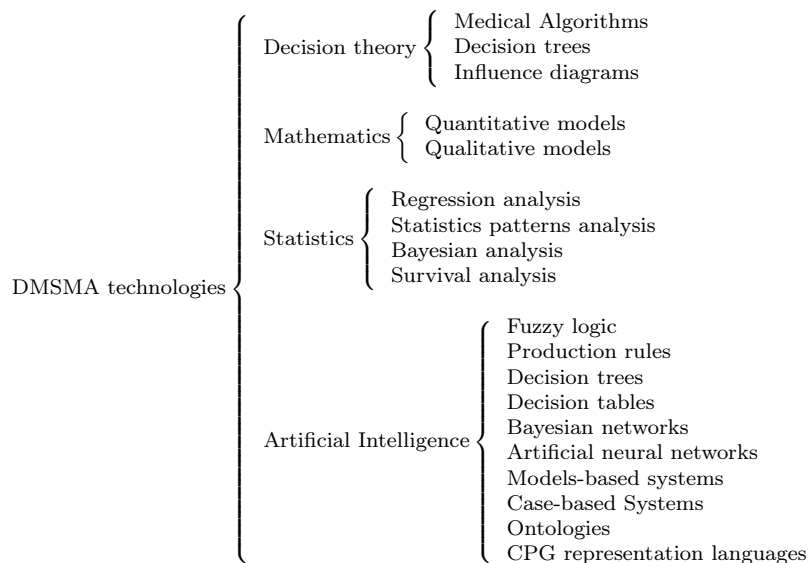


Figure 2.2: Compendium of formal technologies for the DMSMA.

Decision Theory Technologies for the DMSMA

The roots of *decision theory* are based on games theory made in the 40's decade by Von Newman and Morgenstern [NM44]. This theory is based on mathematical characterization of rational choice

Acronym	System	Support by	Website
GALEN	Generalized Architecture for Languages, Encyclopedias and Nomenclatures in Medicine	University of Manchester University of Nijmegen (NL)	www.opengalen.org
HHCC	Home Health Care Classification	American Nurses Association (USA)	www.sabacare.com
ICD	International Classification of Diseases	World Health Organization (USA)	www.who.int/whosis/icd10
ICF	International Classification of Functioning, Disability and Health	World Health Organization (USA)	www3.who.int/icf/icftemplate.cfm
LOINC	Logical Observation Identifier Names and Codes	Regenstrief Institute (USA)	www.loinc.org
SNOMED	Sistemized Nomenclature of Medicine	College of American Pathologists (USA)	www.snomed.org
UMLS	Unified Medical Language System	National Library of Medicine (USA)	www.nlm.nih.gov/research/umls

Table 2.4: Systems of classification and encoding of medical data.

called utility theory which provides a mathematical foundation to make decision under uncertainty. *Utility theory* (UT) is based on that given a number of hypotheses about a rational behaviour, objectives of decision making are expressed with numerical quantities called utilities and the optimal solving to the decision making problem is found on numerical maximization of global utility [Pee00]. Traditional tools which use UT to the DMSMA are [SCC00]: medical algorithms, decision trees and influence diagrams.

First, *medical algorithms* [Tud68] are procedural models used to help in the diagnostic and therapeutic decision, where decision sequences are codified in logical diagrams of ramifications or *flowcharts*. Decision alternatives are chosen following the most logical sequence of the algorithm, according to a binary decision function (e.g., yes/no or similar) [MMWea93]. For instance, figure 2.3 [SH06] shows the blood pressure control algorithm. This algorithm makes part of the diagnostic and treatment general management of patients that suffer diabetes mellitus type II². It shows that the treatment starts with an assessment of the systolic blood pressure which, in case of being greater than 130 mmHg, requires a treatment with ACE (Angiotensin Converging Enzyme) and ARB (Angiotensin II Receptor Blockers) inhibitors. Later, diastolic blood pressure is evaluated and if this is not less than 80 mmHg, it will require a non specified treatment in the algorithm. When both blood pressures are in the required limits, the patient is derived to a management treatment and follow-up of the diabetes.

Second, *decision trees* (DT) [PK87], different from medical algorithms, are based on probability analysis and UT to provide a quantitative measure to each available option. From the structural point of view, a DT is composed by decision nodes, chance nodes and utility nodes. *Decision nodes* (commonly represented by squares) allow the health care professional to select the most appropriate strategy according to the given medical situation. *Chance nodes* (commonly represented by circles) represent random variables on analysis and indicate available answers to these variables that do not have control from the health care professional part. It means that answers to random variables can be owned to specific data of the patient. *Utility nodes* (represented by the DT leaves) condense a set of all possible medical results for the chosen domain. The DT evaluation is always made from left to right, the associated utility to each branch and each node is calculated taking into account that: (1) for a chance node, the expected utility is calculated taking into account the *utility* and the *probability* of each branch which comes out of that node, and (2) the utility of a decision node

²Diabetes mellitus type II (DM) includes a set of metabolic disorders which share the common phenotype of the hyperglycemia. Particularly, the DM type II is a heterogeneous group of disorders which are characterized by variable levels of resistance to insulin, insulin secretion disorders and increase of glucose production [BFKea02].

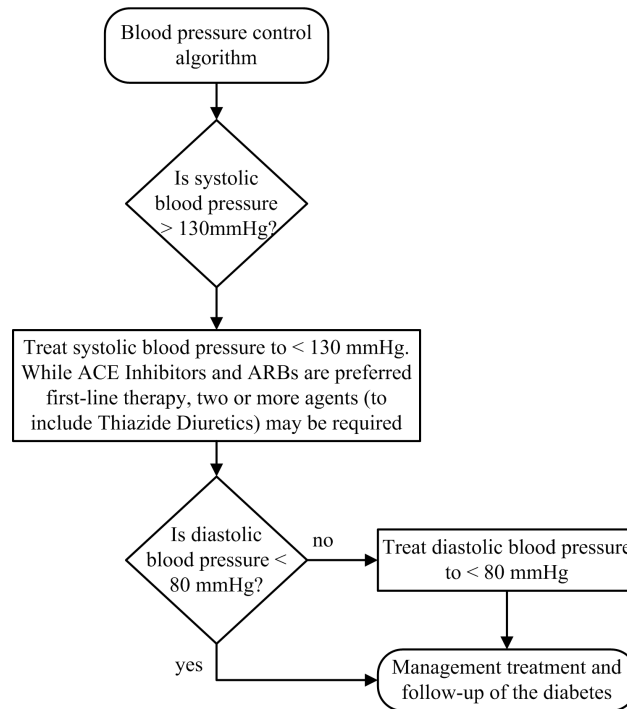


Figure 2.3: Medical algorithm to blood pressure control.

is the *maximum expected utility* of its branches.

Some examples of DT application are in the cardiology domain [MSL⁺95, SMAR97, PFMP00]. Figure 2.4 [SMAR97] shows a DT which presents three possible therapeutic alternatives for an ischemic cardiopathy³: surgery, percutaneous coronary angioplasty (percutaneous coronary intervention or PCI) and medical treatment. The DT indicates that, first a test of inducible ischemia must be done in which 60% of cases is positive, then the treatment type must be decided (i.e., surgical, PCI or medical treatment), the first two with a 22% and 7% probability of death, and 78% and 93% of success, respectively. Following the medical treatment does not imply a risk of death, so there is no probability distribution associated to this branch. A second DT branch indicates respective alternatives and probabilities to the cases in which the test of induced ischemia is negative. Also, this DT shows in the right margin the survival probabilities to 3 and 5 years to each alternative.

Third, *influence diagrams* (ID) [HM81, Sha86] are compact representations and mathematically equivalent to the DTs. Just like DTs, IDs contain decision nodes, chance nodes and utility nodes

³Ischemic cardiopathy is the resulting disease of the coronary arteries incapacity of taking necessary oxygen to a determined place of the cardiac muscle, which difficult this muscle functioning, and having as consequences angina pectoris, acute myocardial infarction (MI) or sudden death [Spanish Heart Foundation (www.fundaciondelcorazon.com)].

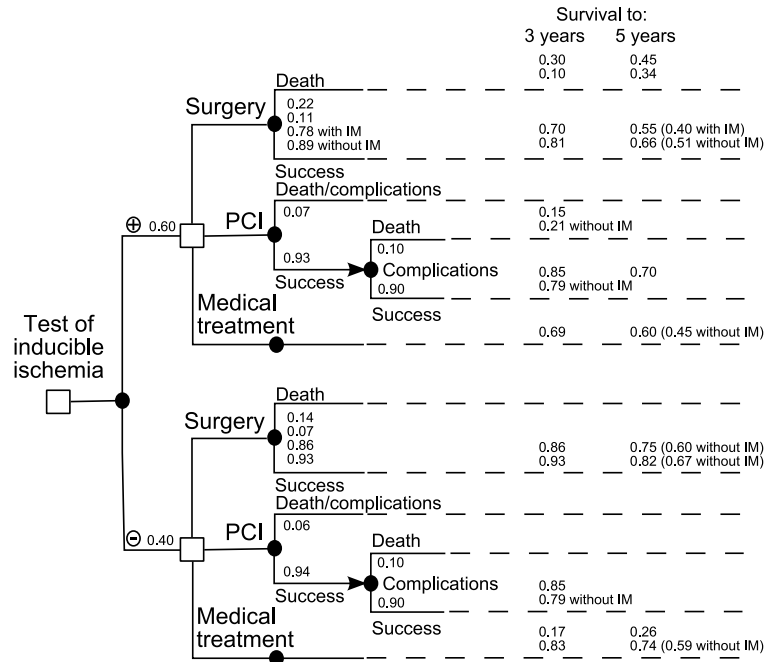


Figure 2.4: Decision tree to the ischemic cardiopathy treatment.

[PW05]. The arrows between two nodes can indicate information influence or conditional influence. *Information influence*, represented by arrows which lead to a decision node, indicate what variables are known by the health care professional when making the decision. *Conditional influence*, represented by arrows leading to a chance node, show the variables where the conditioned probability assignment is made to the chance node. Information influence over a decision node represents a cause-effect relation, while conditional influence over an chance node represents an arbitrary order of conditions, which do not necessarily correspond to cause-effects relations, and which can be modified through probability law application (e.g., Bayesian rules) [HM05].

Some application examples of ID are in the cancer domain [NO97, HM05, LEK⁺06]. Figure 2.5 [LEK⁺06] shows an ID to bone metastasis detection, in patients with breast cancer, and whether they were or not were correctly classified according to the TNM staging system⁴. The ID contains five chance nodes: *B* (bone metastasis), *S* (bone scanning), and the tumour markers⁵ *CA* (carbohydrate antigen 15-3), *C* (carcinoembryonic antigen) and *AP* (alkaline phosphatase). Node *B*

⁴TNM is a staging method of cancer according to the cancer size inside the patient's body. The letter T is use to describe the tumour size and whether the tumour invaded close tissue. The letter N is used to describe any lymph node which is compromised and the letter M is used to describe metastasis (dissemination of the tumour from one place to another inside the body) [American Joint Committee on Cancer (www.cancerstaging.org)].

⁵It is consider as tumour makers every substance produced or induced by the neoplastic cell which reflect its growing and/or activity, and which let know the presence, evolution or therapeutic answer of a malignant tumour [National Cancer Institute (www.cancer.gov)].

represents the real state of the patient. The presence or absence of bone metastasis is represented by the symbol “ \sim ”. Tests results are represented with the symbols “+” and “-”, indicating positive and negative results, respectively. In the same way, decision node results (metastasis?) are represented with “ $M+$ ” and “ $M-$ ”, indicating if the metastasis diagnosis is positive or negative, respectively. Utility value, represented by “*correctness*”, indicates that if it has a value of 1, the staging has been correct, otherwise, the value will be 0.

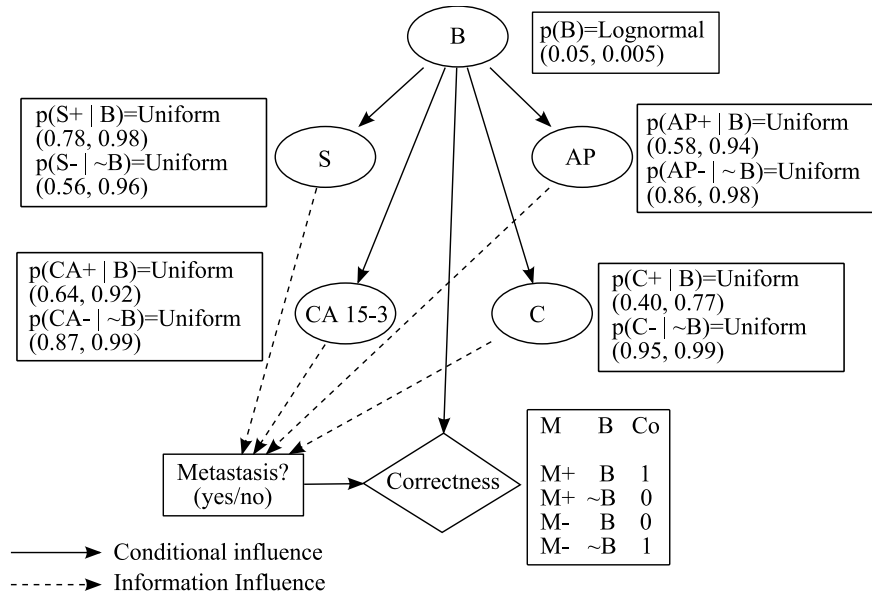


Figure 2.5: Influence diagram to detect bone metastasis in breast cancer patients.

Mathematics Based Technologies for the DMSMA

Regardless of decision theory, in *mathematics* several quantitative and qualitative analytic models for decision making have been developed. In medicine, these models have been used to predict the future situation of a patient basing in his/her current situation and a representation of his/her medical history. *Quantitative models* are used, for instance, on the estimation of diagnostic tests accuracy [KBF⁺07]. As table 2.5 shows, this estimation is based on four indicators: true positives rate, false negatives rate, true negatives rate and false positives rate. *True positives rate* or *sensibility*, allows correctly identifying to the patients that present the disease. Its opposite, *false negatives rate*, is defined as $(1 - \text{sensibility})$. *True negatives rate* or *specificity*, allows correctly identifying the patients that do not present the disease. Likewise, its opposite, *false positives rate*, is defined as $(1 - \text{specificity})$. A perfect test should present a sensibility and specificity of 100% so that it

allows a perfect separation between the patients that present the disease of those that do not have it.

Outcome	Disease Situation	
	Presence	Absence
Positive	True Positive (TP)	False Positive (FP)
Negative	False Negative (FN)	True Negative (TN)
Subjects identification with disease		
True positive rates (sensitivity) = $TP/(TP+FN)$		
False negative rates = $FN/(TP+FN)$		
True positive rate = $1 - \text{False negative rates}$		
Subjects identification without disease		
True negatives rates (specificity) = $TN/(TN+FP)$		
True false rates = $FP/(TN+FP)$		
True negative rates = $1 - \text{False positive rates}$		

Table 2.5: Diagnostic tests accuracy estimation.

Qualitative models [Kui86] analyze the time depending behaviour of a clinical practice to represent patient situation trails. This behaviour is represented as a set of connected nodes and links between nodes which reflect restrictions on the transitions in the system. The decisions made by this kind of models are of the sort evaluation and therapy planning. For instance, in the *QSIM* (Qualitative SIMulation) algorithm [Kui86], the value of a time-dependent variable is adjusted by the notion of qualitative state. QSIM takes, several times, an active state and generates all possible successors states to this one, filtering the states which do not accomplish a determined consistence criterion. So, QSIM builds a state tree which represents the possible behaviours of the problem under study (e.g., the disease evolution).

Statistic Based Technologies for the DMSMA

Statistics has been the most applied field for decision making in medical assistance. Regression analysis [Fur76, SKJ84], statistical patterns recognition [Fei70, Fei73], Bayesian analysis [WTVS61, GB68, dDLS⁺72] and survival analysis techniques [AHL01, Mac01] are some examples of developed technologies from this discipline, which have been widely applied in the medical decision making [SCC00].

Regression analysis [Fur76, SKJ84] has been used to model relations between a response variable of interest for the decision making, and a set of explainable variables. For it, the regression coefficients are adjusted (i.e., model parameters) until a “better adjustment” for data is reached.

APACHE score (Acute Physiology, Age and Chronic Health Evaluation) [KWD⁺91] for a disease severity determination, based on prognostic survival, is a good example of a logistic regression model which has been used to routine health care [Mac01]. As figure 2.6 shows, APACHE score III uses different physiological variables of a patient as the hearth frequency (pulse), mean blood pressure (mean BP), temperature, respiratory rate, serum creatinine, serum albumin, serum bilirubin, etc., to determine the survival in an Intensive Care Unit (ICU).

Statistical pattern recognition [Fei70, Fei73] on data can be formulated as a problem of the statistical classification of clinical conclusions in decision regions that are mutually exclusive but collectively exhaustive. It means that not only physiological data (i.e., entry variables) can be classified, but also the pathologies which result (i.e., diagnostic variables) and available therapy options to treat a disease (i.e., treatment variables) [JDM00]. This way, these models help to the decision making in diagnosis and in the treatment selection. For instance, some patterns in a complex data set were recognized to improve the health care attention in head injured patients [TMM⁺81]. Also, the patterns recognition were the support to develop technological methods in cardiac arrhythmias analysis [Mor84].

Bayesian analysis [WTVS61, dDLS⁺72] has been one of the most popular methods used to medical decision making support. Bayesian classification is an example of a parametric method for the estimation of classes given a probability density function. The optimal decision rule which minimizes the classification average frequency is called the *Bayes rule*. This rule is used as inference mechanism to calculate the probabilities of each possible event when specific medical outcomes of a patient are available [WHBea87]. For instance, the Leeds abdominal pain system [dDLS⁺72] was a decision support system, based on Bayesian analysis, to the diagnosis of abdominal pain. This system used the information about sensibility and specificity in conjunction with data about signs, symptoms and diagnostic tests outcomes for calculating the probability of seven abdominal pain causes: appendicitis, diverticulitis, perforated ulcer, cholecystitis, small bowel obstruction, pancreatitis and non specified abdominal pain.

Finally, *survival analysis* [AHL01] provides a set of statistical techniques for data analysis in which, the response variable measures the time between two events. Survival is not limited to life or death terms, but to situations where the time is measured until an interesting event occurs, as the recurrence time of a disease, the efficiency time of an intervention, etc. So, survival is a time measure to a reply, failure, death, relapse or developing of a determined disease or event.

In survival analysis, data analysis can be realized using parametric and non parametric tech-

TABLE 1a

APACHE III scoring system, comprised of the sum of three components: an acute physiology score, an age score, and a chronic health problems score. Scores range from 0 to 299 (physiology, 0 to 252; chronic health evaluation, 0 to 23; age, 0 to 24), with higher values representing a worse prognosis.

Pulse		8	5	0	1	5	7	13	17	
		≤ 39	40-49	50-99	100-109	110-119	120-139	140-154	≥ 155	
Mean BP (mmHg)		23	15	7	6	0	4	7	9	10
		≤ 39	40-59	60-69	70-79	80-99	100-119	120-129	130-139	≥ 140
Temperature (°C)		20	16	13	8	2	0	4		
		≤ 32.9	33-33.4	33.5-33.9	34-34.9	35-35.9	36-36.9	≥ 40		
Respiratory Rate		17	8	7	0	6	9	11	18	
		≤ 5	6-11	12-13	14-24	25-34	35-39	40-49	≥ 50	
PaO₂* (mmHg)		15	5	2	0					
		≤ 49	50-69	70-79	≥ 80					
AaDO₂** (mmHg)		0	7	9	11	14				
		≤ 100	100-249	250-349	350-499	≥ 500				
Hematocrit (%)		3	0	3						
		≤ 40.9	41-49	≥ 50						
WBC Count (cu/mm) x 1000		19	5	0	1	5				
		< 1.0	1.0-2.9	3.0-19.9	20-24.9	≥ 25				
Serum Creatinine† (mg/dl) without ARF		3	0	4	7					
		≤ 0.4	0.5-1.4	1.5-1.94	≥ 1.95					
Serum Creatinine (mg/dl) with ARF		0	10							
		0-1.4	≥ 1.5							
Urine Output (cc/day)		15	8	7	5	4	0	1		
		≤ 399	400-599	600-899	900-1499	1500-1999	2000-3999	≥ 4000		
Serum BUN (mg/dl)		0	2	7	11	12				
		≤ 16.9	17-19	20-39	40-79	≥ 80				
Serum Na⁺ (mEq/L)		3	2	0	4					
		≤ 119	120-134	135-154	≥ 155					
Serum Albumin (g/dl)		11	6	0	4					
		≤ 1.9	2.0-2.4	2.5-4.4	≥ 4.5					
Serum Bilirubin (mg/dl)		0	5	6	8	16				
		≤ 1.9	2.0-2.9	3.0-4.9	5.0-7.9	≥ 8.0				
Serum Glucose (mg/dl)		8	9	0	3	5				
		≤ 39	40-59	60-199	200-349	≥ 350				
Age		0	5	11	13	16	17	24		
		≤ 44	45-59	60-64	65-69	70-74	75-84	≥ 85		
Comorbidities		• AIDS 23 • Hepatic Failure 16 • Lymphoma 13 • Metastatic Cancer 11 • Leukemia/Multiple Myeloma 10 • Immune Compromised 10 • Cirrhosis 4								

APACHE III

was introduced to address some of the flaws of APACHE II. Although APACHE III resembles APACHE II, it includes new variables such as prior treatment location and the disease requiring ICU admission. In APACHE III scoring, the patient's age and chronic health history are worth up to 47 points. Within 24 hours of ICU admission, 17 physiologic variables are measured and may add up to a maximum of an additional 252 points. The resulting total score, in combination with prior treatment location and principal ICU diagnosis provides a predicted mortality. .

BENEFITS OF APACHE III:

- Saves lives by better managing the care of critically ill individuals
- Reduces frequency of complications
- Evaluates and improves ICU performance
- Optimizes ICU resource allocation

TABLE 1b

APACHE III acute physiology scoring for neurologic abnormalities.

Motor (Verbal) see ‡		Oriented, Converses	Confused Conversation	Inappropriate Words & Incomprehensible Sounds	No Response
Obeys verbal command		0 / NA	3 / NA	10 / NA	15 / 16
Localizes pain		3 / NA	8 / NA	13 / NA	15 / 16
Flexion withdrawal/decorticate rigidity		3 / NA	13 / NA	24 / 24	24 / 33
Decerebrate rigidity/no response		3 / NA	13 / NA	29 / 29	29 / 48

TABLE 1c

APACHE III acute physiology scoring for acid-base disturbances.

Acute Physiology		pCO ₂ < 25	25 to < 30	30 to < 35	35 to < 40	40 to < 45	45 to < 50	50 to < 55	55 to < 60	pCO ₂ ≥ 65
pH < 7.15		12								4
7.15 to < 7.20		12								4
7.20 to < 7.25		12								4
7.25 to < 7.30		9	6	3	2					
7.30 to < 7.35		0								1
7.35 to < 7.40		0								2
7.40 to < 7.45		5	12							
7.45 to < 7.50		0								2
7.50 to < 7.55		0								2
7.55 to < 7.60		0								2
7.60 to < 7.65		3	12							
pH ≥ 7.65		0	12							

TABLE 1a SCORE **a**

TABLE 1b SCORE **+** **b**

TABLE 1c SCORE **+** **c**

APACHE III SCORE = a+b+c

‡ Scoring for: Eyes open / do not open spontaneously or to painful/verbal stimulation
 NA = Not applicable
 *If FiO₂ is =50%, record AaDO₂; ** Alveolo-arterial Oxygen Difference; † If FiO₂ is <50%, record PaO₂;
 † Acute renal failure (ARF) is defined as creatinine ≥ 1.5 mg/day and urine output < 410 cc/day and no chronic dialysis.
 References: 1. Knaus WA et al. Chest 1991; 100(6): 1619-36. 2. Yung-Chang C et al. Renal Failure 2002; 24(3): 285-96.

Figure 2.6: APACHE III decision system based on regression analysis.

niques, as figure 2.7 shows [Mac01]. The *parametric techniques* require a probability density function to estimate the survival functions and risks which give support to the medical decisions making. In this sense, the most used parametric techniques in survival analysis are [CE58]: exponential distribution, Weibull distribution or lognormal distribution. On the contrary, *non parametric techniques* produce estimations of the same functions without any necessity of being adjusted to a specific probabilistic model. Some examples of non parametric techniques used in survival analysis are: actuarial analysis [CE58], product-limit or Kaplan-Meier analysis [KM58] and Cox's regression [Cox84]. Both parametric and non parametric techniques have been used to explain the disease progression [KM03]) and not for predicting the survival of new cases. In the prediction of new cases, some techniques as *logistic regression* [MH59] and neural networks [RM86], have been widely used [PM02, GBF⁺06, BBAM06, LHHGR08].

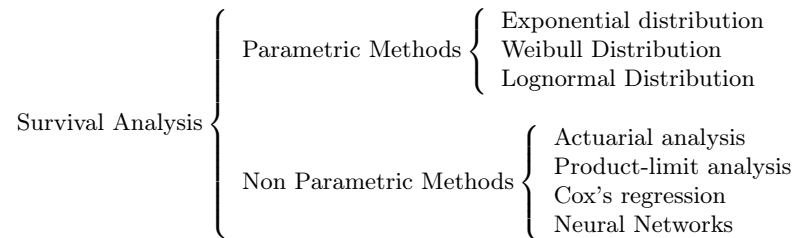


Figure 2.7: Compendium of survival analysis techniques.

Artificial Intelligence Based Technologies for the DMSMA

Artificial intelligence in medicine (AIM) was conceived from artificial intelligence (AI) to model expert knowledge which allows developing systems and tools that can be used to improve medical assistance and general medicine [Sho93]. Unlike traditional methods based on decision theory, mathematics and statistics, AIM technologies were based in symbolic models which allowed representing disease entities, its relations with the patients, and its medical manifestations. Examples of AIM technologies in DMSMA are the medical knowledge based systems. A *medical knowledge based system* (MKBS) is a computer-based program which captures the human experience elements and perform reasoning tasks that are normally performed by expert knowledge [MB02]. The MKBS are characterized for making an explicit distinction between the domain knowledge of medical problem which is represented and the knowledge used to reason and to solve the current medical problem using the available data. These systems make intensive use of domain knowledge and separate it from mechanisms that control its use. So, the basic components of the MKBS are: a knowledge

base and an inference engine. The *knowledge base* contains the domain specific knowledge. The *inference engine* contains the algorithms to manipulate the knowledge represented in the knowledge base with the aim to resolve a problem presented in the system.

The developing of AIM Technologies to represent, acquire and reason about specific medical knowledge, have been the principal lines of research in the last decades. Technologies as fuzzy logic [Zad65], production rules [Mic87], decision trees [Qui86], decision tables [Hol75], Bayesian networks [CGH97], artificial neural networks [RM86], ontologies [Gru93], the CPG representation languages [SHJ⁺94, Shi97, SMJ98, FJR98, TM99, JTB⁺00, PBOea00, BCH⁺02], the models-based systems (MBS) [Uck92] and cases-based systems or case-based reasoning (CBR) [Kot88], are examples of these type of AIM technologies applied to medicine.

Fuzzy logic (FL) [Zad65] has been generally used in medical diagnostic, for example, in the inadequate analgesia diagnostic in patients under influence of anaesthesia [JLH02], in the decision support in radiation therapy [PSG03], in the breast cancer [Has03], lung cancer [SPBea03] and prostate cancer detection [SOPN03], in the MedFrame/CADIAG-IV consultation system [BAH⁺04] used in the disease diagnostic of internal medicine, the ESTDD system [KK08] used in the thyroid disease diagnostic, or recently, the developing of classification frames based on fuzzy logic to improve the disease diagnostic [GM09].

Production rules [Mic87] have been the most popular technologies to represent the expert knowledge. Some examples of DMSMA system based in rules are: INTERNIST [PMM75] designed for the disease diagnostics in internal medicine, MYCIN [Sho76] developed to diagnose and recommend treatments of blood infectious diseases, ONCOSIN [Sho81] developed to help the health care professionals in the cancer treatment of patients that receives chemotherapy, PUFF [AKSR83] developed for the diagnostic and seriousness of lungs diseases, or, rules based approaches for the coronary disease diagnostic [RBW04].

Decision trees [Qui86] (also called classification trees) have been used in the diagnosis of cardiac problems [SLPK04], in the survival prediction of breast cancer patients [DWK05], in the prognostic of coronary diseases [KTK08], in the diagnosis of optical nerve diseases [PKGG08], in the diagnosis of the leukemia patients [CPRB09], or in combination with logistic regression to predict the periventricular leukomalacia [SBK⁺09], or with artificial neural networks to diagnose the Parkinson disease [Das10].

Decision tables [Hol75] have been used for the diagnostic of depression in the EsPeR system (preventive medicine) [CAJZ⁺05], or in combination with influence diagrams to select the best

course of action in the treatment of Gastric lymphoma no-Hodgkin [BdPL08]. Also, the decision tables have been used as CPG representation language [Shi97].

Bayesian networks (BNs) [CGH97] (also called causal networks, causal probabilistic networks or belief networks) have been used in DMSMA system as MUNIN [AWFA87] designed for the diagnostic of muscular diseases, DIAVAL [Die94] for the diagnostic of cardiac diseases, DIABNET [HGdPC96] for therapy planning in gestational diabetes, MammoNet [KRS97] as support in the breast cancer detecting, integrating findings obtained by a mammography, with demographic factors and physical exploration, to determine the malignancy probability of a tumour, PAIRS (Physician assistant Artificial Intelligence System) [JJ99] for the disease diagnostics in internal medicine, NasoNet [GADM02] to help the oncologist in the diagnostic and prognostic of spread nasopharyngeal cancer in a patient, SAMOA [FGA⁺03] for the classification of sleep apnea, ProCarSur [PVTSS⁺07] for the prognostic reasoning in the cardiac surgery domain. Also, BNs have been used in the prognostic of morbidity and mortality of cardiac disease patients [RBW04], to predict the appearance of carcinoid heart disease [vGJT⁺07], to predict the patients evolution with prostate cancer after intensity-modulated radiationtherapy treatment [SDM⁺09], for the diagnostic and treatment of lung diseases [VLSB09] or the use of BN for survival analysis [SDBB09].

Artificial neural networks [RM86] (ANN) are DMSMA technologies which simulate the human mind and make its learning through examples. The ANN have been used in the patients classification by risk groups [LWHS03], in the prognostic of coronary disease [MSM⁺05, KTK08], in the survival prognostic of breast cancer patients [BBAM06], or in the prognostic of virology response to combination HIV therapy [WLR⁺09].

Model-based systems (MBS) [Uck92] (also called second generation expert systems [Coi03]) are designed for using disease models with aim to cover a great group of medical problems. So, the knowledge base is represented as a set of disease models instead of a logic rule to describe that disease. Among the systems which incorporated pathophysiological models to decision support making are: CASNET [Wei74] for the diagnostic and treatment of glaucoma, Digitalis Advisor Program [GSP78] for the diagnostic and drugs prescription, ABEL [PSS82] for the diagnostic of acid-base and electrolyte disorders in patients, KARDIO [BML89] for the diagnostic of cardiac arrhythmias, systems for disease diagnostics in internal medicine [Luc97] and the Intensive Care Unit [ZMS97, HLV⁺06].

Case-based systems or case-based reasoning (CBR) [Kot88, AP94, BM06] appear in the conception of, instead of obtain solutions through of a general model of domain knowledge, the CBR

systems recover and re-use the solutions of similar problems. These systems need a collection of experiences and *cases* which is stored in a *cases base*, where each case is composed by a description of the problem (causes of a disease) and the solution applied (diagnostic or treatment of that disease). The fundamental hypotheses which are based the CBR systems are that a DMSMA system or a health care professional, can solve problems without having any complete knowledge of the relation among a problem and its solution, provided it has sufficient experience (patient's cases already treated or diagnosed). Furthermore, the problems tend to repeat themselves again, and for that, the experience is an useful tool. Examples of DMSMA systems based in CBR are CASEY [Kot88] for the diagnostic of cardiovascular diseases, MNAOMIA [Bic96] for the diagnosis and treatment of eating disorders in the psychiatry domain, or researches in the diagnosis and prognosis of prostate cancer [Bar96], the risk estimate of bowel disease [RR08] or the diagnostic of liver disease [Lin09].

Ontologies [Gru93] have been used in encoding and classification systems as the MANELAS system [Zwe94] in coronary diseases domain, GALEN (Generalized Architecture for Languages, Encyclopaedias and Nomenclatures in medicine) [RRP96], the SNOMED system (Systematized Nomenclature of Medicine) [SCC97] and the UMLS system (Unified Medical Language System) [HLSB98] in general medicine and FMA (Foundational Model of Anatomy) [RM03] in the anatomy domain or CPO (Case Profile Ontology) [RRC⁺09] to characterize patients in home. Also, the ODDIN [GCRM⁺10] and TimeDDx [DP10] systems use ontologies to realize differential diagnostic.

CPG representation languages are formal representations developed to interpret in a computable way the knowledge contained in the CPG. Their uses are focused in the medical treatment planning activities. The main CPG representation languages are: Arden Syntax [SHJ⁺94], augmented decision tables [Shi97], Asbru [SMJ98], PROforma [FJR98], EON [TM99], PRODIGY [JTB⁺00], GLIF [PBOea00], SAGE [BCH⁺02]. Also, the ATHENA system [ATO⁺99, GHRea00], based in the EON language, implements CPG for the comorbid disease treatment or the LISA system [BHBea02], based in PROforma language, implements CPG for the treatment support of childhood acute lymphoblastic leukemia.

2.4.2 Using Formal Technologies for DMSMA

From the point of view of decision and planning problems in diagnosis, treatment and medical prognosis, table 2.6 shows the technologies based in decision theory, mathematics and statistics for the DMSMA mentioned previously in this chapter. For all of them, except the survival analysis, antecedents of use to support the decision activity in the medical diagnosis are provided [dDLS⁺72,

Mor84, Kui86, MSL⁺95, WW00, SLPK04, SH06, LEK⁺06, KBF⁺07]. In the decision support of medical treatment activity, technologies as medical algorithms [SH06], decision trees [SMAR97, PFMP00] and influence diagrams [BdPL08] based in the decision theory, and pattern recognition [TMM⁺81, JDM00] based in statistics, are the most used ones. Likewise, in the decision support of medical prognosis activity, technologies as influence diagrams [NO97] based in decision theory, qualitative models [Kui86] based in mathematics, regression analysis [MR88, KWD⁺91, TMGZ97, PM02, GBF⁺06, LHHGR08] and the survival analysis [Mac01, KM03, Roz06] based in statistics, are the most used ones. Respect to the planning activity, we found no evidence of use of these technologies.

Table 2.7 shows the AI based technologies for the DMSMA. All these technologies, except artificial neural networks and decision trees in the treatment activity, have been used to support the decision activity in diagnostic and medical treatment. Likewise, in the prognosis decision activity, Bayesian networks [GADM02, PVTSS⁺07] and artificial neural networks [PM02, JAGRJR⁺03, MSM⁺05, GBF⁺06, BBAM06, KTK08, LHHGR08], are the technologies based in AI which more application has had in DMSMA. The contrary happens with the planning activity, due to the fact that the CPG representation languages are the only AI based technologies for the DMSMA used in the diagnosis and medical treatment [SHJ⁺94, Shi97, SMJ98, FJR98, TM99, ATO⁺99, JTB⁺00, PBOea00, BCH⁺02, BHBea02].

2.4.3 Historical Evolution of Formal Technologies for DMSMA

The evolution of formal technologies for DMSMA started in the *sixties*, when the main representation paradigm in the decision making was based on decision theory [LL59, Ble69], mathematics [WTVS61] and statistic [WTVS61, GB68] (§2.4). These methods permitted a priori probability subjective estimation in diagnostic probabilities calculation. However, these methods suffered one common inconvenient: although all methods worked in specific problems, statistically well defined and with adequate example from which probabilities were estimated, these were not incorporated in the daily medical practice. The reason of the not acceptance of these models were its difficulty to explain decision, which was based on strict probability computational theories, in terms of a qualitative language and with not familiar arguments to the health care professionals. An alternative to this problem was the decision sequence codification of experts in ramifications logical diagram or *flowcharts*, also known as medical algorithms [Tud68]. These *medical algorithms* (figure 2.3), which are still used, had the advantage of its clarity, its easy explanation, and its possible valida-

Activity MA	Technology DMSMA	Diagnosis	Treatment	Prognosis
Decision	Medical algorithms	[SH06]	[SH06]	
	Decision tree (based on decision theory)	[MSL ⁺ 95], [SLPK04]	[SMAR97], [PFMP00]	
	Influence diagrams	[LEK ⁺ 06]	[BdPL08]	[NO97]
	Qualitative models	[KBF ⁺ 07]		
	Quantitative models	QSIM [Kui86]		QSIM [Kui86]
	Regression analysis	[WW00]		[MR88]; APACHE score [KWD ⁺ 91]; [TMGZ97], [PM02], [LHHGR08], [SBK ⁺ 09]
	Statistic pattern recognition	[Mor84]	[TMM ⁺ 81], [JDM00]	
	Bayesian analysis	Leeds abdominal pain system [dDLS ⁺ 72], ILIAD [WHBea87]		
	Survival analysis			[Mac01], [KM03], [Roz06]
	There are not evidence	There are not evidence	There are not evidence	There are not evidence

Table 2.6: Formal technologies based on decision theory, mathematics, statistics for the DMSMA.

Activity MA	Technology DMSMA	Diagnosis	Treatment	Prognosis
Decision	Fuzzy logic	[JLH02], [Has03], [SPBea03], [SOPN03], MedFrame/CADIAG-IV [BAH ⁺ 04], ESTDD [KK08], [GM09]	[PSG03]	
	Production rules	INTERNIST [PMM75], MYCIN [Sho76], PUFF [AKSR83], [RBW04]	ONCOSIN [Sho81]	
	Decision trees (based on AI)	[SLPK04], [PKGG08], [CPRB09], [Das10]		[DWK05], [KTK08], [SBK ⁺ 09]
	Decision Tables	EsPeR [CAJZ ⁺ 05]	[BdPL08]	
	Bayesian networks	CASNET [Wei74], MUNIN [AWFA87], DIAVAL [Die94], MammoNet [KRSH97], PAIRS [JJ99], SAMOA [FGA ⁺ 03], [VLSB09]	CASNET [Wei74], DIABNET [HGdPC96], NasoNet [GADM02], [VLSB09]	NasoNet [GADM02], [RBW04], [vGJT ⁺ 07], ProCarSur [PVTSS ⁺ 07], [SDM ⁺ 09], [SDBB09]
	Artificial neural networks	[Das10]		[PM02], [LWHS03], [JAGRJRJ ⁺ 03], [MSM ⁺ 05], [GBF ⁺ 06], [BBAM06], [KTK08], [LHHGR08]
	Models based systems	CASNET [Wei74], ABEL [PSS82], KARDIO [BML89], [ZMS97], [Luc97], [HLV ⁺ 06]	CASNET [Wei74], Digitalis Advisor Program [GSP78]	
	Case based systems	CASEY [Kot88], MNAOMIA [Bic96]; [Lin09]	MNAOMIA [Bic96]	[RR08]
	Ontologies	MANELAS [Zwe94], GALEN [RRP96], UMLS [HLSB98], SNOMED [SCC97], FMA [RM03], ODDIN [GCRM ⁺ 10], TimeDDx [DP10]	MANELAS [Zwe94], GALEN [RRP96], UMLS [HLSB98], SNOMED [SCC97], FMA [RM03]	
	Planning	CPG representation languages	Arden Syntax [SHJ ⁺ 94], Augmented decision tables [Shi97], Asbru [SMJ98], PROforma [FJR98], EON [TM99], PRODIGY [JTB ⁺ 00], GLIF [PBOea00], SAGE [BCH ⁺ 02], ATHENA [ATO ⁺ 99, GHRea00], LISA [BHBea02]	Arden Syntax [SHJ ⁺ 94], Augmented decision tables [Shi97], Asbru [SMJ98], PROforma [FJR98], EON [TM99], PRODIGY [JTB ⁺ 00], GLIF [PBOea00], SAGE [BCH ⁺ 02], ATHENA [ATO ⁺ 99, GHRea00], LISA [BHBea02]

Table 2.7: AI based technologies for the DMSMA.

tion, but they were generally too rigid when capturing context specificities (e.g., *uncertainty* and *variability*) without becoming very extensive, complex and computationally expensive. The HEME program [LEBea61] for diagnostic of haematologic disorders and the CONSIDER system [LRB⁺68], a medical instruction system to identify disease on CMIT (manual of diseases compiled and previously maintained by the American Medical Association), are examples of developed systems in this decade.

Given the low expressiveness of the first approaches, in the *seventies*, diverse researchers groups (mainly from Rutgers University, Stanford University, Pittsburgh University, and the collaborative group MIT/Tufts) incorporated AI and biomedicine to explore and develop more intense approaches in knowledge, which allowed solving interpretation problems included in the medical decision making. In this sense, they proposed a set of representations and approximations based on three principal aspects [Kul00]: firstly, a more flexible *uncertainty* representation (§2.2.5) which allowed qualitatively the probability visualization. Secondly, a better *medical knowledge* representation (§2.2.2) which motivated and justified a diagnostic, therapeutic or prognostic decision. And thirdly, the development of a medical knowledge descriptive component for some problem resolution general strategy or *reasoning* (§2.2.3) could be applied. As an example, the first consultation systems based on AIM which helped the medical decision making were CASNET [Wei74], MYCIN [Sho76], and later, INTERNIST-1 [PMM75], PIP [PGKS76] and the Digitalis Advisor Program [GSP78].

An important aspect in this decade was the introduction of rules as formalism to symbolic knowledge representation. The rules have the advantages of its simplicity, uniformity, clearness, and inference easiness, which have made them the main paradigm to represent the experts knowledge. The separation of rules based system of its inference engine, mark the guide to development of medical knowledge based systems (MKBS) for the DMSMA. However, a problem came up when trying to represent experts tacit knowledge, because the representation which was made at that time, it was related to predefined patterns. This situation derived in the impossibility to give explanations to reached conclusions because of the non-existence of background scientific knowledge in the system. This emphasized the need of improving the *knowledge acquisition* processes, given that the skill and human experience exist as tacit knowledge, and this one can be directly acquired from the knowledge base and not by traditional methods of interview which had been done until that moment. This problem was defined as the “bottleneck” of the MKBS development [BBB⁺83]. The MKBS basic structure of that first age consisted on elements like a base of certain facts, a knowledge base and an inference mechanism (§2.4, AI base technologies for DMSMA). This inference mechanism applied

the stored knowledge in the knowledge base to the facts of the base of facts to infer new facts. The new inferred facts constituted the system response. Besides, these MKBSs included two additional modules to explain the followed reasoning in the production of different inferences and to facilitate dialogue between user and system.

At the beginning of the *eighties*, tools like *experts systems shells* [WK79] were introduced and widely used in the MKBS development. Also, in this same age, it was evident which acquired knowledge of the experts was inadequate to solve complex problems and which, when MKBS were developed, the data analysis obtained in daily medical practice and stored in medical databases, could play an important role in the decision making support. This helped to the development of the first *machine learning* algorithms which objective was knowledge automatic extraction from data, in shape of *rules* or *decision trees*. Among the first rules learning algorithms we find AQ [Mic87], CN2 [CN89] and PRISM [Cen87]. Inside the algorithm group of decision trees learning we find ID3 [Qui86], ASSISTANT [CKB87] and later the development of C4.5 [Qui93]. The end of this decade was characterized by the increasing gap between the data excessive storing not interpreted and the understanding of those same data, which emphasized the need of having accurate techniques of *data intelligent analysis*. This situation led to a new research line based on databases such as knowledge discovery database (KDD) [PSF91, FSS96], data mining (DM) [CHY96], and intelligent data analysis (IDA) [LKZ00], in which machine learning techniques played an important role. Some examples of MKBS based in these technologies for DMSMA in this decade are: RECONSIDER [BTS81], ONCOCIN [Sho81], DxPLAIN [HCH⁺86], ILIAD [WHBea87], MUNIN [AWFA87], QMR [MM89]. The revolution of communications and information technologies (TICs) marked the guide in the *nineties* with the appearance of the world wide web, the proliferation of web based information services, design facility of user graphics interface, improvement of networks and communications, etc. The incorporation of these TICs in medicine gave a new approach to the DMSMA [Kul00], now even more worried of characterization and knowledge bases construction to improve medical decision making, the integration of these knowledge bases in functional and useful medical computer systems, and validation, standardization and sharing of medical knowledge. Vocabulary standards development, medical codifications and nomenclatures, and the development of unified medical language systems (UMLS) [HLSB98] (see table 2.4) are initiatives of this decade. The knowledge reuse is widely eased by the *ontologies* development to different knowledge types and problem resolution. Protégé [TEG⁺95] is a remarkable example of a system to ontological knowledge management. The software integration to multiple uses was every time more stimulated by propos-

als such as integrated advance information management systems (IAIMS) [Ste97]. The appearance of Arden syntax [SHJ⁺94], a system to connect clinical databases, knowledge, and knowledge bases to support medical decision, marks the beginning of multiple languages and platforms to medical knowledge formal representation based on protocols and clinical practice guidelines (CPG). Some of these are Asbru [SMJ98], PROforma [FJR98], EON [TM99] and PRODIGY [PSBS99]. Automatic extraction of medical data from narrative *corpuses* also progresses due to linguistic and statistic methods combination [CY95]. In this decade we can distinguish the following DMSMA systems: HELP [KGP91], HERMES [BMS⁺93], DIAVAL [Die94], DIABNET [HGdPC96].

In the decade of the 2000's, other areas are emphasized such as natural language processing, ontologies, knowledge management, machine learning, data mining, reasoning and representation temporal, use and formal representation of protocols and CPGs in medical decision making, just like evidenced in [QBA01, DKB03, MHK05, BAHH07]. The classification problem as a particular case in the decision making marks the guide in research at the beginning of this decade. This is reflected in the great quantity of publications done under the *data mining* field [BAT⁺01, AHdK01, HBJ03, Kuk03b, BFMea05, RGAS05]. Particularly, some researches were headed to the combination of diverse machine learning techniques with the objective of taking advantage of the characteristics in every single one of them [AHdK01]. Temporal reasoning is still an active field of research. Questions like: how could temporal information be represented?, what is the abstraction level of optimal granularity to discover temporal patterns and rules later?, or how can the rules information contents be quantified?, are the aspects to solve in this context [DKB03]. Therefore, temporal abstraction and data mining techniques are used to extract, from temporal data, recurrent typical patterns or rules which can be associated to specific situations such as failures or patients normal evolutions [BLMB03]. The use of ontologies for the knowledge search from textual sources [Mey09] or the CORAAL system [NGH09]; the languages development to *CPG formal representation* and in turn, the systems development based on these representations, is still the pursued objective for many researchers. It is the case of the medical decision support system ATHENA [ATO⁺99, GHRea00] which implements CPG using EON language [TM96, TM01], the web based system LISA [BHBea02] which implements CPG using PROforma [FJR98] for the decision support in the cancer domain, the DEGEL system [SYS⁺03] which uses ontologies to specification and recovery of CPG, or the CPG representation environment SAGE (Standards-based Active Guideline Environment) [TMSea04]. Probabilistic networks and Bayesian models are still representative work areas, well adapted to the medical information and dynamic research [FGA⁺03], as for example the PAIRS

system (Physician Assistant Artificial Intelligence System) [JJ99] , ProCarSur system [PVTSS⁺07] and ESTDD [KK08].

Finally, and to summarize, table 2.8 presents, categorized by decades, the principal objectives which were proposed to improve decision making process in medicine from AIM, next to designed approaches for such purposes and some systems examples which implemented these approaches. This summary is based on [Mil94, NN00, Kul00] and the compendium of DMSMA and MKB systems available in *Openclinical* (www.openclinical.org).

2.5 Conclusions

Analysis of the background in medical informatics, referring to medical assistance has revealed a series of events which define and directly condition this thesis. These facts are exposed as chapter 2 conclusions, in form of points:

- The medical assistance activities are the decision and the planning in the diagnosis, treatment and medical prognosis.
- The medical assistance activities are integrated following a medical standard procedure where the health care professionals currently based their decisions. However, this medical standard procedure does not have the functional detail level to be formalized in a computable way.
- The success of decision making by health care professional in the medical assistance activities, are based in the medical skill in front of a particular situation, in the available medical knowledge in that moment and in the medical reasoning used in front of this knowledge.
- The current support which health care professionals have for medical assistance decision making is based in: protocols and clinical practice guidelines, encoding and classification systems of medical data, and technologies and systems developed through disciplines as decision theory, mathematics, statistic and artificial intelligence.
- The decision activities in the diagnosis and treatment, are the activities which have had a greater development from DMSMA Technologies. Also, in the medical prognosis activity, the regression and the survival analysis, both, through statistic methods, Bayesian and artificial neural networks in the AI field, are the DMSMA technologies with a great application.
- The augmented decision tables and the CPG representation languages are the only DMSMA technologies found which have been used for planning activities in the medical assistance.

Time	Objectives	Technologies	Systems
<i>Sixties</i>	To improve the decision making mechanisms used until now.	Statistic methods, Bayesian decision analysis, decision theory, heuristic reasoning.	HEME [LEBea61] CONSIDER [LRB ⁺ 68]
<i>Seventies</i>	To improve expressiveness using a better qualitative language and with familiar arguments to the health care professionals. To develop more intensive knowledge approaches. To improve knowledge representation. To improve inference systems.	Heuristic reasoning vs. symbolic reasoning, decision analysis in terms of problems solving characteristics, intensive knowledge frames for medical reasoning representation, causal networks, reasoning based on modular rules, hierarchical networks, knowledge representation with frames, semantic networks, MKBS development shells, knowledge acquisition, learning and categorical reasoning.	CASNET [Wei74] INTERNIST [PMM75] MYCIN [Sho76] PIP [PGKS76] Digitalis Advisor Program [GSP78] <i>etc.</i>
<i>eighties</i>	To develop approaches to knowledge automatic extraction from databases. To model knowledge level.	Research about medical reasoning, critic based approaches, qualitative models, rules refinement, abstraction paradigms of the knowledge level, temporal reasoning, influence diagrams, probabilistic causal networks, artificial neuronal networks, fuzzy logic, deep knowledge, machine learning.	ONCOCIN [Sho81] RECONSIDER [BTS81] DxPLAIN [HCH ⁺ 86] ILIAD [WHBea87] MUNIN [AWFA87] QMR [MM89] KARDIO [BML89] <i>etc.</i>
<i>nineties</i>	To characterize and to build knowledge bases. To valid, to integrate and to standardize medical knowledge. To develop approaches which allows reusing medical knowledge. To develop approaches which allows extracting medical knowledge from narrative reports.	Machine learning, relations between abductive and temporal reasoning, research on standardization of medical knowledge representation, software re-usability, medical pathways, protocols and clinical practice guidelines (COG), CPGs representation languages, web systems scalability, ontologies based systems, web based systems.	HELP [KGP91] HERMES [BMS ⁺ 93] DIAVAL [Die94] DIABNET [HGdPC96] MammoNet [KRSH97] ATHENA [ATO ⁺ 99] PAIRS [JJ99] <i>etc.</i>
<i>Present</i>	To represent and to reason with temporal knowledge. To adapt representation techniques and knowledge extraction to improve the decision making support in medicine. To develop capable methods of interfering in big databases. To formalize and to develop systems based on computerized CPGs.	Natural language processing, hybrid systems based on: ontologies, machine learning techniques, CPGs, knowledge representation and temporal reasoning, decision support based on computerized CPGs, variational methods to inference in great scale probabilistic models.	NasoNet [GADM02] LISA [BHBea02] NEONATE [HEF ⁺ 03] SAMOA [FGA ⁺ 03] DEGEL [SYS ⁺ 03] ProCarSur [PVTSS ⁺ 07] ESTDD [KK08] CORAAAL [NGH09] <i>etc.</i>

Table 2.8: Historical review of DMSMA and MKB systems.

Chapter 3

Knowledge Formalization in Medical Assistance

This chapter presents a description about knowledge formalization in the medical assistance domain. This description is made from the Knowledge Management and Artificial Intelligence perspective. First, there is a description of the formal knowledge categories in medical assistance. Second, and based in these categories, it is an introduction about the main knowledge representation formalisms and how they are used for reasoning and machine learning.

3.1 Introduction

The quality of medical assistance is directly related with the health care professional experience [Mil94], where such experience is the result of the combination of several types of *knowledge* (§2.2.2). Knowledge is the main part of decision making process on medical assistance, therefore, it is not surprising that in the medical informatics domain a trend has been observed towards the formalization of this knowledge [FJR98, AHL01, PT06, Ria06, KXY08].

Disciplines as Knowledge Management (KM) [MFK99] and Artificial Intelligence (AI) [Sho87] have contributed to knowledge formalization in general, and in medical assistance knowledge formalization in particular. *KM* is centred in the development of techniques which allow to organize, to share and to update this knowledge. Therefore, KM makes a distinction between two main categories of knowledge: declarative knowledge and procedural knowledge. *Declarative knowledge* (or *know-what knowledge*) is the knowledge of objects, facts and principles of a concrete domain. Facts and principles establish the relations and restrictions in the objects and among the objects of a domain. *Procedural knowledge* (or *know-how knowledge*) is the knowledge in which the control information that is needed to use the knowledge is inside the same knowledge. In the medical assistance domain, declarative knowledge refers to diseases, symptoms and signs, prescriptions,

diagnostic tests, etc., likewise, the relations among them elements, for example, what are the symptoms and signs of a particular disease, the contraindications of a medication, etc. On the other side, procedural knowledge refers to the assistance processes as making a diagnosis, treatment of a pathology or a medical-clinical problem.

Meanwhile, *AI* is centred in the development and improvement of formal structures for know-what and know-how knowledge representation. Also, in producing methods and algorithms to make intelligent activities, such as reasoning and inductive learning these knowledge structures.

3.2 Knowledge Representation in Medical Assistance

Knowledge representation can be defined as a series of syntactical and semantic conventions which allow the formalization of a determined type of knowledge. *Syntax* allows to specify a political series to combine symbols so as to form valid expressions. *Semantic* is the specification of how these expressions should be interpreted. This formalization has a double objective. First, to eliminate the uncertainty and variability which are not part of the medical assistance, and second, to allow the automatic manipulation of this knowledge in order to use automatic reasoning methods which arrive to similar conclusions to those that a health care professional would obtain. These conclusions can be solutions to proposed problems in a concrete knowledge domain (i.e., decision making support) or the inference of new knowledge.

Table 3.1 shows a classification of the main formalizations used to knowledge representation in medical assistance. This classification is based in four categories of knowledge representation [KXY08]: fuzzy logic, procedural knowledge, graphs & networks, and structured knowledge.

First, *fuzzy logic* (FL) [Zad65] is one of the logic based formalism which has been most used for knowledge representation in medical assistance. FL is characterized by which is a logic derived of the set theory which allows to represent imprecise, ambiguous and vague knowledge.

Second, *procedural* knowledge formalisms represent the knowledge of a domain in form of procedures, which describe the actions to be made in particular situations. Nowadays, the most popular procedural formalisms to represent medical knowledge are the *production systems* [New73] and *decision tables* [Hol75], where the procedural knowledge is represented by a set of *production rules* which allows to incorporate the domain knowledge.

Third, *graphs & networks* based representations are characterized by representing medical knowledge through directed graphs whose nodes are health care concepts and entities, and arcs represent relations among these concepts and entities. Decision trees [Qui86], partial orders [DM41], Bayesian

Knowledge Representation					
Knowledge	Category	Formalism	Diagnosis	Treatment	Prognosis
Know-What	Fuzzy Logic	Fuzzy Logic	[JLH02], [Has03], [SPBea03], [SOPN03], MedFrame/CADIAG-IV [BAH ⁺ 04], ESTDD [KK08], [GN09]	[PSG03]	
	Procedural	Production Rules	INTERLIST [PMM75], MYCIN [Sho76], PUFF [AKSR83], [RBW04]	ONCOSIN [Sho81])	
	Graphs & Networks	Decision Tables	EsPeR [CAJZ ⁺ 05]	[BdPL08]	[DWK05], [KTK08], [SBK ⁺ 09]
		Decision Trees	[SLPK04], [CPRB09], [Das10]		
Know-How	Structured	Partial Orders	[LVR07], [LVRB10]		
		Bayesian Networks	CASNET [Wei74], MUNIN [AWFA87], DIAVAL [Die94], MammoNet [KRSH97], PAIRS [JJ99], SAMOA [FGA ⁺ 03], [VLSB09]	CASNET [Wei74], DIABNET [HGdPC96], NasoNet [GADM02], [VLSB09]	NasoNet [GADM02], [RBW04], ProCarSur [PV7SS ⁺ 07], [vGJT ⁺ 07], [SDM ⁺ 09], [SDBB09]
	Artificial Neural Networks	[Das10]		[PM02], [LWHS03], [JAGRRJ ⁺ 03], [MSM ⁺ 05], [GBF ⁺ 06], [BBAM06], [KTK08], [LHHGR08]	
	Structured	Ontologies	MANELAS [Zwe94], GALEN [RRP96], UMLS [HLSB98], SNOMED [SCC97], FMA [RM03], ODDIN [GCRM ⁺ 10], TimeDdx [DP10]	MANELAS [Zwe94], GALEN [RRP96], UMLS [HLSB98], SNOMED, FMA [RM03]	
Structured	GPQ Representation Languages	Arden Syntax [SHJ ⁺ 94], Augmented Decision Tables [Shi97], Asbru [SMJ98], PROforma [FJR98], EON [TM99], PRODIGY [JTB ⁺ 00], GLIF [PBOea00], SAGE [BCH ⁺ 02], ATHENA [ATO ⁺ 99], GHRea00], LISA [BHBea02]	Arden Syntax [SHJ ⁺ 94], Augmented Decision Tables [Shi97], Asbru [SMJ98], PROforma [FJR98], EON [TM99], PRODIGY [JTB ⁺ 00], GLIF [PBOea00], SAGE [BCH ⁺ 02], ATHENA [ATO ⁺ 99], GHRea00], LISA [BHBea02]		

Table 3.1: Categories and formalisms of know-what and know-how knowledge representation in medical assistance.

networks [CGH97] and artificial neural networks [RM86], are examples of these types of knowledge representation formalisms.

Finally, the *structured representations* group those formalisms which allow making representations through well defined blocks of knowledge (i.e., classes or entities, their properties and the possible values which can have each property), and their relations. Traditional examples of these types of formalisms are the *semantic networks* [Qui68] and *frames* [Min75]. However, in the last decades the representation and organization of knowledge through *ontologies* [Gru93] and the use of *CPG representation languages* [SHJ⁺94, Shi97, SMJ98, FJR98, TM99, JTB⁺00, PBOea00, BCH⁺02] have been the last advances in the knowledge structured representation in medical assistance.

In the following sections a detailed description of these knowledge representations formalisms is introduced. This description is done taking into account the type of knowledge which they represent (i.e., know-what and know-how knowledge) and the medical assistance activity (i.e., diagnosis, treatment and prognosis) in which they have been used during the last decade [QBA01, DKB03, MHK05, BAHH07, CSAH09].

3.2.1 Know-What Knowledge Representation

Know-what knowledge in medical assistance can be represented through formalisms which allow making a decision by assigning a label or a value to a patient according to the available information. It is basically a classification process which proposes a diagnostic, a treatment or a prognostic from a limited finite or continuous set of possible alternatives. For example, the medical data about a patient can conclude that this patient has a particular disease (i.e., diagnostic), needs a specific therapy (i.e., treatment) or predict a determined evolution for the applied therapy (i.e., prognosis).

So, the formalisms of know-what knowledge representation are characterized by being able to solve decision processes taking into account a set of objects O (e.g., patients) and a set of classes C (e.g., diseases), where each object $o_i \in O$ is described by a finite set A of discrete and/or continuous attributes, which help to explain the medical characteristics of the cases behind the considered medical problem (e.g., demographical data, symptoms and signs, diagnostic tests outcomes, prognostic factors, etc.) and the class $c_i \in C$ to which o_i belongs. Each class c_i represents a particular medical problem. (e.g., set of diseases, treatments list and events to predict, etc.). A decision (e.g., diagnostic, treatment or prognostic) will consist in classifying each one of the objects of O in one of the classes of C , according to the particular medical problem to be considered. That is to say, $d : O \rightarrow C$.

Formalisms of Know-What Knowledge Representation in Diagnosis and Medical Treatment

Traditionally, the most used formalisms to know-what knowledge representation in the diagnostic and medical treatment are: fuzzy logic [Zad65], production rules [New73], decision tables [Hol75], decision trees [Qui86], partial orders [DM41] and, recently, ontologies [Gru93].

Fuzzy Logic

The *fuzzy logic* (FL) [Zad65] is based in the idea, that in a given time, it is not possible to determine the value of an attribute $a_j \in A$ for an object, but only to know the degree of membership of each one of the objects $o_i \in O$, and each value inside the variation range of the attribute a_j . For defining these degrees of membership, FL uses the notion of *fuzzy set*. Each fuzzy set has associated a *membership function* for its elements that indicates in which measure the element takes part of that set.

Fuzzy sets can be used in the representation of input attributes or fuzzy inputs, as in the process of classification in fuzzy classes [KS99]. In *fuzzy inputs*, instead of the original input values (e.g., measurement) its “fuzzy” versions can be used. For example, instead of a value of 145 mmHg for blood pressure, it can be used the vector [0.0, 0.4, 0.6] which defines the degrees of membership of that value to the fuzzy set [low, medium, high]. Also, in *fuzzy classes*, instead of determining that $d(o_i) = c_i$ with $c_i \in C$ the class which o_i belongs to, a *fuzzy classifier* makes a mapping $d : O \rightarrow [0, 1]^n$, with $n = |C|$. That is to say, $d(o_i) = [\mu_1(o_i), \dots, \mu_n(o_i)]$, where each $\mu_x(o_i)$ denotes the degree in which o_i belongs to the class c_x . The fuzzy decision $d(o_i)$ can be oriented to choose an only class of C . This process is called “defuzzification” [LK99].

The FL as formalism of know-what knowledge representation has been used, among others, in the diagnosis of inadequate analgesia for patients undergoing anaesthesia [JLH02], in the decision support of radiation therapy [PSG03], in the detection of breast cancer [Has03], lung cancer [SPBea03] and prostate cancer [SOPN03]. Among the systems which use FL, MedFrame/ CADIAG-IV [BAH⁺04] has been used in diseases diagnosis of internal medicine, and ESTDD [KK08] for diagnosis of thyroid diseases. The FL also has been used in the development of classification frames and to improve the diagnosis of diseases [GM09].

Production Rules

Production rules (PR) [New73] have been one of the most applied formalisms in the knowledge representation of DMSMA systems. Its representation structure is: IF *antecedent* THEN *consequent*, where the *antecedent* represents a condition for being evaluated that is usually represented as a conjunctive boolean expression. This expression is defined as an undetermined number of comparisons expressed as $\{a_i = v\}$, for discrete attributes and $\{a_i \leq v\}$ or $\{a_i \geq v\}$ for continuous attributes; being $a_i \in A$ and $v \in Dom(a_i)$. Likewise, the *consequent* represents a decision c_i , with $c_i \in C$. In this sense, an object $o \in O$ is covered by a decision rule, if the object accomplishes all the comparisons of the *antecedent* in conjunctive form. So, the decision proposed by the rule will be that one found in the *consequent*.

In order to obtain conclusions, the PR based systems use, mainly, two sorts of inference: forward chaining or progressive reasoning and backward chaining or regressive reasoning. *Forward chaining* is a process guided by data which considers as starting point all the known data and it goes progressively advancing towards the solution. The steps to be followed in this inference process are: unification, resolution and execution. In the *unification*, the rules found in the knowledge base are used to prove the known facts in that moment and to determine which of them are satisfied. A rule is satisfied when the rule antecedent is resolved to true. If as result of the unification step, there are different rules satisfied, these rules are solved by *resolution*. In this case, one of the satisfied rules is chosen according to a pre-established criterion such as the most priority rule [Mic87]. The last step is the *execution* of the rule. Execution can give one of the following results: a new fact which can be added to the base of facts, or a new rule which can be added to the knowledge base.

Backward chaining is a process guided by the objective, where a possible solution is chosen and to prove its validity the process searches for the evidence that supports it. The system starts by the objective (consequent part of rules) and acts backward for looking how that objective is deduced from data. It is produced directly or through intermediate conclusions or sub-objectives, trying to prove a hypothesis from the facts contained in the base of facts and which were obtained in the inference process.

Figure 3.1 [MSS06] shows a typical rule used in MYCIN system [Sho76]. In this rule, the MYCIN is able of to conclude about the probable cause of bacterial infection if the five conditions of the antecedent are satisfied by a specific patient.

Production rules as a formalism of know-what knowledge representation have been used, among others, in the following DMSMA systems: INTERNIST system [PMM75] designed for the disease

Rule507

IF

- 1) The infection that requires therapy is meningitis,
- 2) Organisms were not seen on the stain of the culture,
- 3) The type of infection is bacterial,
- 4) The patient does not have a head injury defect, and
- 5) The age of the patient is between 15 years and 55 years

THEN

The organisms that might be causing the infection are
diplococcus-pneumoniae and neisseria-meningitidis

Figure 3.1: Example of a production rule used in the MYCIN system.

diagnosis in internal medicine, MYCIN system [Sho76] developed to diagnose and suggest treatments for blood infectious diseases, ONCOSIN system [Sho81] developed to help the health care professionals in the treatment of patients with cancer that receives chemotherapy, PUFF system [AKSR83] developed for diagnosis and seriousness of lung diseases, or, nowadays, in rules based approaches for the diagnostic of coronary disease [RBW04].

Decision Tables

A *decision table* (DTa) [Hol75] is a matrix which joins a set of decision attributes A (or *conditions*) (e.g., signs, symptoms and diagnostic tests outcomes) with a set of *actions* C (e.g., conclude a diagnostic, starts a treatment, etc.). In a DTa, each decision value can be represented as a categorical value (e.g., the presence or absence of diabetes) or as a range of a continuous attribute (e.g., cholesterol ≥ 270 mg/dl). The number of values that each condition can assume is defined as the condition *module* [Shi97].

As figure 3.2 [SLG94] shows, the conditions and actions in a DTa are of the type stub and entry. The *stub conditions* represent the list of decision attributes (e.g., clinical status, anatomic distribution of disease, risk, ejection fraction) and the *stub actions* represent the list of the relevant medical action names (e.g., sort of pharmacological treatment, diagnostic tests, referrals to specialists, medical procedures). The *entry conditions* contain the values or states of decision attributes (e.g., PAIN, LOW, HIGHT, MODERATE) and the *entry actions*, optionally marked with a X in the DTa. Each entry column in the table represents an appropriate decision give the pertinent combination of decision values. Each column in the entry area is a rule, whose antecedents are

derived from the entries conditions and whose consequents are indicated by the entries actions. For example, the rule described in the column three of figure 3.2 can be read as: “IF clinical status is carcinogenic shock (SHK) AND Anatomic distribution of disease is 2-vessels including proximal left anterior descending (2V+P) AND risk is normal or low (LO) THEN CABG is appropriate”.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
Clinical status	SHK	SHK	SHK	SHK	SHK	SHK	SHK	SHK	SHK	SHK	SHK	SHK	SHK	SHK	PAIN	PAIN	PAIN	
Anatomy	LM	3V	2V+P	2V+P	2V+P	2V+P	2V+P	2V+P	PLAD	PLAD	PLAD	1V+P	1V+P	1V+P	LM	LM	LM	
Risk	-	-	LO	MOD	HI	LO	MOD	HI	LO	MOD	HI	LO	MOD	HI	LO	MOD	HI	
Ejection Fraction	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
CABG Appropriate	X	X	X	X		X	X		X	X		X	X		X	X		
Uncertain					X			X			X			X			X	
CABG Inappropriate																		
Column Count	9	9	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	
Clinical status	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	
Anatomy	3V	3V	3V	3V	3V	2V+P	2V+P	2V+P	2V+P	2V+P	2V+P	2V+P	2V+P	2V+P	2V+P	2V+P	2V+P	
Risk	LO	MOD	MOD	MOD	HI	LO	LO	LO	MOD	MOD	MOD	MOD	HI	LO	MOD	MOD	HI	
Ejection Fraction	-	NL	RED	LOW	-	NL	RED	LOW	NL	RED	LOW	-	-	NL	RED	LOW	-	
CABG Appropriate	X	X	X			X			X									
Uncertain				X	X		X	X		X	X	X	X	X	X			
CABG Inappropriate																X	X	
Column Count	3	3	1	1	3	1	1	1	1	1	1	1	3	3	1	1	1	3
	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	WDC
Clinical status	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	PAIN	N PN	0
Anatomy	PLAD	PLAD	PLAD	PLAD	PLAD	PLAD	PLAD	PLAD	PLAD	PLAD	1V+P	1V+P	1V+P	1V+P	1V+P	1V+P	-	54
Risk	LO	LO	LO	MOD	MOD	MOD	HI	HI	HI	LO	LO	LO	MOD	MOD	MOD	HI	-	72
Ejection Fraction	NL	RED	LOW	NL	RED	LOW	NL	RED	LOW	NL	RED	LOW	NL	RED	LOW	-	-	135
CABG Appropriate	X	X		X	X													
Uncertain			X			X	X	X		X	X		X	X				
CABG Inappropriate									X			X			X	X	X	
Column Count	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	3	54	

Figure 3.2: Example of a decision table.

The TDa as formalism of know-what knowledge representation has been used, among other medical contexts, to determine the adequate of CABG in acute myocardial infarction [SLG94], for the depression diagnosis in EsPeR preventive medicine system [CAJZ⁺05], to select the best action course in the treatment of gastric lymphoma no-Hodgkin [BdPL08], or to model different sorts of medical decisions [Ria11].

Decision Trees

A *decision tree* (DT) [Qui86] is a set of conditions organized in a hierarchical structure, so that the final decision can be determined following the conditions that are fulfilled from the tree root to

some of its leaf.

DTs represent the knowledge through structures formed by decision nodes (internal nodes) and leaf nodes. Decision nodes specify an attribute $a_i \in A$ which is defined on the objects in the domain O . The arcs which leave of a decision node define a partition of the range $Dom(a_i)$ of the attribute, so, each arc has associated one of the partition components which acts as a filter of the objects in O . Each leaf node has associated one of the categories of C . A DT with k leaf nodes partitions the space of objects O in k disjoint subsets, where one of the possible decisions of C is applied. Any object $o \in O$ will be associated by the DT in only one leaf node. The associated leaf node is determined following, from the root and down the tree, the path formed by the arcs of the decision nodes with a range of values which the object value belongs to that attribute. The DT leaf node achieved at the end of the path determines the class $c_i \in C$ which the object belongs to.

Figure 3.3 [Woz06] shows a DT which presents six possible diagnostic alternatives to hypertension: essential hypertension, fibroplastic renal artery stenosis, atheromatous renal artery stenosis, Conn's syndrome, renal cystic disease and pheochromocystoma. The decision about the sort of hypertension is made taking into account the patients information about the blood pressure measurement (i.e., systolic blood pressure), general information (i.e., palpitation and heart failure) and biochemical data (i.e., level of serum potassium). A diagnostic decision as essential hypertension is assigned to a patient that, following the DT, does not have palpitation symptoms and his/her serum potassium level is greater than 3,2 mEq/L (miliequivalents per litre).

DTs as a formalism of know-what knowledge representation have been used, among other medical domains, in the diagnosis of heart problems [SLPK04], in the diagnosis of optic nerve diseases [PKGG08], in the diagnosis of leukemia patients [CPRB09] or in combination with artificial neural networks in the diagnosis of Parkinson disease [Das10].

Partial Orders

Partial Orders (PO) [DM41] are formalisms which allow to represent binary relations among attributes. Formally, given a set of attributes A , a PO $P \subseteq A \times A$, over these attributes is a binary relation such that P is reflexive (i.e., $a_i \in A \Rightarrow (a_i, a_i) \in P$), antisymmetric (i.e., $(a_i, a_j) \in P$ and $(a_j, a_i) \in P \Rightarrow a_i = a_j$), and transitive (i.e., $(a_i, a_j) \in P$ and $(a_j, a_k) \in P \Rightarrow (a_i, a_k) \in P$).

PO are typically represented as directed acyclic graphs (DAG) where all the deducible nodes by reflexivity and transitivity are omitted. Figure 3.4 shows an example of how a PO represents know-what knowledge in the breast cancer domain according to the TNM staging system (Tumour, Node

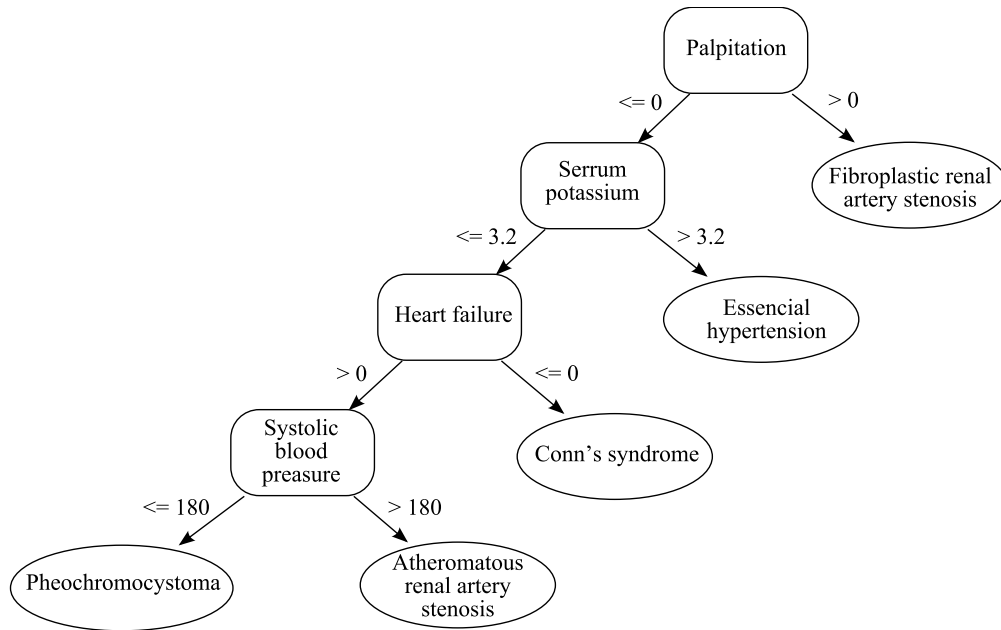
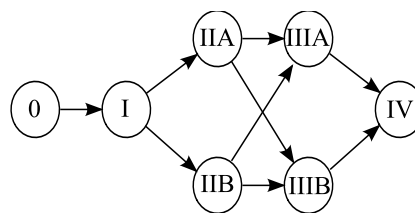


Figure 3.3: Example of a decision tree to the diagnosis of hypertension sorts.

and Metastasis) [SW02]. This PO shows the different disease severity states and their relations. Here, a patient in IIA state has a severity level less than another one patient in IIIA or IIIB states (directly connected), or in IV state (connected by transitivity), and not comparable in terms of severity to patients in IIB state. The 0 state represents the minor severity state of disease and indicates carcinoma *in situ* without any affected lymph node, and the IV state represents the major severity state of disease and indicates that the cancer has affected the armpits lymph nodes and there is metastasis to other parts of the body.



TNM BREAST CANCER CONDITION

Stage 0: carcinoma in situ; no cells in lymph nodes. **Stage I:** the tumor size < 2cm; armpit lymph node not affected; cancer not spread. **Stage IIA:** no cells in lymph nodes, cancer has broken through the outer covering of the bowel. **Stage IIB:** grown through the outer covering of the bowel wall and into tissues or organs next to the bowel, no lymph nodes affected; cancer not spread. **Stage IIIA:** cancer in the inner layer of the bowel wall or has grown into the muscle layer; 1-to-3 nearby lymph nodes contain cancer cells. **Stage IIIB:** cancer has grown through the bowel wall or into surrounding body tissues/organs; 1-to-3 nearby lymph nodes contain cancer cells. **Stage IV:** any size; armpit lymph nodes can be affected; metastasis to other parts of the body.

Figure 3.4: Example of a partial order in the breast cancer domain according to TNM staging system.

PO as formalisms of know-what knowledge representation has been used, in combination with DT, to the diagnosis of disease [LVRC07, LVRB10].

Ontologies

An *ontology* is a formal and explicit conceptualization of a shared knowledge [Gru93]. In this definition, *conceptualization* refers to an abstract model of some phenomenon in the world by having identified the relevant concepts of that phenomenon. *Formal* refers to the fact that the abstract model which represents the ontology should be machine-readable. *Explicit* means that the type of concepts used (e.g., diseases, symptoms, etc.) and the constraints on their use are explicitly defined. *Shared* reflects the notion that an ontology captures consensual knowledge, that is, it is not private to some individual, but accepted by a group.

In the Ontologies the knowledge is formalized according to five levels of components [GB99]: classes, concepts, relations, functions, axioms, and instances. The *Classes* in an ontology are usually organized in taxonomies. Sometimes, the ontology notion is distorted, the sense that the taxonomies are considered as full ontologies [SBF98]. *Concepts* are used in a broad sense. A concept can be anything about which something is said, and, therefore, it could also be the description of a task, function, action, strategy, reasoning process, etc. *Relations* represent a type of interaction between concepts C_i of the domain. That is, $R : C_1 \times C_2 \times \dots \times C_n$. For example, the “subclass-of” and “connected to” binary relations, are parts of these interactions. *Functions* are special cases of relations which the n -th element of the relationship is unique for the $n - 1$ preceding elements. That is, $F : C_1 \times C_2 \times \dots \times C_{n-1} \rightarrow C_n$. *Axioms* are used to model sentences which are always true. *Instances* are used to represent elements or concrete facts in the Ontology.

Figure 3.5 shows the root nodes of the hierarchies of concepts of the “Case Profile Ontology” (CPO) developed within European Project K4CARE (www.k4care.net). This ontology provides a formal representation of medical knowledge about syndromes, signs, symptoms and diseases (e.g., symptoms associated to each disease) and relationships and constraints among them. The knowledge representation is based in six basic *concepts*: problem evaluation (e.g., laboratory analysis, diagnostic test, etc.), signs and symptoms (fever, edema, pain, dizziness, etc.) social aspects (e.g., poverty, violence, etc.), syndromes (e.g., cognitive impairment and immobility), diseases (e.g., dementia, delirium, depression, etc.) and interventions (e.g., pharmacological treatment, rehabilitation, etc.). The *relationships* of these concepts are represented with the properties and constraints of the ontology. For example, the property “can be expression of” allows to relate which syndrome is connected

with what disease (e.g., immobility syndrome *can be expression* of arthritis disease) or the property “has intervention” which links social aspects, syndromes and diseases with possible interventions (e.g., dementia disease *has intervention* nursing care).

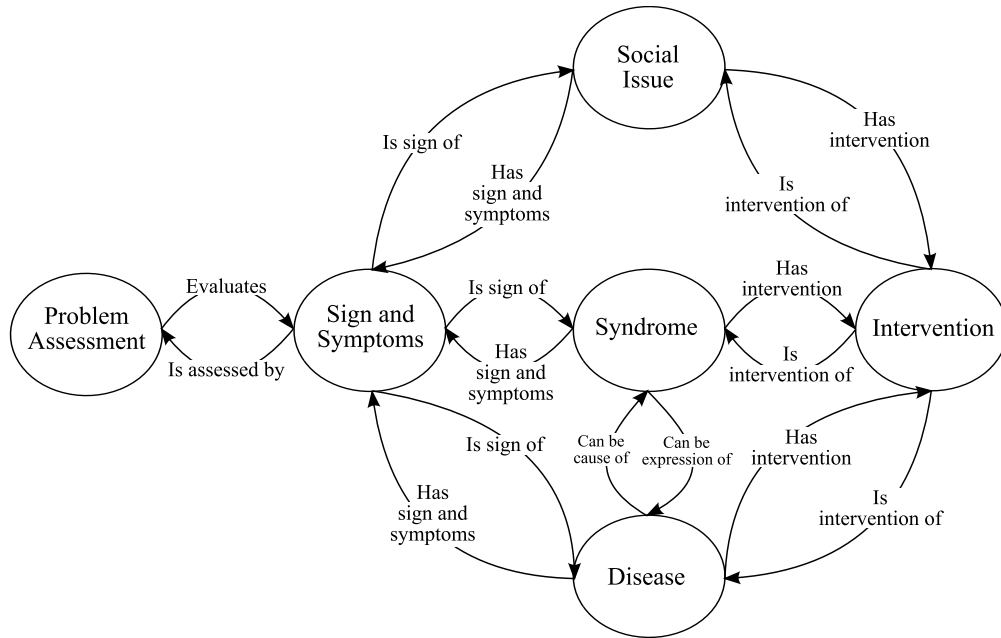


Figure 3.5: Example of an ontology in medical domain.

Ontologies as formalism of know-what knowledge representation have been used in encoding and classification systems as the MANELAS [Zwe94] in coronary disease domain, GALEN (Generalized Architecture for Languages, Encyclopaedias and Nomenclatures in medicine) [RRP96], SNOMED (Systematized Nomenclature of Medicine) [SCC97] and UMLS (Unified Medical Language System) [HLSB98] in general medicine, and FMA (Foundational Model of Anatomy) [RM03] in the anatomy domain. Also, the ODDIN [GCRM⁺10] and TimeDDx [DP10] systems are two cases of ontologies used for the differential diagnosis.

Formalisms of Know-what Knowledge Representation in Medical Prognosis

The traditional formalisms of know-what knowledge representation in medical prognosis activity are Bayesian networks [CGH97] and artificial neural networks [RM86], although both formalisms also have been used in the diagnosis and medical treatment activities, as it is shown in table 3.1.

Bayesian Networks

Bayesian networks (BN) [CGH97] are a formalism to uncertain knowledge representation, which allows to establish reasoning based on probability theory. A BN is a directed acyclic graph (DAG) whose nodes A represent attributes or uncertain events and whose relationships define probability dependencies between these events. These relationships are quantified by the association of a conditional probability table to each node a_i . Each conditional probability table contains the probability distribution of values in a node a_i , taking into account any configuration of its parent's values. For the root nodes, only their *a priori* probabilities are necessary. Prediction in a BN will consist in providing the values of observed events and the calculation of posterior probability of some not observed events, in the following way: let, c the class to be predicted, A the set of attributes of an object O ; $P(c|A)$ the probability of an object with attributes A belongs to the class c . So, the aim is to find the class c verifying $P(c'|A) = \max_c P(c|A)$. Using the Bayes theorem, we have $P(c|A) = \frac{P(A|c)\pi_c}{\sum_k P(A|k)\pi_k}$, where π_k denote the a priori probability of each class.

Inference in a BN, and in the probabilistic networks in general, consist in *evidence propagation* through of the network in order to know the posteriori probability of the variables. The propagation consists in giving values to some attributes (*evidence*), and to obtain the posterior probability of the other attributes given the known attributes (or *instantiated*). This propagation is one of the most important tasks because it allows to obtain conclusions when there is new information (e.g., signs, symptoms, etc.) [CGH97], and it will depend of the type of network structure which is being used, for example, a tree [KP83], a polytree¹ [Pea86] or a multi-connected network² [Coo90].

An example of BN application is shown in figure 3.6. This network is used in the ProCarSur system [PVTSS⁺07] and it allows to make, after a cardiac surgery, prognosis about exitus, length of stay in the intensive care unit, and occurrence of complications. For making the prognosis, this BN uses twenty four variables which allow to distinguish three phases: the preoperative phase composed by eight variables, the operative phase composed by four variables and the postoperative phase composed by twelve physiological variables and of surgery complication. Also, the network has an outcome variable *hospmort* which represents mortality during hospitalization.

BN as formalisms of know-what knowledge representation in medical prognosis, have been used, among others, in the NasoNet system [GADM02] to predict the nasopharynx cancer extension in

¹A polytree is a network in which a node can have many parents, but without existing multiple paths between nodes (connected network in a simple way).

²A multi-connected network is a non-connected network in a simple way, that is, where there are multiple paths between nodes).

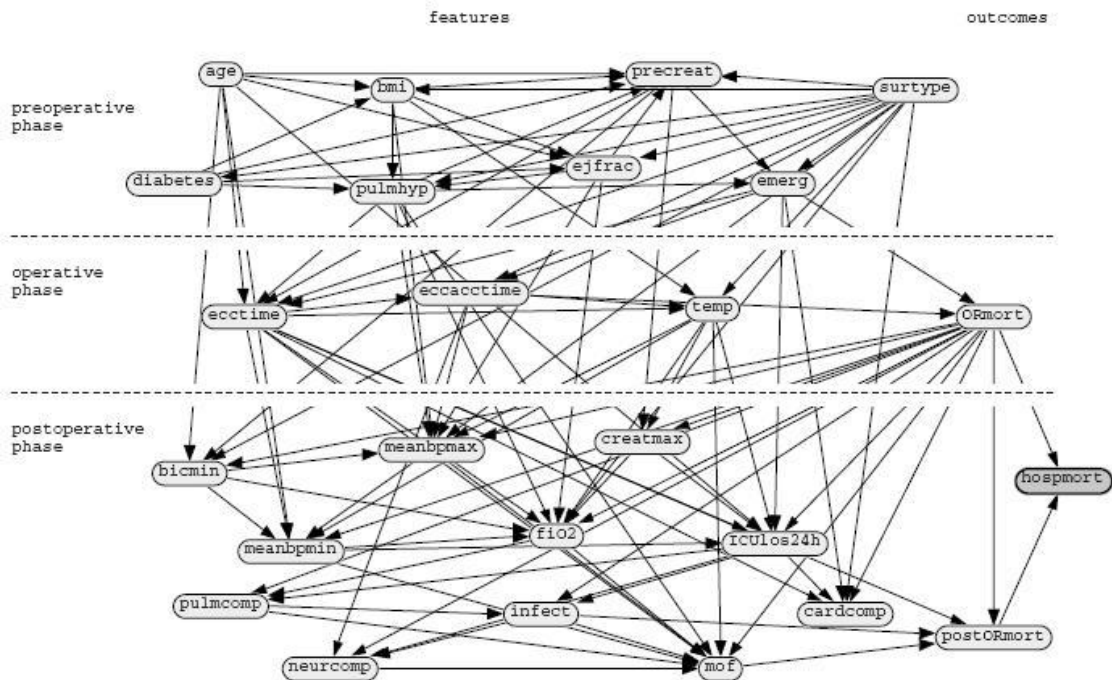


Figure 3.6: Prognostic BN in the ProCarSur system.

a patient, to predict the morbidity and mortality of patients with cardiac diseases [RBW04], to predict the development of carcinoid heart disease [vGJT⁺07], to predict the patients evolution with prostate cancer after the intensity modulated radiation therapy [SDM⁺09], or the survival analysis of prostate cancer domain [SDBB09].

Artificial Neural Networks

Artificial neural networks (ANN) [RM86] are formalisms of know-what knowledge representation based in the emulation of information biological processes. ANNs model the knowledge in classification problems by means of a structure which presents as *input nodes* the predictive variables A , as *output nodes* the different variables for being classified C , and several intermediate layers of nodes, called *hidden layers*, that provided freedom degrees to the ANN through which it is able to represent the environment characteristics to be modelled. The nodes in a particular level are connected to the nodes in next level, quantifying that connection by means of synaptic weights w_{ij} , which in the learning process, sometimes they are calculated by a backpropagation algorithm [RM86].

Formally, an ANN represents the knowledge through a direct graph, where each node (or neuron) n_i has:

- A set of inputs A_i (or connections with the n neurons of previous layer), each one with a synaptic weight w_{ij} with $j = 1, \dots, n$.
- A propagation rule h_i defined from the set of inputs A_i and the synaptic weight w_{ij} . That is, $h_i(a_{i_1}, \dots, a_{i_n}, w_{i_1}, \dots, w_{i_n})$. The most used propagation rule is a lineal combination of the inputs, weighted with the synaptic weight (i.e., $\sum_{j=1}^n w_{ij}a_{i_j}$).
- A activation function, which simultaneously represent the neuron output and its activation state. if y_i denotes this activaton function, then $y_i = f_i \circ h_i$.

An example of ANN application in medical prognosis is shown in figure 3.7 [MSM⁺05]. This ANN was designed to predict whether a coronary arteriography³ on a particular patient could reveal a significative coronary stenosis⁴ (>50%), very often, coronary stenosis leads to a coronary intervention. For making the prognosis, the ANN uses eleven independent variables in the input layer: age (32-79 years old), height (54-78 in), weight (105-350 lbs), pain classification according to Canadian Cardiovascular Society (1-4), stable angina (0,1), atypical chest pain (0,1), rest pain (0,1), positive stress test (0,1), negative stress test (0,1), diabetes (0,1) and hypertension (0,1). Also it uses thirty-six neurons in the hidden layer and an only neuron in the output layer representing the SIG-CAD (Significant Coronary Artery Stenosis) prediction.

The ANN as formalisms of know-what knowledge representation in medical prognosis, have been used, among other applications, in the classification of patients into prognostic risk groups [LWHS03], to predict the survival of breast cancer patients [BBAM06], to predict the presence the coronary artery disease [KTK08] or to predict the virulence response, in combination with therapies, to the AIDS (acquired immunodeficiency syndrome) [WLR⁺09].

3.2.2 Know-How Knowledge Representation

Unlike the know-what knowledge representation, the know-how knowledge in medical assistance is represented through formalisms that allows guidance to the health care professionals in decision making, when they do not have enough information about the patient or his/her disease which prevents them from reaching conclusions respect to a diagnostic or to a specific treatment. In this sense, these formalisms allow us to represent explicit knowledge about sequences of actions to be

³Coronary arteriography (or coronary angiography) is a procedure that uses a special dye (contrast material) and x-rays to see how blood flows through your heart.

⁴Coronary stenosis is a disorder characterized by the narrowing of the coronary artery which threatening the arriving of oxygen to the myocardial.

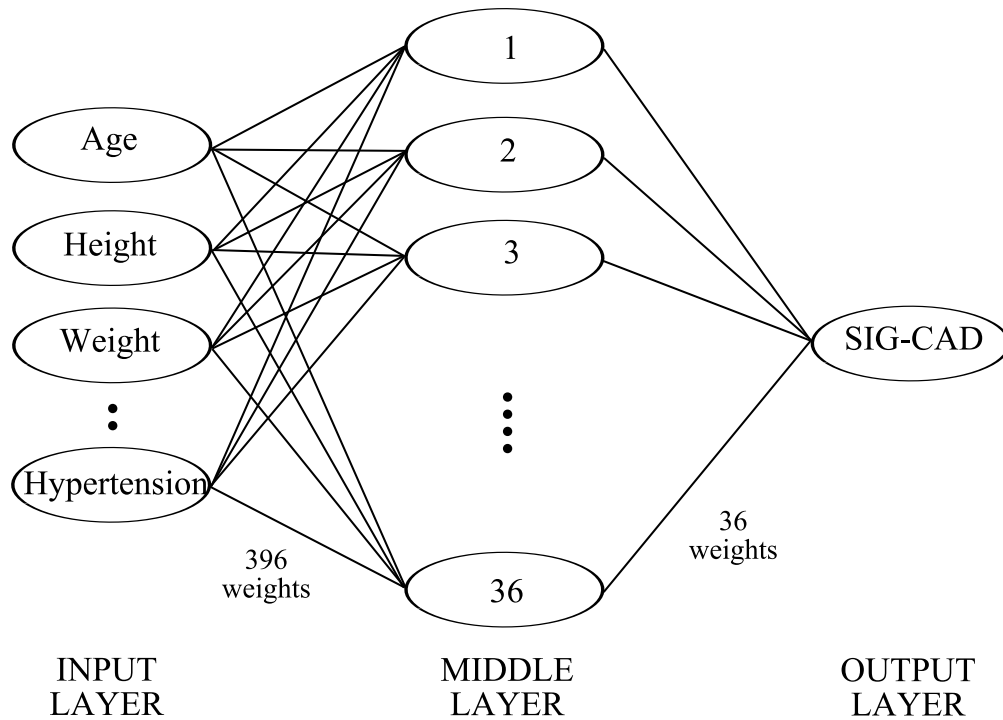


Figure 3.7: Example of ANN used to predict significant coronary artery disease.

taken, with the aim of reaching a decision on the final process. Basically, these actions can be testing, analysis and other medical procedures as prescriptions, life style modifications, etc.

Formalisms of Know-How Knowledge Representation in Diagnosis and medical Treatment

Languages to represent computer-iterpretable guidelines [SHJ⁺94, Shi97, SMJ98, FJR98, TM99, JTB⁺00, PBOea00, BCH⁺02] are systems to describe know-how knowledge about diagnostic and therapeutic activities. These languages have primitives which are used for representing specific clinical tasks [WPT⁺02, WTSR10]. These primitives, according the type of task which we want to represent, are classified in two categories: actions and decisions. Also, some languages have primitives which are used to represent intermediate states in a specific context during the CPGs application. These intermediate states can be descriptions of the patient medical situation, or of a guideline implementation system.

An *action* is a clinical or administrative task which is recommended to perform, maintain or avoid during the process of the CPG application (e.g., recommendation of a medication, or invocation of another CPG, etc.). A *decision* is a selection from a set of alternatives based on predefined

criteria in a CPG (e.g., selection of a diagnostic test from a set of potentials). A *patient state* is a clinical individual description of a patient based on actions and decisions which have been made for that patient (e.g., the state of “*eligible-for-the-second-dose*” contains the description of a patient who has received the first dose of the influenza vaccine and is eligible for the second dose). An *execution state* is a description of a CPG implementation system based on the action and decision tasks defined previously (e.g., after that a patient is in the state “*eligible-for-the-second-dose*”, the CPG execution system could change to the “*ready*” execution state for the CPG influenza vaccine.)

CIG Representation Languages

In sections 2.3.1 and 2.4.1 CPGs and the medical algorithms (MA) were introduced as the current alternatives of know-how knowledge representation in medical assistance. However, these representations show the medical information in a textual and narrative way, present recommendations based in population, and the information contained within them are of difficult access and application to a specific patient during a medical consultation. An alternative to solve these disadvantages has been the development of formal representations which allow computational interpretation of the medical knowledge contained in the CPGs. This required the development of several languages to formalize the CPGs in form of Computer Interpretable Guidelines (*CIG's*). Table 3.2 summarizes chronologically the main CPG representation languages, emphasizing, for each one of them, the primitives which use and the institutions that have developed them.

- *Arden Syntax* [SHJ⁺94] is a model developed to represent know-how knowledge through logic modules called *Medical Logic Modules* (MLMs). Each MLM has three descriptive parts or categories: a *maintenance* category which contains specific information about the module (e.g., module title, version, author, etc.), a *library* category which contains the module meaning (e.g., purpose, explanation, keywords, etc.) and a *knowledge* category which describes the module meaning. The representation primitives in Arden Syntax are based in two slots: action and logic slots. The *action slot* indicates the appropriate actions to the condition. The *logic slot* contains the current decision criterion which allows leading to a determined action. Also, Arden Syntax has a *data slot* used to obtain the concepts values which have been mentioned in the MLM from a hospital database and an *evocation slot* that specifies the context in which the MLM should be executed.

Figure 3.8 [Hea02] shows a MLM example used by Arden Syntax. This MLM is used to alert when a patient is allergic to the penicillin according to his/her medical record.

CPG Representation Languages						
Language	Representation Primitives			Execution State	Developed by	
	Action	Decision	Patient State			
Arden Syntax	action slot	logic slot	no	no	HL7 Arden Syntax Special Group and Clinical Decision Support Technical Committee www.hl7.org/library/bookstore/	
Augmented Decision Tables	action stub	decision stub	n/a	n/a		
Asbru	plan	condition, preference	temporal pattern	state plan	The Asgaard project (The Vienna University of Technology (AT) and Stanford Medical Informatics (USA)) www.asgaard.tuwien.ac.at	
PROforma	action, queries	decision	n/a	task state	Advance Computation Laboratory of Cancer Research (UK) www.acl.icnet.uk/lab/proforma.html	
PRODIGY	action, activity	decision	scenario	n/a	The Newcastle University (UK) www.openclinical.org/gmm_prodigy.html	
GLIF3	action step	decision step	patient state step	no	The Stanford University (USA), The Harvard University (USA), The McGill University (USA) and The Columbia University (USA) http://www.glif.org	
EON	action, activity	decision step	scenario, state	no	The Stanford University (USA) www.smi.stanford.edu/projects/eon/index.html	
SAGE	action nodes	decision nodes	context nodes	routing state	GE Healthcare, Apelon, Inc. (USA), Intermountain Healthcare (USA), Stanford University School of Medicine (USA), The Mayo Clinic (USA) and the University of Nebraska Medical Center (USA) http://sage.whatever.org	

Table 3.2: CPG representation languages

Contraindication Alert MLM:

```

maintenance:
  title: Check for penicillin allergy;;
  mlmname: pen_allergy;;
  arden: ASTM-E1460-1995;;
  version: 1.00;;
  institution: Columbia-Presbyterian Medical Center;;
  author: George Hripcsak, M.D.;;
  specialist: ;;
  date: 1991-03-18;;
  validation: testing;;
library:
  purpose:
    When a penicillin is prescribed, check for an allergy. (This MLM
    demonstrates checking for contraindications.);
  explanation:
    This MLM is evoked when a penicillin medication is ordered. An
    alert is generated because the patient has an allergy to
    penicillin recorded.;
  keywords: penicillin; allergy;;
  citations: ;;
knowledge:
  type: data-driven;;
  data:
    /* an order for a penicillin evokes this MLM */
    penicillin_order := event {medication_order where class =
    penicillin};
    /* find allergies */
    penicillin_allergy := read last {allergy where agent_class =
    penicillin};
    ;;
  evoke:
    penicillin_order;;
  logic:
    if exist(penicillin_allergy) then
      conclude true;
    endif;
    ;;
  action:
    write "Caution, the patient has the following allergy to
    penicillin
    documented: " || penicillin_allergy;;
  urgency: 50;;
end:

```

Figure 3.8: Example of a MLM in Arden Syntax.

- *Augmented decision tables* [Shi97] are a representation based in a decision table (§3.2.1) which incorporates in its rows and columns additional information about probability and utility. This additional information is stored in slots of several levels under the decision table and allows to relate several representation components with cells, rows and columns. The representation primitives are the action stub and the decision stub, which operation is similar to the decision tables described previously in section 3.2.1.
- *Asbru*[SMJ98] allows to represent know-how knowledge through a set of hierarchical plans (skeletal-plan). Each plan is identified by a unique name and a arguments set which include time annotations that represents the temporal link of plan. Asbru uses as representation primitives five basic components: plan, conditions, preferences, temporal patterns and a plan body. The *plan* describes the set of intentions which define the objective to be achieved. The *conditions* represent the control mechanisms for executing the plans. These mechanisms correspond to filter and execute, suspend, abort, complete and reactivate conditions. The preferences allow to limit the selection of a plan to achieve a determined objective, or to express the plan behaviour level (strategy). The *temporal patterns* allow to activate the functional relations of model between the plan arguments and the measurable parameters. The *state plan* contains a set of plans to be executed in parallel, in sequence, in any order or with some frequency.

Figure 3.9 [Bos01] shows an Asbru hierarchical plan. The objective of this plan is the diagnostic and treatment of the hyperbilirubinemia or excess of bilirubin in the blood.

- *PROforma*[FJR98] represents the CPG knowledge as a directed graph which nodes are instances of a closed set of classes, called *PROforma task ontology*. Each CPG is modelled as a plan which consists in a sequence of tasks, where all of them are derived from a root task. PROforma task ontology defines four tasks as representation primitives: actions and queries, decisions and plans. The *actions* represent some procedure which needs to be issued in an external environment (e.g., a clinical user, external software or a device). *Queries* represent CPG points in which the information should be provided by an expert or an external system. A *decision* is represented as a set of possible candidate outcomes, and several types of logic expressions which support or oppose to each candidate. Each candidate is associated with a set of schemes. Each scheme contains rules, qualitative variables, weights and certainty factors in agree or disagree of the candidate, establishing the preference for that candidate. The *plans*

PLAN	Diagnostics&Treatment-Hyperbilirubinemia
TIME ANNOTATION	
PREFERENCES	
INTENTIONS	Avoid intermediate state: (bilirubin = transfusion)
CONDITIONS	Abort-condition: ((term-child = no) Explanation: "Exiting the protocol to individualized clinical evaluation, including assessment of jaundice in light of prematurity" OR (age = day1) Explanation: "Exiting the protocol to individualized clinical evaluation, including assessment of jaundice and non-immune hemolytic disease" OR (pathologic-reason = yes)) Complete-condition: ((jaundice-clinically-significant = no) Explanation: "Follow this infant in routine clinical supervision" OR (completed(treatment-hyperbilirubinemia)))
EFFECTS	
PLAN-BODY	Sequential subplans: <i>Continuation specification: none</i> Ask Term-child Ask Age-child Diagnostics-hyperbilirubinemia Treatment-hyperbilirubinemia

Figure 3.9: Example of a plan represented in Asbru.

are collections of tasks that are grouped according to logic criteria (e.g., tasks performed at the same time).

Figure 3.10 [FJR98] shows a general plan, based on PROforma, to the managing of acute asthma.

- *GLIF* (Guideline Interchange Format) [OMGM⁺98, PBOea00] is a model for the structuring representation of the CPG to three different levels of abstraction: conceptual, computable and implementable. In the *conceptual* level the CPGs are represented as flowcharts for their dissemination. In the *computable* level the CPGs are expressions which define the patients data, medical actions and algorithmic control structures, allowing their logic analysis for its coherence and integrity. The *implementable* level allows its integration in some information system for being computerized. The CPG representation is made as flowcharts of temporarily sequenced nodes. These nodes are called steps and define the following representation primitives: action step, decision step and patient state step. The *action step* specifies medical actions made to patients during the process of patient care. The *decision step* represents decision points in the CPG. These decision points can be deterministic (case step) as non-

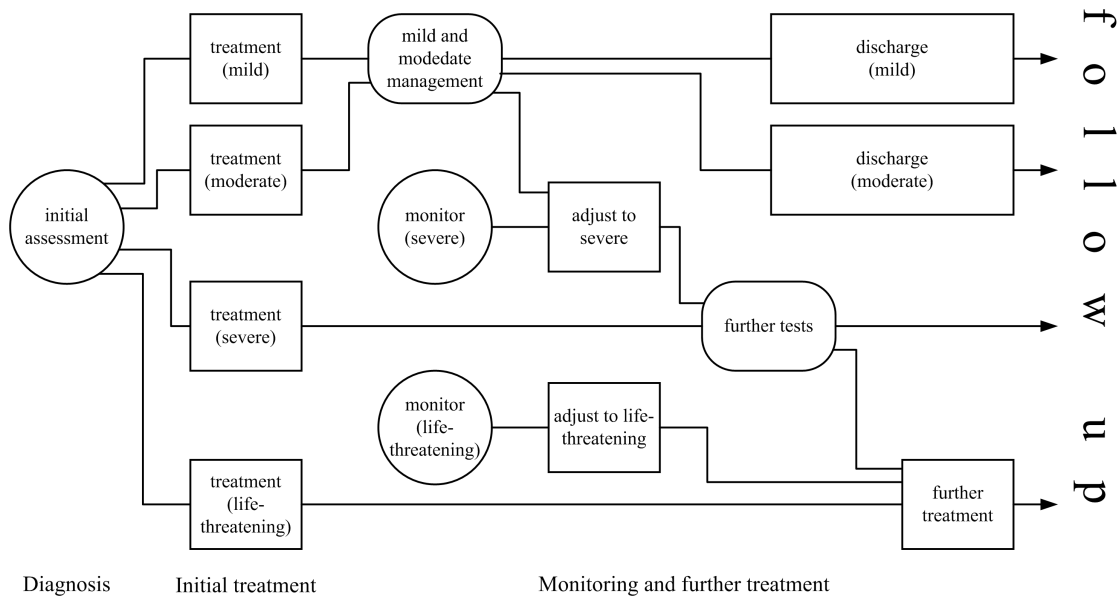


Figure 3.10: Example of a plan represented in PROforma.

deterministic (option step). The *patient state step* is used as a label to describe the patient state that is achieved in previous steps, or, as entry point in the CPG. Moreover, it uses a *branching step* to guide the flow to different steps in parallel or in any order, and a *synchronization step* used in conjunction with the branching step to model simultaneously multiple paths through CPG.

Figure 3.11 [PBOea00] shows an example of GLIF based representation for patients management with chronic stable angina. The action steps are represented through squares and the decision steps, case step and option step, are represented by diamonds and hexagons, respectively.

- *EON*[TM99], represents know-how knowledge through graphs of temporal sequences (flowchart) of instantiated classes. For representing that knowledge, EON uses the following primitives: action and activity steps, decisions, scenarios and activity state. *Actions* describe the practice workup that should be made immediately, unlike to the *activities* which are continuous processes. *Decisions* represent options from a set of available alternatives. Actions and decisions can have associated *objectives* represented by boolean criteria, which defines the intention to be accomplished in these steps. A *patient scenario* is used to describe a patient state according to decisions made and the actions completed. These sceneries allow to a health care professional synchronize the patient management with a part of the CPG and moreover, are

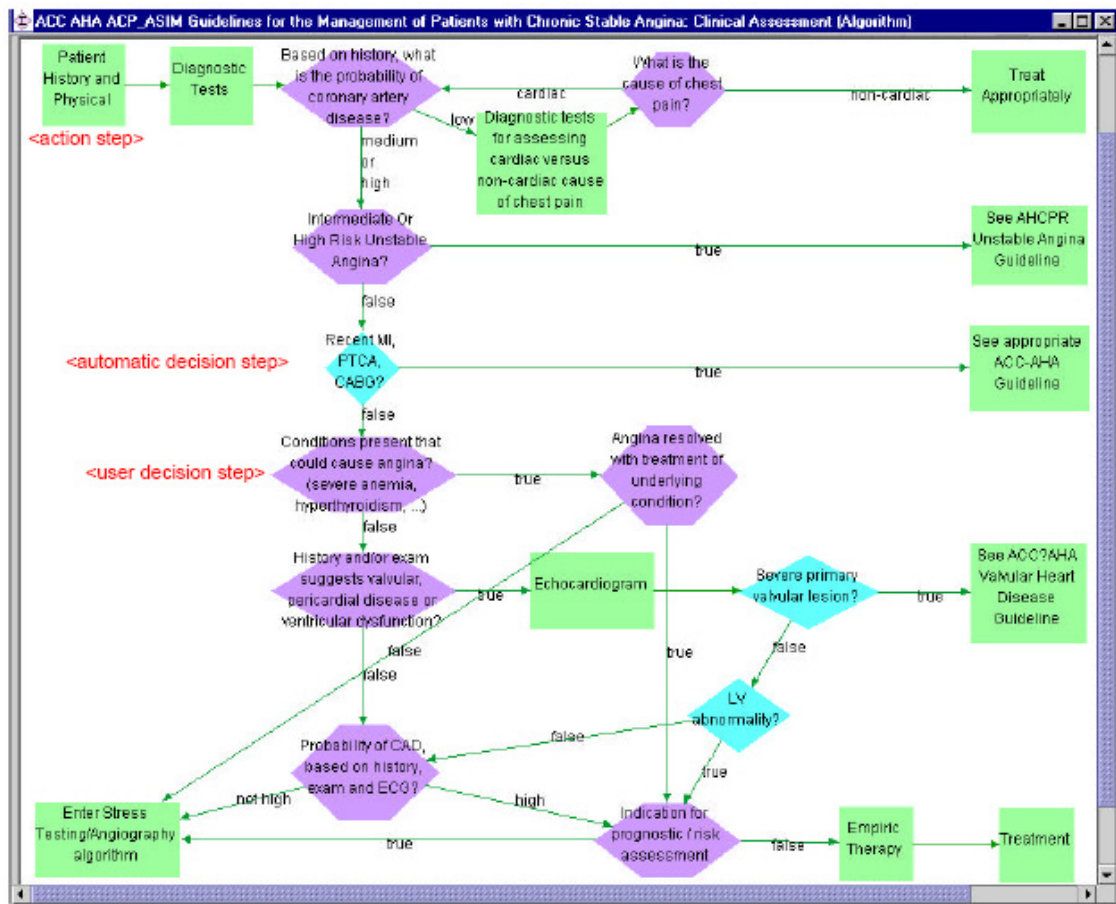


Figure 3.11: Example of a plan represented in GLIF.

commonly used as an entry point to the CPG. An *activity state* is used to describe the patient state respect to the activities.

Figure 3.12 [GHRea00] shows the representation primitives used by EON. The screen on the left of the figure shows part of the class hierarchy used by EON. The right hand side screen of the figure, shows how EON represents, decision points and action alternatives in terms of patient scenarios in the setting of managing hypertension patients.

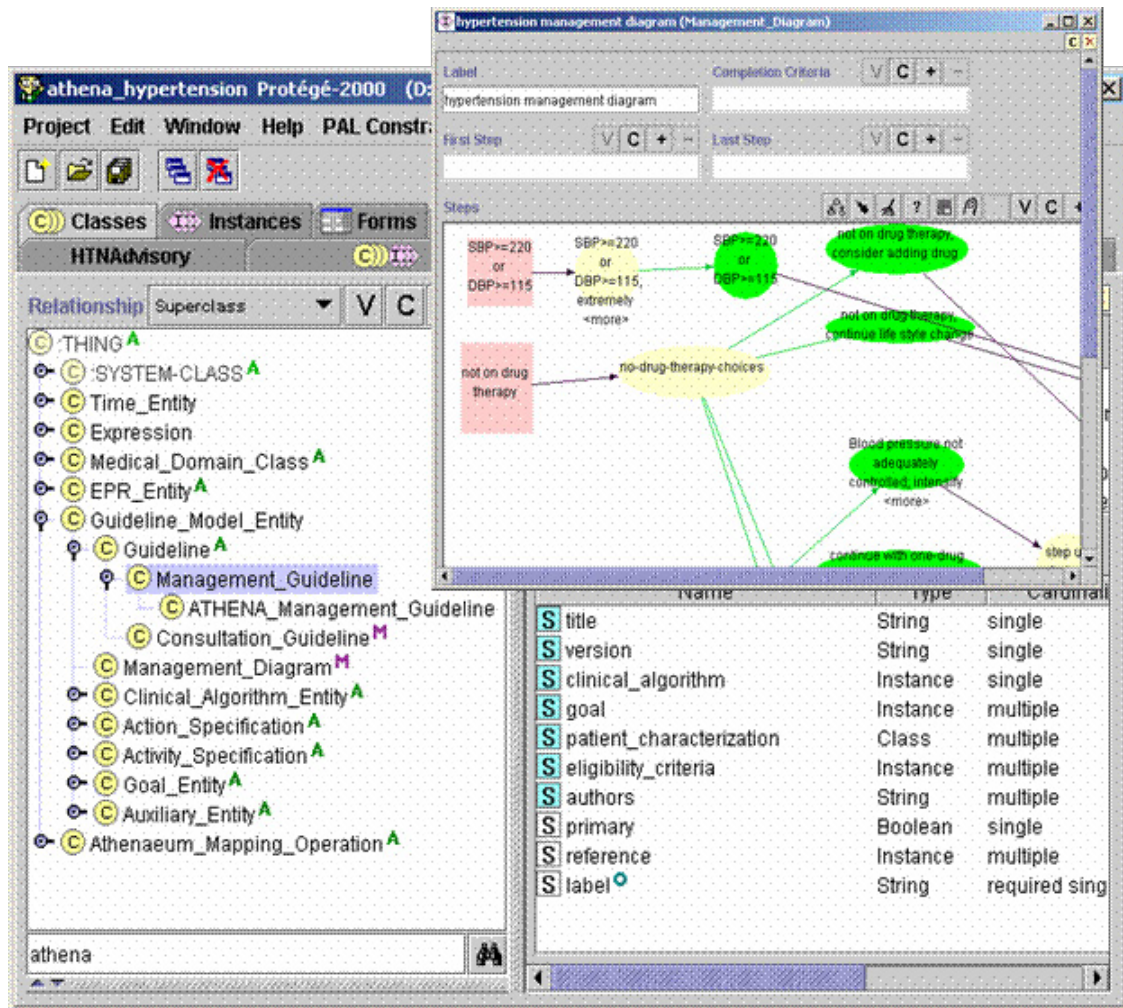


Figure 3.12: Example of a CPG represented in EON.

- *PRODIGY* [JTB⁺00], as EON, uses representation primitives based on action and activities steps, decisions and scenarios. Here, the scenarios are patient states defined by the patient condition and his/her current treatment. Each scenario is associated with a consultation template which describes the best-practice workup for a patient in that scenario and an option

between different action alternatives.

Figure 3.13 [TM00] shows an example of a representation based in PRODIGY. This representation is based in two possible scenarios *Taking no antihypertensive medication* and *Taking antihypertensive medication* which represent the patient states, and decision criteria *rule-in* which help to determine what action will be the most adequate, either *continue lifestyle change* or *Initiate drug therapy*.

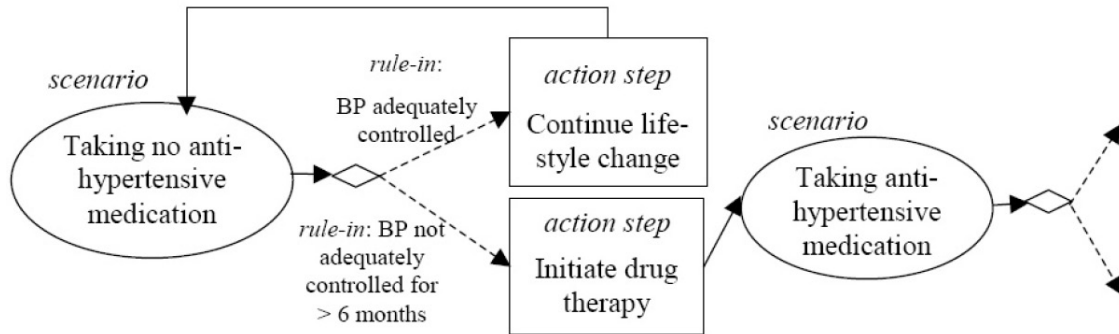


Figure 3.13: Example of CPG representation based on PRODIGY.

- *SAGE*(Sharable Active Guideline Environment)[BCH⁺02] is a model which allows to formulate the CPG content in a set of recommendations. The *recommendation set* is a formalization of the CPG actions and decisions to a workflow context in a specific medical situation. For that, SAGE is based in a set of nodes which describe the actions, decisions, context and the know-how knowledge routing. The *action nodes* are used to support the recommendations set (e.g., implementation options), also, the action nodes can include support to the messaging between the system devices, the objectives specification, recovery and storage in database, planning events, etc. The *decision nodes* describe the acquisition of data (directly from an Electronic Patient Record or in interactive way through questions to the health care professional) and the decision which allows to evaluate the most logic branch to be followed. The *context nodes* allow to define attributes for specifying the events, the medical properties and the patient states. The *routing nodes* allow the synchronization of the different activity routes of the model.

Figure 3.14 [RBT⁺04] shows a set of recommendations which are based on actions (*A1*, *A2* and *A3*), decisions (*D1* and *D2*), context (*C1* and *C2*) and routing (*R1*) for the triage⁵ and

⁵Triage is a medicinal emergency and disaster management process to determine the priority of patients' treatments

treatment of patients that have been suffered an acute ischemic stroke.

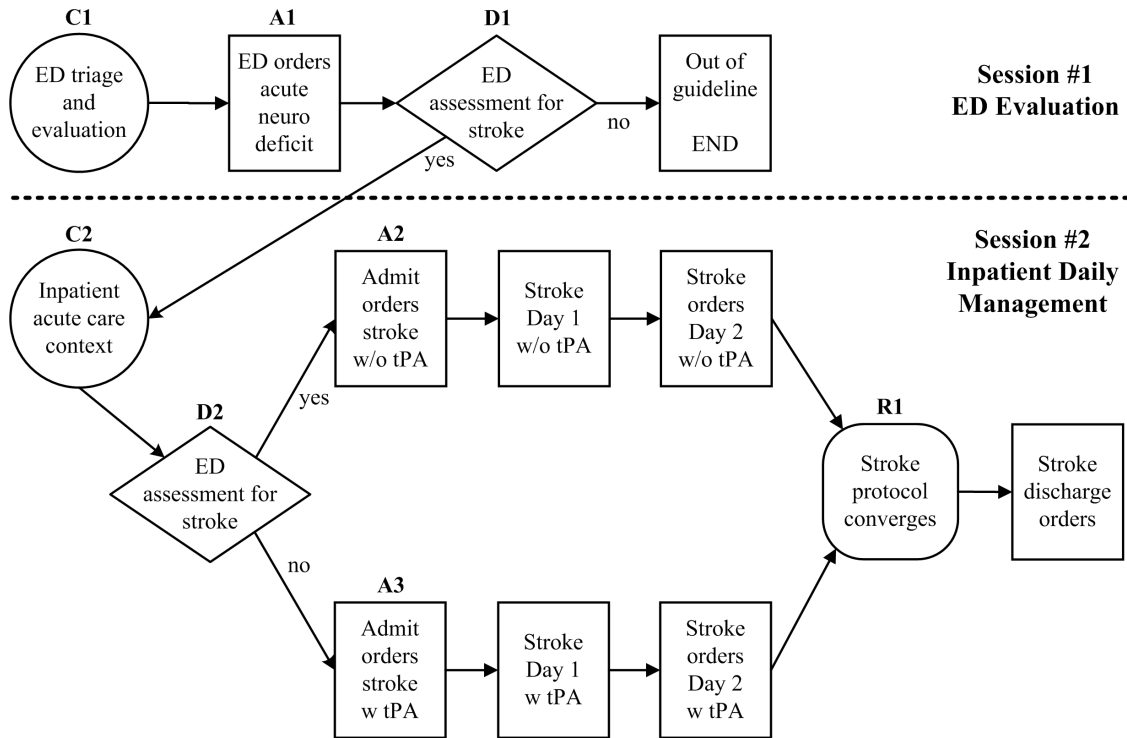


Figure 3.14: Example of CPG representation based on SAGE.

3.3 Machine Learning of Knowledge in Medical Assistance

Machine learning (ML) objective is the development of computationally methods that, automatically, optimize a performance criterion using data or previous experience. These methods establish learning systems able to acquire high level knowledge and strategies to solve problems through objects, in analogous way to the human mind. From the objects given by an instructor and the background or previous knowledges, the learning system creates general descriptions of concepts. There are four ML paradigms [Shi92, Mit97]): analogy learning, analytic learning, connexionist learning and inductive learning.

Analogy learning or instance-based learning (IBL) [AKA91] is based in which the relations that are fulfilled in a determined domain, also they are fulfilled in another domain. So, this type of learning is based on similarity hypothesis in which objects with similar attributes are of the same based on the severity of their condition, improving the survival possibility according to the therapeutical needs and the available resources.

class. The most known methods of this type of learning are the k-nearest neighbour (KNN) [AKA91] or the case-based reasoning (CBR) [AP94].

Analytic learning or explanation-based learning (EBL) [DM86] is based in the use of the domain knowledge. This type of learning has as objective to complete the processes originated by incomplete theories through the establishing of valid assumptions. So, given a known conclusion, several hypotheses are proposed which explain this conclusion. Inductive Logic Programming (ILP) [LD94] is the most known method of this type of learning.

Conexionist learning or learning of artificial neural networks [RM86, Koh88] is based in which the mental phenomenon can be described by simple units of a network that are interconnected, where the network units represent neurons and the connections represent synapses. Learning of the artificial neuronal networks consists in modify, somehow, the weights associated with the connections, so, the network generates the desired outputs for each input. The most known method is *backpropagation* or propagation of error [RM86], which modify the weights from the output layer to the input in function of the error done by the output signs (the difference between the get outputs and the desired outputs).

Inductive learning (IL) is a special type of learning which obtains from particular cases (objects), general cases (rules) that generalize or abstract the evidence. That generalization is based in the application of independent knowledge about of application domain. Inductive learning has as objective to establish the common features of a object set of a unknown class, so that, the description obtained does not include the rest of the objects that are not concrete cases of that class. The presence of a negative object within a class is due to the presence of noise in the set of observed data. In terms of the information available, two sorts of inductive learning can be distinguished: supervised and unsupervised inductive learning. In *supervised inductive learning* the available objects have the “true” value that needs to be predicted for each one of them. When this information is not available it is interesting to discover patterns which allow to grouping and distinguishing some objects from others; this type of learning is called *unsupervised inductive learning*.

Among all the paradigms of machine learning previously introduced, this thesis is exclusively concerned with the inductive learning one.

3.3.1 Supervised Inductive Learning of Know-What Knowledge

In *supervised inductive learning* (SIL) the most common type of problem in which this learning operates is classification. *Classification* (§3.2.1) is based in a set of objects O and respective ranges,

where each object $o_i \in O$ is described by a finite set of discrete and/or continuous attributes $A = \{a_1, \dots, a_m\}$, and also the class C to which they belong to. The SIL objective is to induce a model M that allows predicting the class $c_i \in C$ for all the objects $o_i \in O$, given the values of the attributes A . That is, $c_i = M(o_i)$.

Some SIL methods used in classification are: ID3 [Qui86], C4.5 [Qui93] and C5.0 for inducing decision tree induction and CN2 [CN89] for the induction of production rules.

- *ID3* (Interactive Dichotomizer) [Qui86] is an induction method which implements a simple mechanism to find a classification structure from a set of objects O which may belong to two classes. Each object is described in terms of a fix collection of attributes, each one of them having their own values set. ID3 builds a classification structure as a decision tree which correctly classifies all the given objects. Each internal nodes of tree is labelled with an attribute, while the branches that get out of the node, are labelled with their possible values. The building of tree is heuristically guided choosing the attribute a_i that maximizes the information gain in each step, minimizing the expected number of tests. The *information gain maximization* for an set O with objects which can belong to k different classes, is the average of the information quantity need to identify the class of an object O , as shows the formula 3.1, where p_j is the objects proportion of the class c_j in the set O .

$$info(O) = - \sum_{j=1}^k p_j \cdot \log_2 p_j \quad (3.1)$$

With this measure the effectiveness of an attribute a_i is calculated to subdivide a set of examples in subsets (one for each possible value a_i in $Dom(a_i)$), obtaining the expected value of the entropy after the partition as a weighted sum of the entropy of each subset C_i , which is calculated with formula 3.2.

$$infoAtrib(O, a_i) = \sum_{j=1}^{|Dom(a_i)|} \frac{|O_j|}{|O|} \cdot info(O_j) \quad (3.2)$$

At the time of choosing an attribute to establish a test in a tree node, it is important to select one that maximizes the information gain. This *information gain* is calculated as the difference between the entropy of original set and the subsets obtained by separating O in function of the value a_i , with formula 3.3.

$$gain(O, a_i) = info(O) - infoAtrib(O, a_i) \quad (3.3)$$

- *C4.5* [Qui93] is an evolution of ID3 algorithm, where an improvement of the *gain information* measure is incorporated. This improvement allows the choice of attributes with many possible values, which redound in a worst generalization of the observations. So, the C4.5 algorithm introduces an alternative measure called *gain ratio* to improve this deficiency. *Gain ratio* is calculated with formula 3.4, where *infoPart* represents the entropy associated with the fact of partitioning the set of objects O in the subset O_i .

$$ratio(O, a_i) = \frac{gain(O, a_i)}{infoPart(O, a_i)} \quad (3.4)$$

This entropy is calculated with equation 3.5.

$$infoPart(O, a_i) = - \sum_{i=1}^{|Dom(a_i)|} \frac{|O_i|}{|O|} \cdot \log_2\left(\frac{|O_i|}{|O|}\right) \quad (3.5)$$

Also, the C4.5 algorithm includes a *pruning* of the classification tree once it has been induced. The pruning is based in the application of a hypothesis test which indicate whether it is necessary or not to expand a determined branch [Qui93].

Other methods for the induction of decision trees are: CART [BFOS84], ASSISTANT [CKB87] and C5 [Qui03].

- *CN2* [CN89] combines the efficiency and the information management with noise which allows the ID3 induction algorithm of decision trees [Qui86] with the flexibility of AQ [Mic87], in its strategy of *IF – THEN* rules searching. This algorithm produce a set of rules *IF – THEN*, called “decision list” [Riv87], using heuristically techniques based in a estimation of noise present in the data to reduce the searching space. The rules obtained by CN2 are the form:

IF complex THEN class

Where *complex* is a conjunction of attribute-value operations on the attributes in A . The last rule of the order list is a rule which assigns by default the more common class c_i of the training set to any object O that arrives to it. At classification time, it's only necessary to follow the

decision list in order until a rule with a satisfiable condition is found. If none rule is satisfied, the object is assigned to the most common class in the training set.

The CN2 algorithm works in an iterative way, each iteration searches a complex covering a large number of objects O of a single class c_i and few of other classes. The complex must be both predictive and reliable, as determined by CN2 evaluation functions. Having found a good complex, the examples that it covers are removed from the training set and the rule *IF complex THEN c_i* is added to the end of the decision list. This greedy process iterates until no more satisfactory complexes can be found.

Other induction methods of production rules are AQ [Mic87], AQ15 [Mic87], RIPPER [Coh95], RISE [Dom96], INNER [Lua99].

3.3.2 Unsupervised Inductive Learning of Know-What Knowledge

Unsupervised inductive learning (UIL) is an automatic learning method where a model is adjusted to the observations. It is distinguished from the supervised learning because there is not an *a priori* knowledge. In UIL, a set of data on the input objects is treated. So, UIL typically treat the input objects as a set of attribute values with the objective of building a density model for that data set.

An UIL type is clustering [Mac67] which consists in making groups with the objects of a set O , each group being characterized by a set of discrete and/or continuous attributes of a set A , so that the objects of a cluster are similar and the objects of different groups are dissimilar. The similarity measure is based on the attributes that describe the objects and it is defined by proximity in a multidimensional space. Measuring the similarity between objects can be done with different distance measures of distance [AKA91]: Euclidean, Manhattan, etc.

Among the variety of non-hierarchical clustering [Mit97, Wit00, ORF04], the most used ones are: the k-means algorithm [Mac67] and the expectation-maximization (EM) algorithm [DLR77].

- *K-Means* [Mac67] is an algorithm for heuristical clustering which is based in partitioning the set of objects O in a predefined number of K classes. This algorithm is based in the minimization of the internal distance, as equation 3.6 shows. In this case the algorithm minimizes the sum of squared distance between the assigned patterns to a cluster and the centroid of that cluster, where p represents the centroid and μ_i the mean of cluster C_i (both are multidimensional objects).

$$d(p, C) = \sum_{i=1}^k \sum_{p \in C_i} |p - \mu_i|^2 \quad (3.6)$$

The algorithm is simple and efficient. Also, it processes the patterns sequentially, so, it requires a minimum storing. Moreover, it is biased by the patterns presentation ordering (i.e., the first patterns determine the initial configuration of the clusters) and its behaviour depends of the parameter K . There are two versions of the K-means algorithm. The first version, known as Forgy algorithm [For65], it is based in the iteration of two steps: first, it assigns all the points to its nearest centroids, and second, it recalculates the centroids according to the objects contained in the new groups created previously. The process continues until a stop criterion is reached (e.g., there are not reassignments). The second version [DH73], reassigns the points based on the most detailed analysis of the effects caused over the objective function to move a point of its cluster to another new. If the moving is positive, it is made, if not, it will stay where it is.

- *Expectation-Maximization algorithm* (EM) [DLR77] is an efficient iterative procedure to compute the maximum likelihood estimate (MLE) in the presence of missing or hidden data. Given a likelihood function $L(\theta; x, z)$, where θ is the parameter vector, x is the observed data and z represents the unobserved latent data or missing values, the MLE is determined by the marginal likelihood of the observed data $L(\theta; x)$.

Each iteration of the EM algorithm consists of two steps: expectation step (E-step), and maximization step (M-step). E-step calculate the expected value of the log likelihood function, with respect to the conditional distribution of z given x under the current estimate of the parameters $\theta^{(t)}$, as shows equation 3.7:

$$Q(\theta|\theta^{(t)}) = E_{(Z|x, \theta^{(t)})}[\log L(\theta; x, Z)] \quad (3.7)$$

M-step: Find the parameter that maximizes this quantity according to the equation 3.8:

$$\theta^{(t+1)} = \underset{\theta}{argmax} Q(\theta|\theta^{(t)}) \quad (3.8)$$

Convergence is assured since the algorithm is guaranteed to increase the likelihood at each iteration.

3.3.3 Supervised and Unsupervised Learning of Know-How Knowledge

In the development of this document, we found small evidence about the development of supervised and unsupervised learning methods to the know-how knowledge in medicine. An approximation in this area is the developing of a new induction methodology, based in medical data, of decision trees and background knowledge, to generate formal intervention plans (FIP's) [RBR07]. Also, in the workflow mining context [Man11], the problem of know-how knowledge learning in medicine is solved inducing clinical-pathways represented as Petri nets [vdAvDH⁺03, vdAWM04, MSL⁺08] or as causal Bayesian networks [MC07]. However, the structures induced by those systems are not explicit medical structures that health care professionals are as familiar to work with as with clinical algorithms.

3.4 Conclusions

The analysis of antecedents in the ambit of formalizing medical assistance knowledge, a series of facts have been revealed that contextualize the present thesis work. These facts are exposed as conclusions of chapter 3:

- The main areas of knowledge formalization in medical assistance are diagnosis, treatment and medical prognosis.
- Knowledge management distinguishes between two types of knowledge: know-what and know-how knowledge. This classification is extrapolated to the domain of medical assistance.
- The majority of knowledge representation formalisms that are used in medical assistance are: fuzzy logic, production rules, decision tables, decision trees, partial orders, Bayesian networks, artificial neuronal networks, ontologies, and the CIG representation languages.
- Table 3.3 contains a summary of the types and knowledge areas of medical assistance in which, broadly speaking, the formalisms of knowledge representation and the machine learning methods introduced in this document are used. We note that:
 - The main formalisms of know-what knowledge representation in diagnosis and medical treatment are: fuzzy logic, production rules, decision tables, decision trees, partial orders and ontologies.

- The main formalisms of know-what knowledge representations in medical prognosis are: Bayesian networks and artificial neuronal networks.
 - The main formalisms of know-how knowledge representation in diagnosis and medical treatment are the CIGs representation languages.
 - Machine learning methods are used in the induction of know-what knowledge in the three knowledge areas of medical assistance: diagnosis, treatment and prognosis.
 - Approaches based on workflow mining context such as Petri nets and Bayesian networks, are the most representative machine learning methods used in the induction of know-how knowledge.
-
- The formalisms of know-what knowledge representation in medical prognosis, have been used in the prediction of medical facts as the morbidity, mortality, recurrence and disease evolution, and survival analysis. These predictions depend on whether there are or not temporal restrictions related to the prediction. An additional feature of these formalisms is their ability to predict a concrete fact (e.g., survival) or whether they are able to predict several facts simultaneously.
 - The formalisms of know-how knowledge representation provide structure to the knowledge contained in protocols and CPGs, where medical information appears in a textual and narrative way, and describing recommendations based in the population and not patient-oriented.

Sort of Knowledge	AI Technology	Medical Knowledge Area	
		Diagnosis/Treatment	Prognosis
Know-what	Knowledge Representation	fuzzy logic [Zad65], production rules [New73], decision tables [Hol75], decision trees [Qui86], partial orders [DM41], ontologies [Gru93]	Bayesian networks [CGH97], artificial neural networks [RM86]
	Machine Learning	KNN [AKA91], CBR [AP94]; LP [LD94]; ID3 [Qui86], C4.5 [Qui93], CART [BFOS84], ASSISTANT CBK87, C5 [Qui03]; AQ [Mic87], AQ15 [Mic87], CN2 [CN89]; RIPPER [Coh95], RISE [Dom96], INNER [Luu99]; K-means [Mac67] and EM [DLR77]	backpropagation [RM86]
know-how	Knowledge Representation	CIG representation languages [SHJ ⁺ 94, Shi97, SMJ98, FJR98, TM99, JTB ⁺ 00, PBOea00, BCH ⁺ 02]	N/A
	Machine Learning	Workflow mining (petri nets and Bayesian networks)	N/A

Table 3.3: Representation formalisms and machine learning methods used in the medical assistance

Part III

Modelling of a Holistic Architecture for the Diagnosis, Treatment and Prognosis in Medicine

Chapter 4

Modelling Know-How Knowledge in Medical Assistance

In this chapter we propose the state-decision-action (SDA) knowledge model to represent health care procedures as SDA diagrams which are similar to medical algorithms. This model presents an alternative to the current languages of know-how knowledge representation in medicine.

In order to introduce this new knowledge model, this chapter is organized in five sections. In section 4.1, an introduction to the know-how knowledge representation in medicine is provided. In section 4.2, the SDA model is described according to the SDA elements and to the way that SDA represents know-how knowledge, sequences, concurrences, loops, and non-determinism. In section 4.3, several examples of application of the SDA model in health care are introduced. In section 4.4, a comparison between SDA diagrams and medical algorithms is made. Finally, section 4.5 contains the conclusions of chapter 4.

4.1 Introduction

Clinical Practice Guidelines (CPGs) are systematically developed statements to assist health care professionals and patient decisions about appropriate health care for specific clinical circumstances [FL90](§2.3.1). CPGs are used to gather all the available evidence related to a disease. The main arguments justifying the use of CPGs are: to provide a homogeneous practice, to improve the quality, the equality and the equity of patient care, and to reduce costs [WGH⁺99][BTZ⁺01]. Some CPGs include Medical Algorithms (MAs) [Mea92, Had95] (§2.4) as a means of summarizing some of the medical procedures that the CPG describe. As defined by the International Society for Medical Decision Making [Mea92], MAs are flowcharts that start with a clinical state box defining the clinical state or problem, and then a combination of both, decision boxes representing “yes-no” questions leading the process to alternative paths, and action boxes describing actions, either therapeutic or

diagnostic. All these boxes are connected by arrows that show the logical sequence of application of the MA. For example, the MA in figure 4.1 was published by the Institute for Clinical Systems Improvement [ICS06] as a generalization of the long term treatment and follow up of hypertension. This MA starts with a *state box* that identifies the patients with an elevated blood pressure (BP) that must be confirmed, as the *action box* indicates. Then the patient is classified according to whether BP is in stage 1 or 2 (see related table, in figure 4.1) and alternative treatments are provided depending on the suspicion of secondary causes. This differentiation is represented with a *decision box*: if there is an evidence that the BP condition is the result of a secondary cause, then an action box orders additional work-up and it recommends considering referral to a specialist. If there is not a secondary cause for high BP, lifestyle modifications and/or drug therapy define the initial treatment. If this treatment is not efficient, then a change of treatment is started. If this change of treatment does not improve BP, then the MA tells us to consider whether hypertension is resistant or not. BP is defined to be resistant when the pressure goals are not met despite compliance with optimal doses of three antihypertensive drugs of different classes with one of the agents being a diuretic. In the MA, if BP is not resistant, a second change of treatment is tried; otherwise the patient is referred for consultation. Note that the level of abstraction of this MA is such that the decision about the concrete drug therapy and the sorts of lifestyle modifications is left to the health care professional since there is not an agreed configuration of drug treatments but many accepted combinations.

Publication of CPGs aims at reducing medical errors and unjustified variations in medical practice, and also at supporting evidence-based medicine [BTZ⁺01]. Unfortunately, CPGs tend to be published in a textual format. This and other factors reduce their possibilities of making them known and applicable [CRP⁺99]. The idea of using a formal representation to describe and exploit CPGs gave rise to the idea of Computer-Interpretable Guidelines (CIGs) [BTZ⁺01] [WPT⁺01] as the way to make computers a means to make CPGs actionable. This idea has been the departing point of multiple and successful languages to formally represent CPGs as CIGs: Arden Syntax [SHJ⁺94], Asbru [SMJ98], PROforma [FJR98], GLIF [OMGM⁺98, PBOea00], EON [TM99], PRODIGY [JTB⁺00] and SAGE [BCH⁺02] (see §2.4 and §3.2.2). The approach of all these systems is to convey knowledge from human to machine structures, and then provide health care professionals with computer machine tools to access and exploit that knowledge. Due to this man-to-machine approach, we may conclude that all the systems to represent CIGs share, among others [PPT⁺02, WPT⁺02, MvdAP07, IM08, WTSR10], two significant features which are: a great ex-

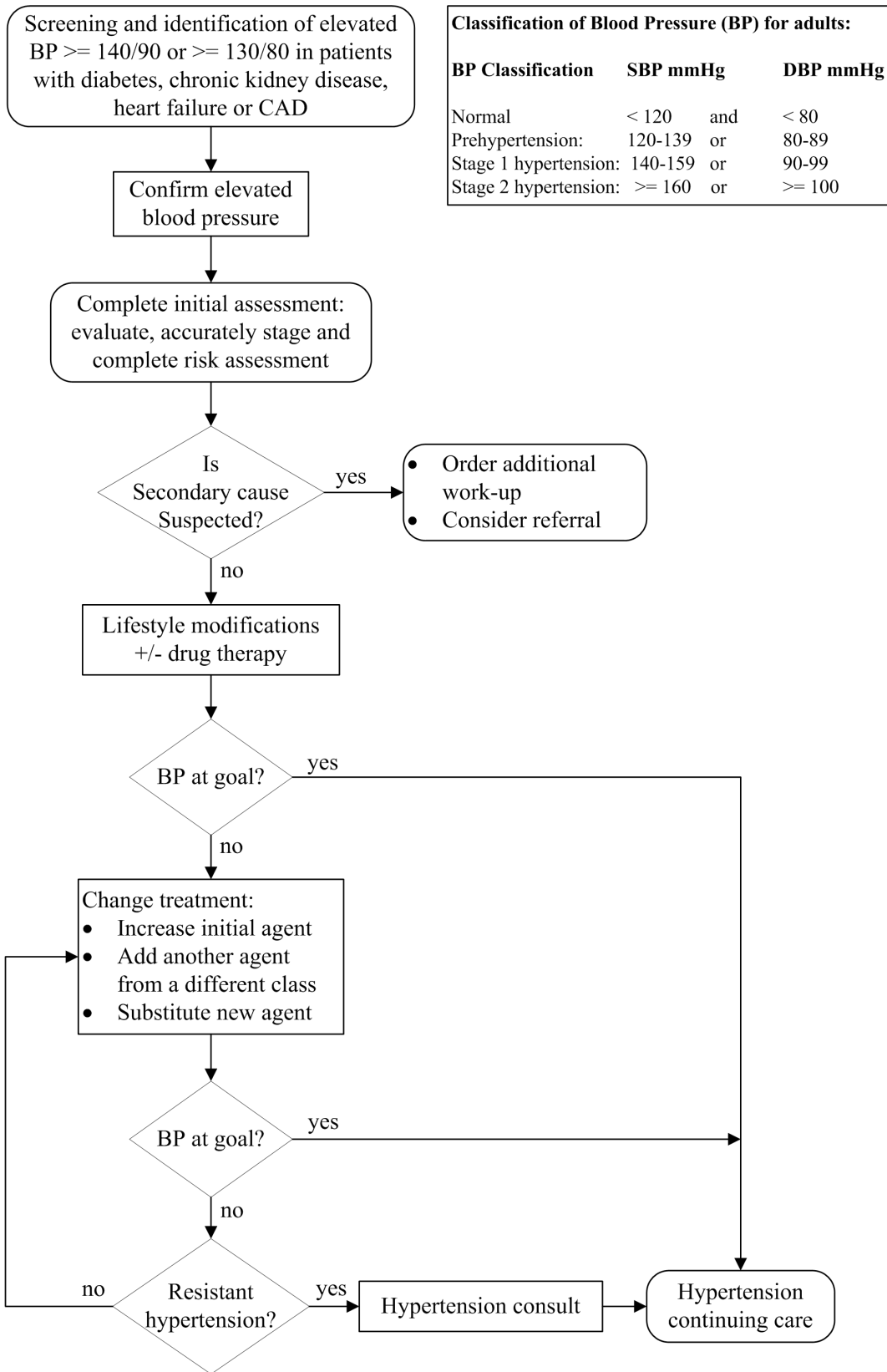


Figure 4.1: ICSI medical algorithm for the treatment of hypertension.

pressiveness of their constructs, and a computer orientation. *Expressiveness* is required since they have to provide a way to incorporate all the medical variability that may appear in a CPG, which is potentially very high, in the CIG. On the other hand, the *computer orientation* of such systems is the consequence that they are not designed to be directly applied by health care professionals but through the use of computer tools, and therefore CIGs are computer structures rather than medical structures.

As an alternative to these languages here, we propose the SDA model. The SDA model promotes the representation capability (i.e. procedural knowledge in medicine can be represented with this language) and simplicity (i.e. the understanding and management of the language does not need hard training) in such a way that not only computers but also health care professionals are able to work with it. The SDA model is based on the concept of MA but it is extended with several elements to ease health care know-how knowledge representation, as for example, the use of states as starting points that allow the execution of the chart from different points, the introduction of time constraints to incorporate time restrictions in medical procedures, or the application of non-determinism to represent alternatives in the treatments.

4.2 The SDA Model

The SDA model [Ria07] was defined as a combination of all the representation primitives that any CIG system is expected to have (see §3.2.2) [PPT⁺02, WPT⁺02, MvdAP07, IM08, WTSR10] (i.e., actions, decision, patient states, execution states, sequences, concurrences, alternatives, and loops) with the simplicity of MAs. This model is founded on the concept of term or vocabulary item in the medical domain where procedural knowledge is being generated. These terms can be of the sort state, decision, or action. *State terms* define the vocabulary that is used to describe the feasible patient conditions and situations in the area of interest (e.g., terms as “*Elevated_Blood_Pressure*” or “*Following_Drug_Treatment*” to establish a differential treatment). *Decision terms* are the terminology that health care professionals use to condition the sort of treatment to be followed (e.g., terms as “*Secondary_Cause_Suspected*” or “*BP_at_Goal*” that may derive the course of professional activities in one direction or another). Action terms are the way that medical, surgical, clinical or management activities are defined (e.g., terms as “*LifeStyle_Modifications*” or “*Drug_Therapy*” are respective examples of counsel and prescription, which are two of the types of medical actions that may appear in the description of a treatment).

4.2.1 The SDA Elements

State, decision and action terms are employed to construct three sorts of elements that once interconnected they describe a medical procedure. These elements are, respectively: states, decisions and actions. *States*, which are subsets of state terms, represent patient conditions, situations, or statuses that deserve a particular course of action which is totally or partially different from the actions followed when the patient is in another state, for example, to differentiate between initial treatment and subsequent treatments or between the different stages of a disease. *Decisions* allow the integration of all the variability that a treatment may have by means of conditions on decision terms which represent some of the available information about the patient and the current situation. *Actions*, which are subsets of action terms, constitute the proper health care activities involved in the health care procedure represented.

4.2.2 The SDA Knowledge Representation

The three elements of the SDA model (i.e., states, decisions, and actions) are combined to represent procedural knowledge in medicine. This sort of knowledge can describe a diagnostic process (e.g., find out the patient disease or disease stage), a therapy (e.g. what are the steps to follow in the treatment of a disease), or any other health care procedure. Similar to the MA notation, the SDA model represents states as circles, decisions as rhombus, and actions as squares. These elements are related with connectors (arrows) in order to provide a join representation of a health care procedure. The connectors can be of three sort: plain connectors, decisional connectors, and otherwise connectors.

- *Plain connectors* represent evolutions of the health care procedure that any patient is able to follow.
- *Decisional connectors* link decisions with other elements, they contain decision terms, and only the patients who meet all the terms in a connector are able to follow this connector.
- *Otherwise connectors* link decisions with other elements, they are identified with the word 'otherwise', and only the patients who fulfil none of the connectors leaving a decision are able to follow the otherwise connectors of that decision.

For example, figure 4.2 shows a transcription of the MA in figure 4.1 as a SDA in which the treatment of all the patients arriving to the "Initial State" evolve across a *plain connector* to a

decision element in which only *High_Risk* patients may follow the *decision connector* that leads to "*LifeStyle_Modification*" and "*Drug_Therapy*". The rest of the patients who are not in *High_Risk* follow the *otherwise connector* towards a different treatment. All the initial treatments converge to the "*Intermediate State*" where all the patients are expected to be after the first encounter with the health care professional. Connectors may have time constraints of the form $[min, max]$; *min* representing the minimum time the process must stop before following the connector (e.g., wait two hours before measuring BP again to confirm high BP), and *max* the maximum time the process must stop before moving forward in the treatment (e.g., next visit must be scheduled for not later than one week). For example, the time constraints $[15d, 1m]$ in figure 4.2 means that "after the first encounter takes place a second encounter should be scheduled for between 15 days and one month", or $[-, 1m]$ means that "monitoring never delays more than one month" or $[2d, 7d]$ means that "if a change of treatment does not reduce BP in a week, the case must be reconsidered".

4.2.3 SDA Sequences, Loops, and Concurrences

The SDA model allows the description of sequences, loops and concurrences of medical procedures in an intuitive way, by means of the element connectors. A *SDA sequence* connects one state with a decision and each branch of that decision with an action. For example in figure 4.2, the elements "*Initial State*", "*High_Risk*" and "*LifeStyle_Modification*" and "*Drug_Therapy*", describe a SDA sequence.

SDA sequences can be simplified with the elimination of one or several of the elements in the SDA sequence. So, the elimination of the state must be interpreted as if there is not a health care reason to describe the state of the patient at this point of care (e.g., lack of medical meaning, medical irrelevance, cause of confusion, disagreement, etc.). Sometimes, the application of a set of actions is mandatory for all the patients arriving to the SDA sequence. In this case the decision element is eliminated from the sequence and only one action block with all the common actions is connected after the state. Also, if a decision element is not enough informative to reach a conclusion about the proper sort of actions to carry on or if the representation of all the possibilities with a single decision is confusing, then the action block must be eliminated from the SDA sequence in order to chain several decisions one after the other. See, for example, decisions after the initial state in figure 4.2.

SDA sequences can be concatenated one after the other in order to define complex and long medical procedures. See for example in figure 4.2 the concatenation of sequences starting in "In-

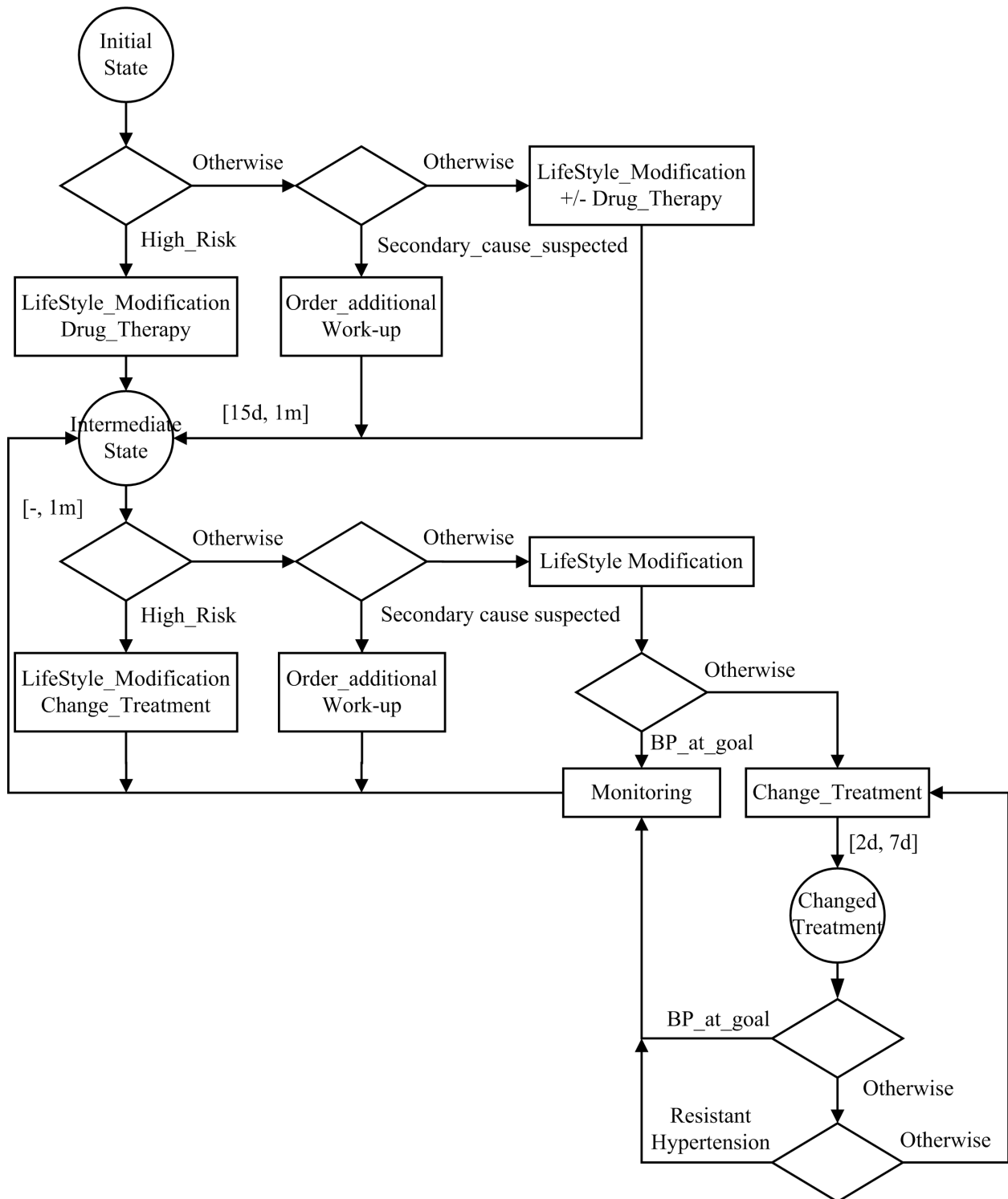


Figure 4.2: SDA for the hypertension treatment.

intermediate State” and following the otherwise branches (i.e., no *High_Risk*, no *secondary cause suspected*, and no “BP at goal”), and a “Change of Treatment” that deserves “monitoring” if BP is finally at goal.

SDA loops are defined as repeated sequences of elements in a SDA procedure. Loops may be used to represent repetitions in a medial process or jumps to an already previously observed situation in the course of action followed. Loops in this model do not have explicit termination conditions; the exit of a loop occurs when one of the decisions of the loop drives the patient to an outgoing connection which is not part of the loop. For example in figure 4.2, the elements “*Intermediate State*”, “*High_Risk*”, “*LifeStyle_Modification*”, “*Change_Treatment*” and “*Intermediate State*”, describe a loop.

SDA concurrence is described as a set of actions that should be executed in parallel. In the SDA model, there are two alternative ways to represent concurrences: on the one hand, when several actions are part of the same action element (e.g., “*LifeStyle_Modification*” and “*Drug_Therapy*”), this means that all of them are started simultaneously in time.

4.2.4 Non-Determinism in SDAs

Determinism is the principle by which every event, act, and decision (called effect) is the consequence of some antecedents (called cause). In health care, causes can be medical, surgical, genetic, environmental, managerial, familiar, social, etc. Therefore, *non-determinism* states that in health care there are events which do not correspond to a cause. Historically, there have been defined three sorts of non-determinisms [Cla05]: one that holds that some events are uncaused (e.g., from a practical point of view, in health care, uncaused events are equivalent to events with an unknown unfindable cause), another one that holds that there are non-deterministically caused events (e.g., a health care professional that follows alternative therapies for equivalent cases without an explicit explanation), and the third one that holds that there are agent-caused events (e.g., external events like the arrival of a patient whose health condition allows the treatment to start at different points).

Independently of the semantics of non-determinism, the SDA model can deal with all the above sorts of non-determinism. In this sense, the SDA model defined three sorts of non-determinism: type 0, type I and type II.

- *Type 0 non-determinism* describes the situation in which a patient with a particular condition can match several states. This means that the treatment of the patient can non-deterministically start different alternative treatment sequences.

- *type I non-determinism* describes the situation in which the condition of a patient can satisfy several branches of the same decision, and therefore the treatment can follow alternative paths at the same point of decision.
- *type II non-determinism* describes the situation in which either a state or an action is connected to several elements causing the treatment to follow one out of several alternative evolutions.

In a SDA diagram these three sorts of non-determinism can be interpreted in this way: when a patient arrives, all the SDA states whose state terms are observed in the current patient condition are eligible to start the treatment. If several states are eligible, a health care professional has to decide the one to start at among all the eligible states (*type-0 non-determinism*). Once this is decided, the connectors are followed until either a non-eligible state is found or a connector with a positive *min* delay is reached. In this process, all the actions of the followed path are the SDA recommendations for the treatment of that patient. When a decision is reached, all the outgoing decision connectors whose decision terms are part of the patient condition are eligible to determine the treatment of that patient. If only one decision connector is eligible, the connector is followed. If there are several eligible connectors, then a health care professional has to choose one of them to follow the treatment (*type-1 non-determinism*). If none of them is eligible, but there is an otherwise connector, then this connector is followed. If several otherwise connectors exist, then a health care professional decides which one is the one to be followed (this is also considered *type-1 non-determinism*). In case that there are several plain connectors leaving a state or an action, all of them are eligible and it is the health care professional who has to decide the one to be followed (*type-2 non-determinism*).

In our medical context, non-determinism is only observed when there is not a single accepted and evidence-based procedure to deal with a particular situation and the choice criterion between the alternatives is not defined.

4.3 Examples of SDA Diagrams

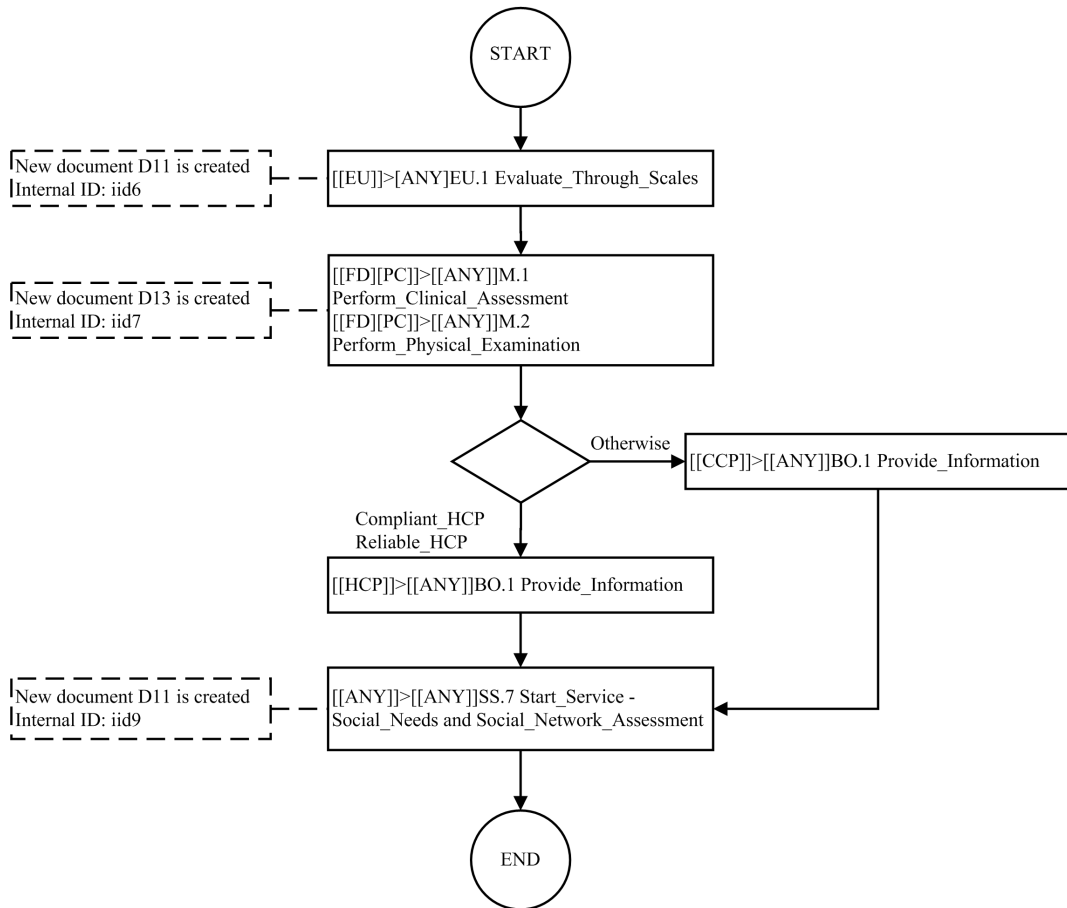
The SDA model has been tested in the context of the K4CARE project (www.k4care.net) where it has been successfully used to represent different sorts of procedural knowledge in medicine, particularly in home care. In this context, the SDA model has been used to represent home care services and procedures, and formal intervention plans.

In K4CARE, a *service* is any home care activity related to the attention of a particular patient, and a *procedure* is the implementation of a home care service by means of the combination of actions. Examples of these sorts of services are the ones listed in table 4.1 [CARea06]. The *patient care services* are classified into problem assessment, intervention plan definition, and intervention plan performance. All the services for *assessing the problem* aim at diagnosing the patient situation and reevaluating in time the results of the intervention. The services to define the *intervention plan* aim at choosing the most promising course of actions (i.e. treatment) based on the individualization of best practice. The services to *perform the intervention plan* are those addressed to the application of the intervention plan to the concrete home care patient. The intervention plan includes and defines the means and modalities aimed at evaluating results and measuring the implications of the application of the intervention plan itself.

Some examples of procedures based on SDA model are depicted in figures 4.3 and 4.4. The procedure in figure 4.3 implements the patient care service Comprehensive Assessment. This service is devoted to detect, in home care, the patient diseases, conditions, and difficulties, from both the medical and social perspectives. It is performed at admission, at periodical and at end-treatment re-evaluation times defined inside the individual intervention plan, but also in case of emerging peculiarities during the follow-up. The procedure in figure 4.4 implements the patient care service of planning an intervention plan. This service represents the course of actions to be performed in order to provide care to a home care patient in terms of treatment and support. It aims at taking care of diseases and conditions, with the goal of improving functions and self-dependency. It includes a social assistance program to provide and start up all the social services the home care patient needs, including social, financial, and legal support.

Patient Care Services
<p>I. Problem Assessment and Re-Evaluation</p> <ol style="list-style-type: none"> 1. Comprehensive Assessment (CA) 2. Multi-Dimensional Evaluation 3. Clinical Assessment 4. Physical Examination 5. Request of Diagnostic Examination 6. Request of Laboratory Analysis 7. Consultation 8. Social Needs and Social Network Assessment 9. Follow-up <p>II. Intervention Plan Definition</p> <ol style="list-style-type: none"> 1. Planning Intervention Plan 2. Prescription of Pharmacological Treatment 3. Prescription of Non-Pharmacological Treatment 4. Prescription of Nursing Care 5. Prescription of Assistive Devices <p>III. Intervention Plan Performance</p> <ol style="list-style-type: none"> 1. Case Management 2. Special Medical Services 3. Nursing Care 4. Social Assistance 5. Counselling

Table 4.1: List of health care service and procedures defined within K4CARE project



EU: Evaluation Unit Actions, FD: Family Doctor, PC: Physician in Charge of the Home Care, M: Medical Activities, CCP: Continous Care Provider, BO: Back Office Activities, SS: Social Activities

Figure 4.3: K4CARE procedure for comprehensive assessment.

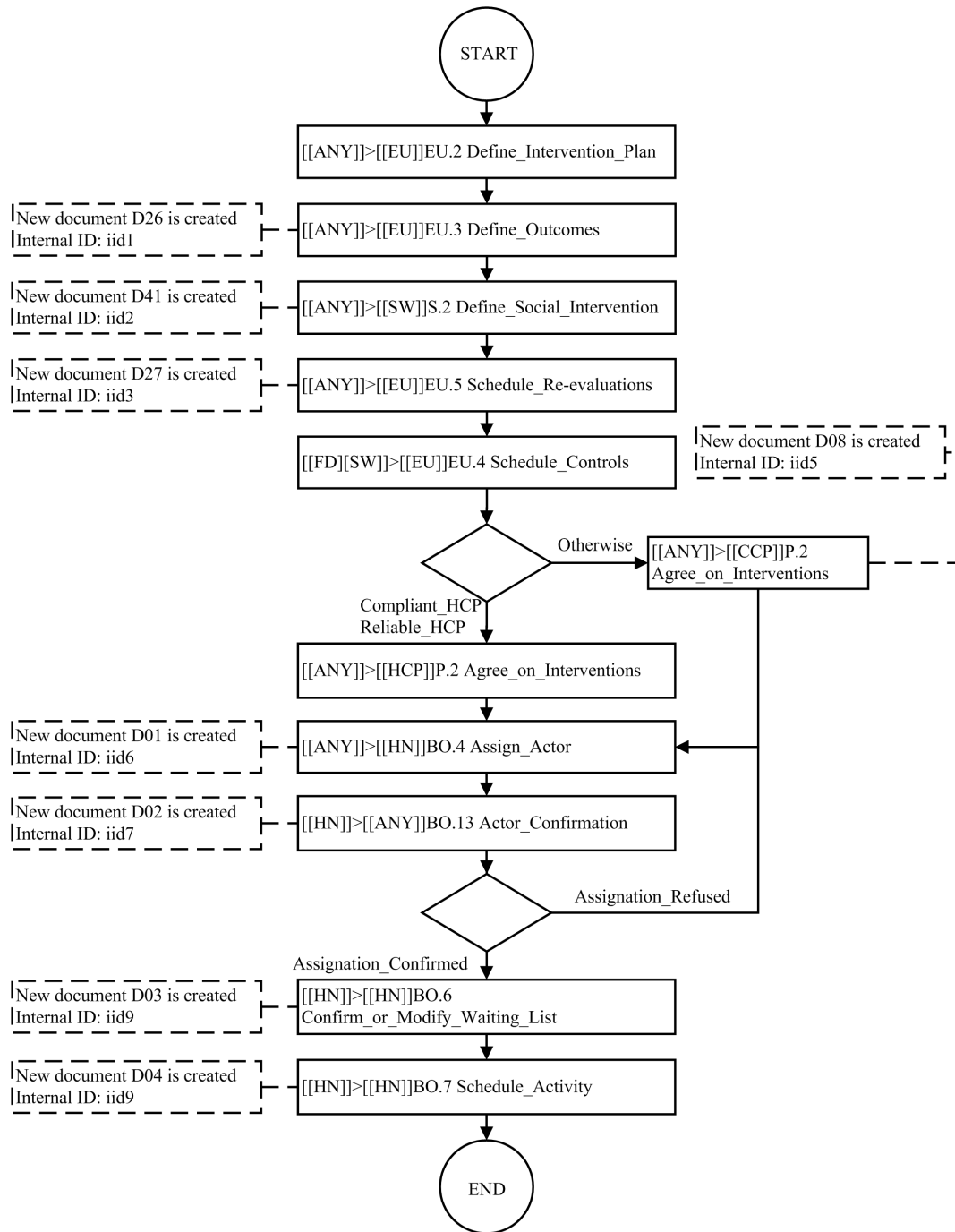


Figure 4.4: K4CARE procedure for planning of intervention plan.

In K4CARE, *formal intervention plans* (FIP) are formal structures representing the health care procedures to assist patients suffering from particular diseases or syndromes. The K4CARE project provides a family of FIPs for fifteen of the most common syndromes, diseases, and social issues in

home care¹. The full list of these syndromes, diseases, and social issues is provided in table 4.2. These FIPs are represented as SDA diagrams and they are validated and ready, after professional authorisation, to guide the treatment of the K4CARE patients [CRea08a, Cea08, CRea08b].

Syndromes, Diseases and Social Issues
A. Syndromes SY1.0 Cognitive Impairment SY2.0 Immobility
B. Diseases DI01.0 Anaemia DI02.0 Arthritis DI03.0 cerebrovascular diseases DI04.0 Chronic ischaemic heart disease DI05.0 Chronic Obstructive Pulmonary Disease DI06.0 Decubit ulcer DI07.0 Delirium DI08.0 Dementia DI09.0 Depression DI010.0 Diabetes DI011.0 Heart failure DI012.0 Hypertension DI013.0 Iatrogenic cognitive impairment DI014.0 Parkinson disease
C. Social Issues SI01 No Family support SI02 Low Income SI03 No Social-network SI04 Bad Environment SI05 Insanity

Table 4.2: List of FIPs based on SDA model to represent health care procedures

Some examples of FIPs are depicted in figures 4.5 and 4.6 [CRea08b]. These SDA diagrams were directly constructed by health care professionals from the MA on the recognition, assessment, treatment, and monitoring of Anaemia [AMD] that is shown in figure 4.7 and the MA on the treatment of Chronic Heart Failure [NHS, ESC] that is shown the figure 4.8, respectively.

¹The codification used to the syndromes, diseases and social issues is the standard provided by the “International Classification of Diseases, Injuries and Causes of Death, 10th revision Clinical Modification” (ICD-10-CM).

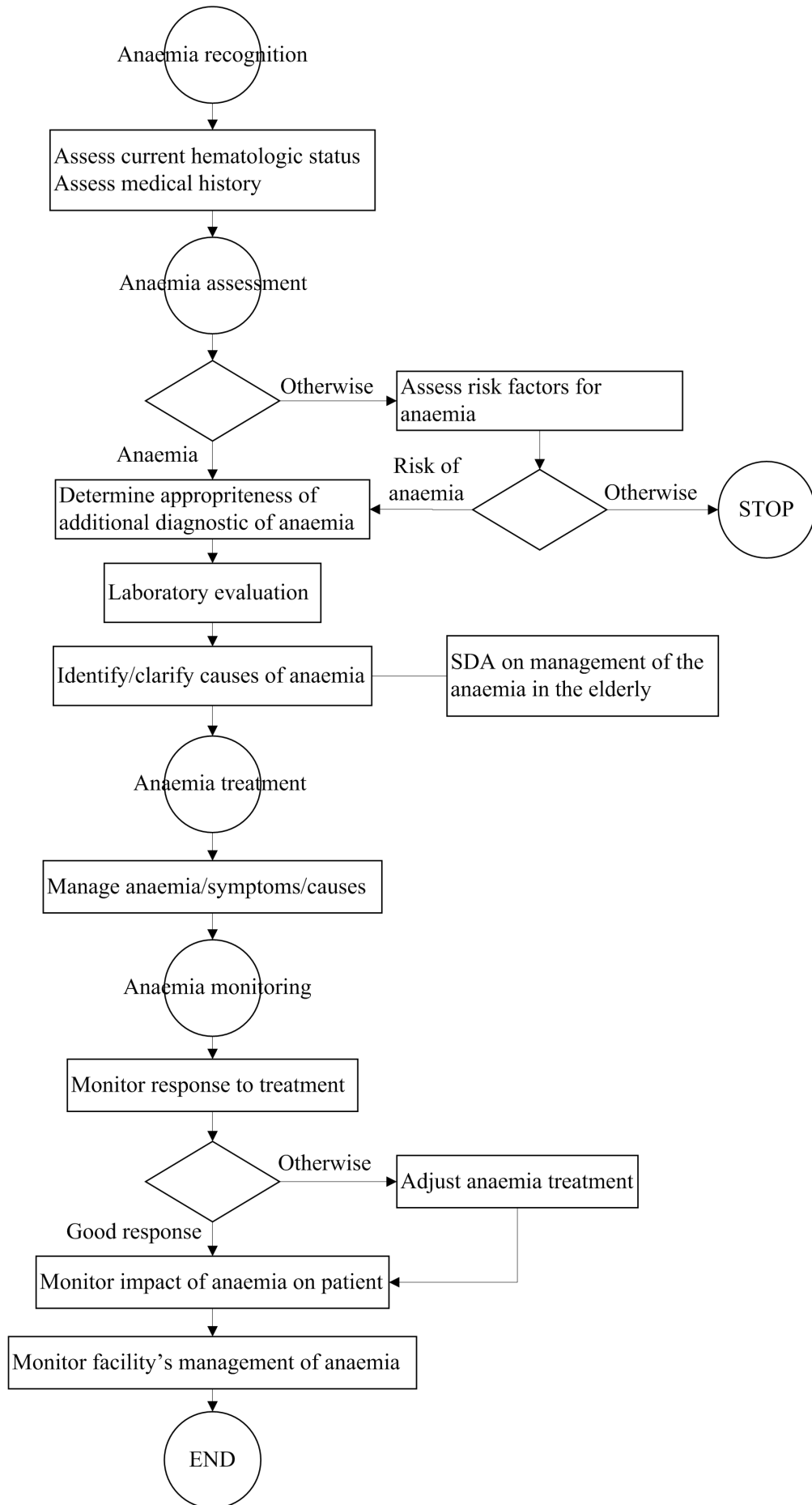


Figure 4.5: SDA diagram on the recognition, assessment, treatment, and monitoring of anaemia.

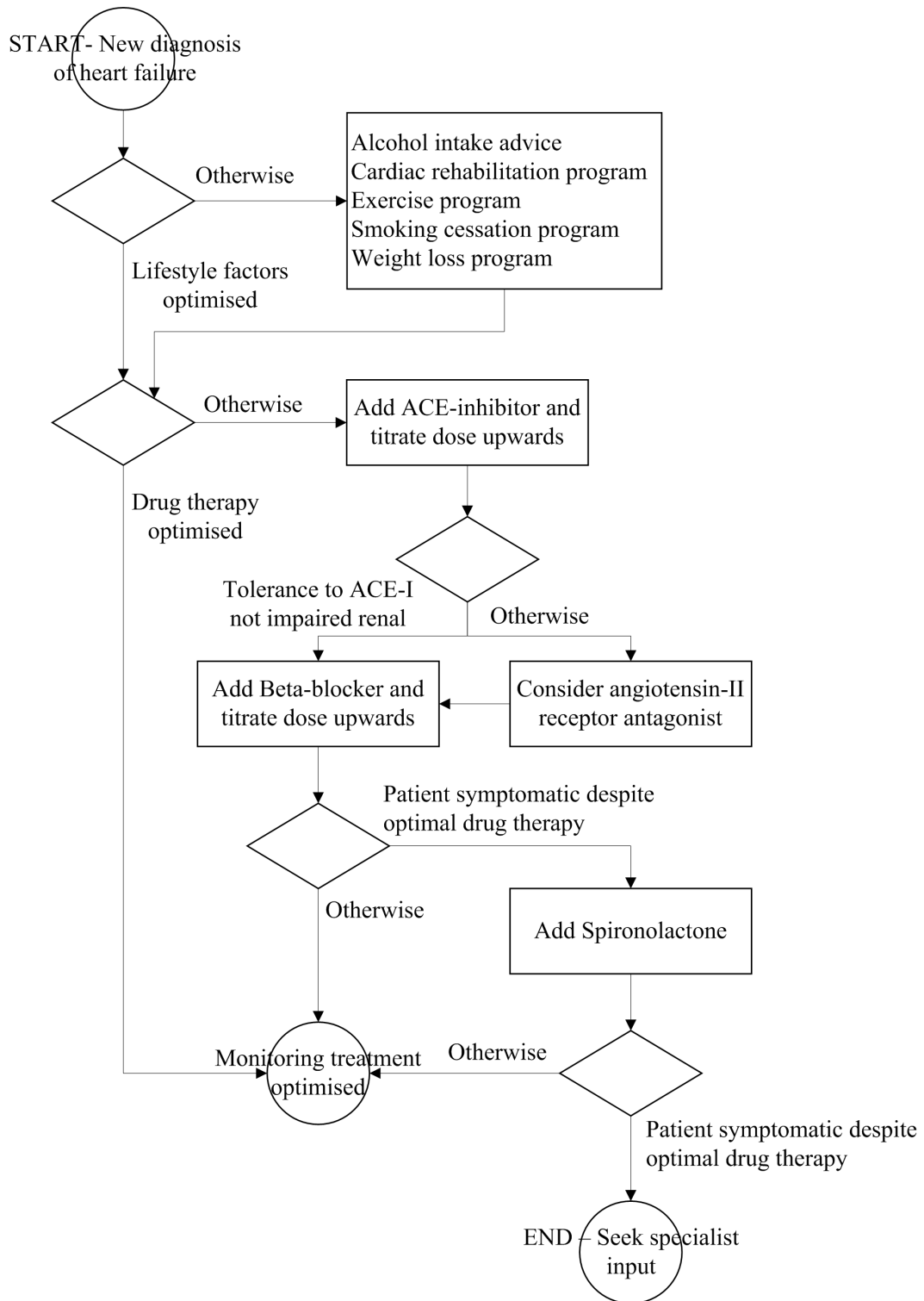


Figure 4.6: SDA diagram on the treatment of chronic heart failure.

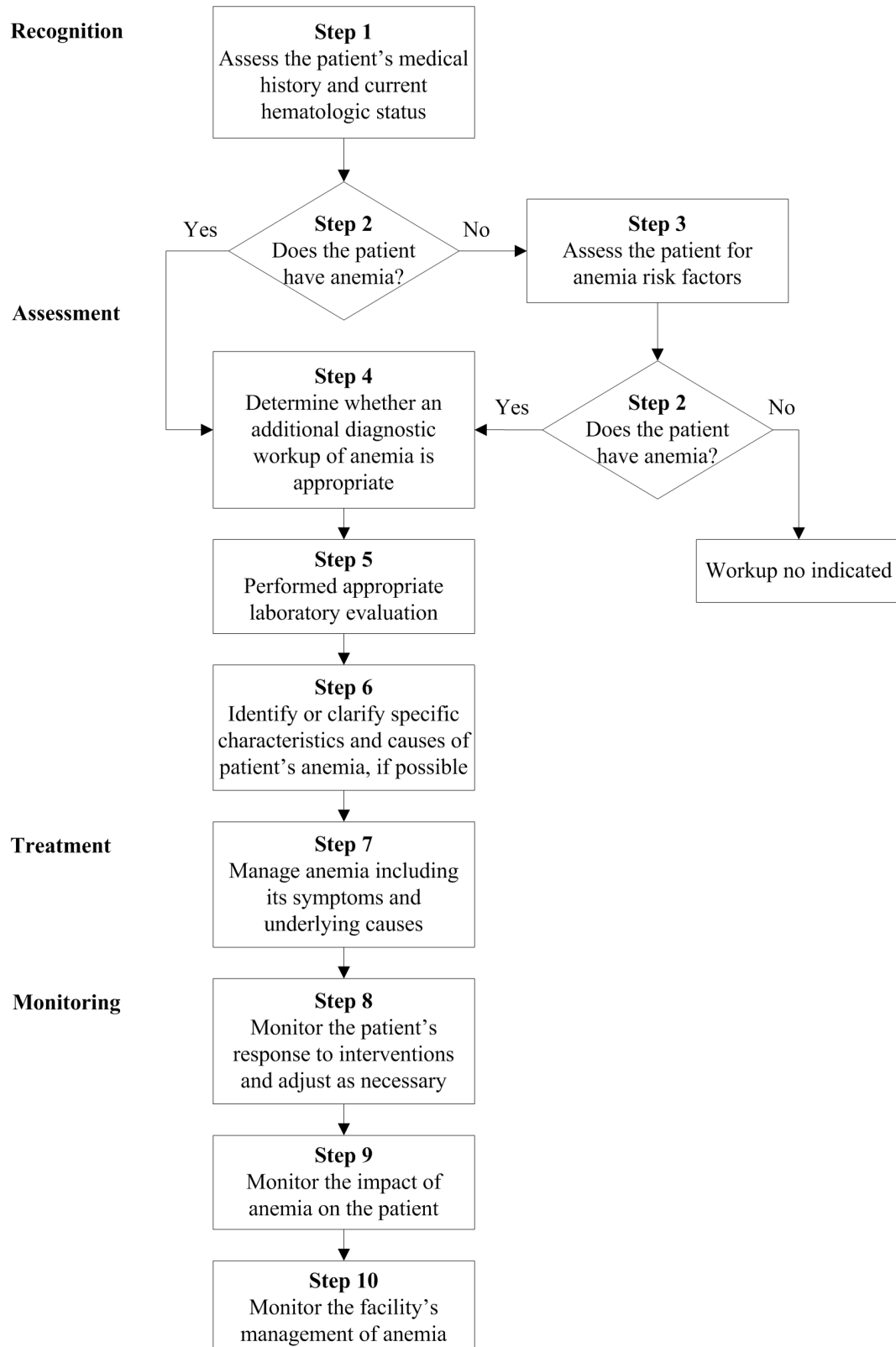


Figure 4.7: MA on the recognition, assessment, treatment, and monitoring of anaemia.

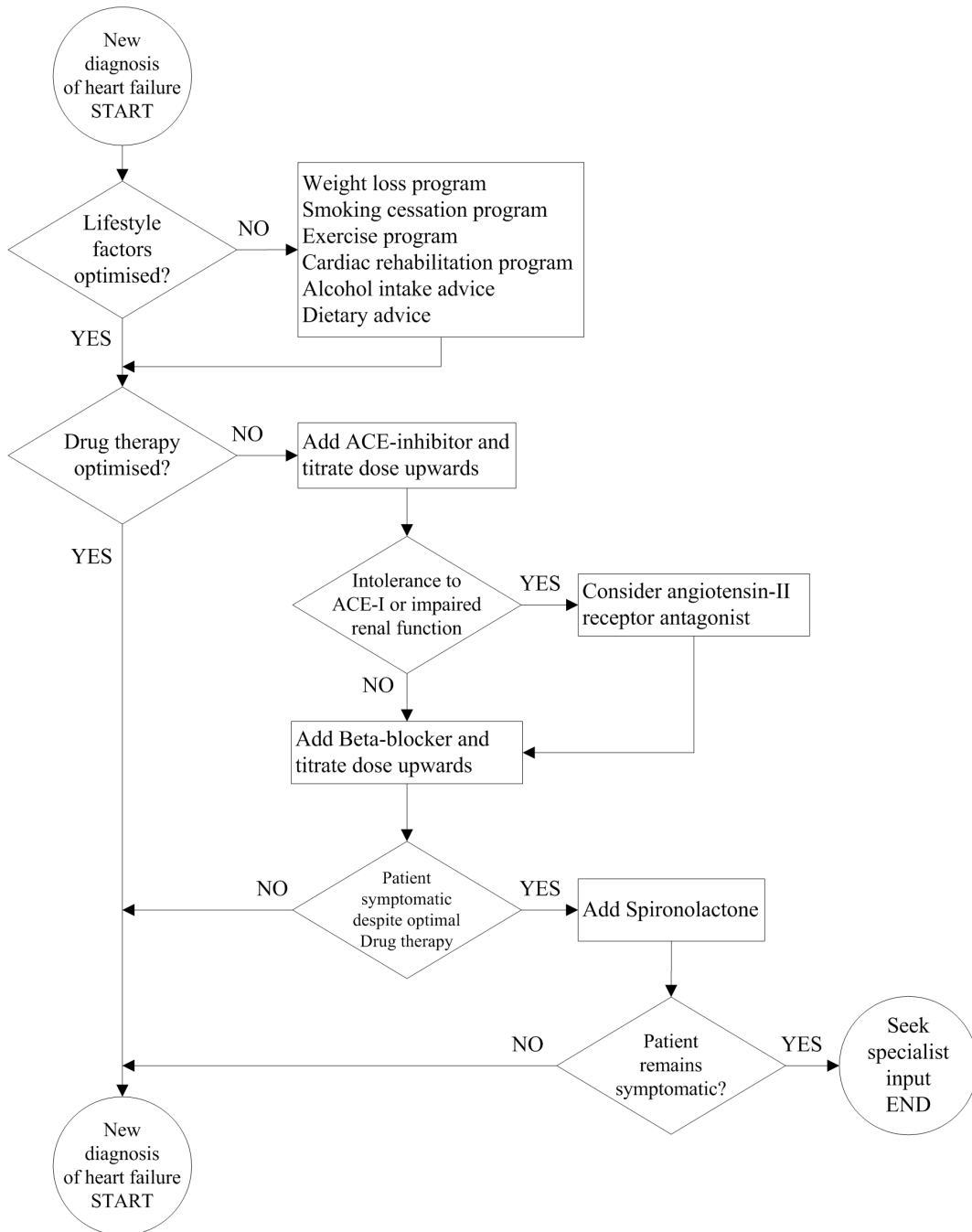


Figure 4.8: MA on the treatment of chronic heart failure.

An important feature of SDA model is that the SDA knowledge can be translated without any complexity in other knowledge representation structures such as CIG Systems (see §2.4 and §3.2.2). For example, the SDA knowledge shown in figure 4.5, which represents the management of anemia disease can be translated into languages to represent CIGs such as Asbru and Proforma, it is shown in the figures 4.9 and 4.10, respectively. In both examples, only the general plan and the assessment

plan of anaemia have been translated.

In Asbru, the anemia plan has an *intention* of "manage anaemia / symptoms / causes", a *condition* (abort-condition) of if "risk of anaemia = false" and a *plan body* with four sequential subplans: "recognition plan", "assessment plan", "treatment plan" and "monitoring plan". Likewise, the *assessment plan* has an intention of "identify/clarify causes of anaemia", a *condition* (filter-condition) of "risk of anaemia = true" and a *plan body* with three sequential plans: "determine appropriateness of additional diagnostic of anaemia", "laboratory evaluation" and "identify / clarify causes of anaemia".

PLAN	Anaemia
TIME ANNOTATION	
PREFERENCES	
INTENTIONS	Manage anaemia/symptoms/causes
CONDITIONS	Abort-condition: (Risk of anaemia = false)
EFFECTS	
PLAN BODY	Sequential subplans: <i>Continuation specification:</i> (recognition, assessment, treatment and monitoring of anaemia) Anaemia recognition Anaemia assessment Anaemia treatment Anaemia monitoring
.	
.	
.	
PLAN	Anaemia assessment
TIME ANNOTATION	
PREFERENCES	
INTENTIONS	Identify/clarify causes of anaemia
CONDITIONS	Filter-condition: (Risk of anaemia = true)
EFFECTS	
PLAN BODY	Sequential subplans: <i>Continuation specification:</i> all Any-order subplans: <i>Continuation specification:</i> all Determine appropriateness of additional diagnostic of anaemia Laboratory evaluation Identify/clarify causes of anaemia
.	
.	
.	

Figure 4.9: SDA Knowledge translated to Asbru

In PROforma, the anaemia plan has an *enquiry* which defines requests for further information or data. This is required before the anemia management can proceed with four *plans*: "recognition plan", "assessment plan", "treatment plan" and "monitoring plan". In the assessment plan, the

decisions of "anaemia" and "risk of anaemia" determine the *actions* to follow in the anaemia assessment: "determine appropriateness of additional diagnostic of anaemia", "laboratory evaluation" and "indetify/clarify causes of anaemia".

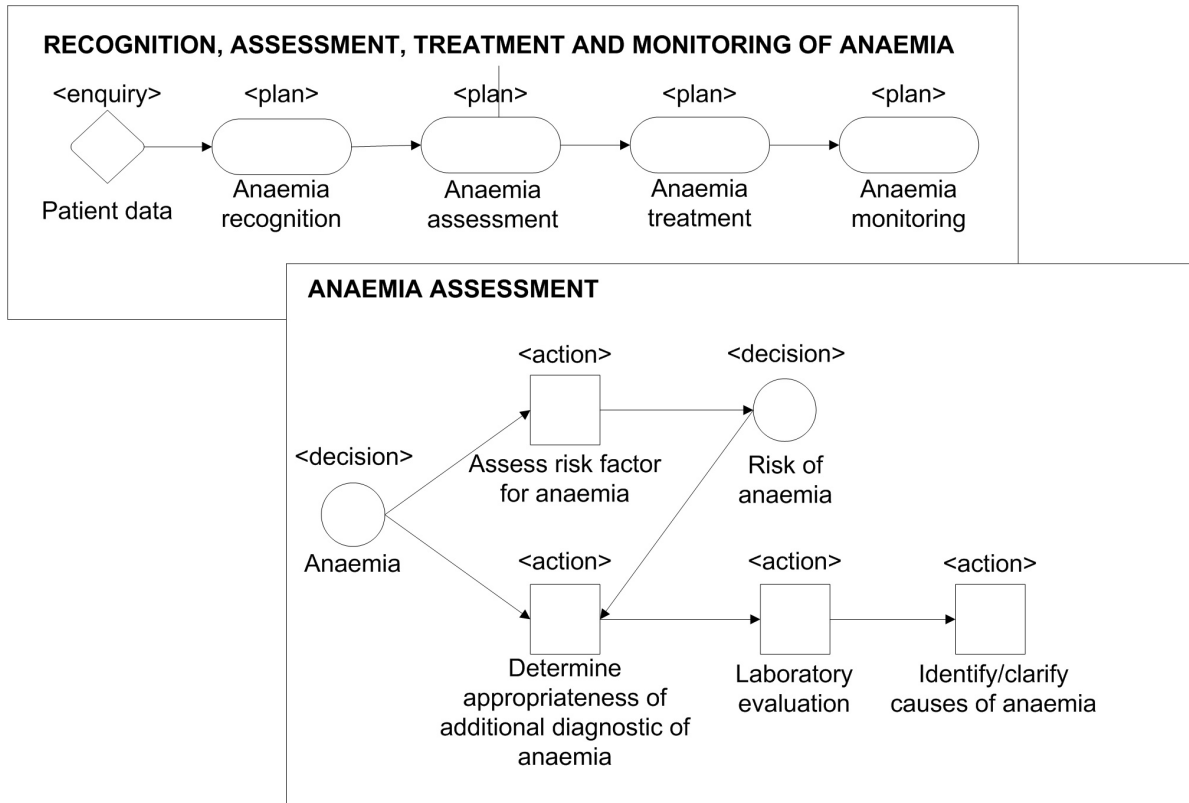


Figure 4.10: SDA Knowledge translated to PROforma.

4.4 Comparison of SDAs with MAs

SDAs do not only comply with the representation primitives required to CIGs [Ria07] (i.e., actions, decision, patient states, execution states, sequences, concurrences, alternatives, and loops), but they also extend the expressiveness and the flexibility of MAs while maintaining their simplicity. The main features of MAs [Had95] can be categorized as summarization, quality improvement, case standardization, precision, and computerization. *Summarization* is the ability of MAs to summarize at a glance the types of patients, as well as the range of management decisions and the strategies addressed in a procedure described in a CPG. *Quality improvement* refers to MAs as elements to improve the quality of CPGs since they have been shown to result in faster learning, higher retention, and better compliance with established practice standards than standard prose text [Had95].

Case standardization refers to the fact that MAs are focused on the standard typologies of patients described in the CPGs. *Precision* is the ability that, given a certain patient typology, the MA proposes a precise set of actions to be performed. This beneficial feature is sometimes criticized by part of the medical community arguing that MAs impose an excessive rigidity on health care professionals who share the opinion that patients are too variable in their presentations and preferences to encapsulate them within predefined roadmaps. However, this criticism is diminished by the benefits of MAs. *Computerization* is the feature of MAs of being readily translatable into computerized formats, which permits the systematic application of CPGs recommendations improving the quality of the medical assistance.

SDA diagrams extend the above features with the possibility of representing long term procedures, multiple entry points, multi-term decisions and non-determinism. Firstly, the presence of states for the different stages of a certain disease or disorder lets the SDA model to depict several treatments in an integrated diagram allowing the representation of long term procedures. Another feature of the SDA model is that it can deal with multiple entry points corresponding to the states that represent the different initial patient conditions and, therefore, not only to integrate the treatment of all these conditions in a single diagram, but also to address each patient directly to the corresponding part of the treatment. SDA diagrams also extend the expressiveness of MAs using multi-term decisions. In MAs, decisions are always [Mea92] yes-no questions but, in the SDA model, decisions may have more than two branches with different decision terms in each one of them. In addition, each decision may have alternative otherwise branches which are followed by the patients that fulfil none of the other branches. This results in a more readable sequence of decisions and also is a more compact representation of treatments. Finally, the rigidity and strictness of MAs, previously referred to as their main criticism, is reduced in the SDA model which increases the flexibility of CAs by dealing with non-determinism. *Non-determinism* is frequent in medicine and it allows the participation of health care professionals when there is not proven evidence on a unique or better treatment. The SDA model distinguishes between type-0, type-1, and type-2 non-determinisms (see §4.2.4).

4.5 Conclusions

The development of a knowledge-based model for the planning activity in the medical assistance is one of the objectives of this thesis. Therefore, aspects of its solution are exposed as conclusions of chapter 4, in form of points:

- With the purpose of solving problems of planning activity in the medical assistance, we have introduced a novel model, called SDA model, to represent know-how knowledge in medicine.
- The SDA model is presented as a alternative to the current CPG representation languages which convey knowledge from human to machine structures.
- The SDA model is based on the concept of MA but it is extended with several elements (i.e., multiple states, multivalued decisions, otherwise connectors and non-determinism) to ease health care know-how knowledge representation.
- The SDA model was defined as a combination of all the representation primitives that any CIG system is expected to have (§3.2.2) (i.e., actions, decision, patient states, execution states, sequences, concurrences, alternatives, and loops) with the simplicity of MAs.
- The knowledge of the SDA model can be easily translated to other knowledge representation structures such as CIG systems (see §3.2.2).
- The SDA model can deal with the sorts of non-determinism that are found in decision process in medical assistance.
- In the SDA model, the know-how knowledge has two purposes: (1) provide an explicit representation of long-term therapies that integrate differential treatments that are conditioned both to the patient condition and also to the patient feasible evolutions, and (2) allow the exploitation of this knowledge by a decision support system that could recommend medical actions in the treatment of concrete patients. This second purpose is achieved with the execution of SDA know-how knowledge. Given a patient, the SDA is used to suggest a treatment composed of the action terms contained in all the actions in one of the paths of the SDA. The possible paths are those starting in the eligible states, continuing through one of the possible sequences of connectors that the patient satisfies, and ending when the path reaches a non-eligible state or a connector with a time delay representing a momentary stop in the treatment.

The SDA model has been widely tested and evaluated in the context of the K4CARE project (www.k4care.net). The SDA model was successfully used to represent different sorts of procedural knowledge in medicine related to the procedures that implement the home care services and 21 formal intervention plans that represent the more common syndromes, diseases and social issues in home care.

Chapter 5

Automatic Generation of Know-How Knowledge in Medical Assistance

In this chapter we propose a methodology to automatically induce state-decision-action (SDA) diagrams from health care databases and electronic health records in order to show health care professionals an explicit representation of the past health care procedures and to use these representations to study their deviations with respect to official and predefined protocols and medical algorithms.

To describe the induction methodology of SDA diagrams, this chapter is organized in five sections. Section 5.1 describes the context of our work introducing the different ways of generating know-how knowledge in medicine. Section 5.2 proposes the methodology to induce know-how knowledge as SDA diagrams from health care databases. The results of our work are presented in section 5.3. Finally, a discussion of the work and some conclusions are reported in sections 5.4 and 5.5, respectively.

5.1 Introduction

The databases of health care centres are an unavoidable source of information about the medical procedures followed in these centres. They can be the basis for important studies on the adherence of the treatments to the medical standards that are published as clinical practice guidelines (CPGs), and also to foster quality, equality, equity, and cost reduction of medical procedures. This sort of studies for the analysis of health care procedures can be carried out using either a statistical [Mur04] or a symbolic [BR04, RLVT07] approach.

Currently, these medical procedures are obtained by systems that convey knowledge from hu-

mans to machine structures, such as it was discussed in chapter 4. Contrarily, the approach of our work is to convey knowledge in the opposite way, i.e., from computers to health care professionals. With this machine-to-man approach, the knowledge obtained is not necessarily based on the medical evidence but on the experience of the medical daily practice. Some previous works (§3.3.3) in medicine on this approach include the induction of clinical pathways represented as Petri Nets [vdAvDH⁺03, vdAWM04, MSL⁺08] or as causal Bayesian Networks [MC07]. However, the structures induced by those systems are not explicit medical structures that health care professionals are as familiar to work with as with MAs. Moreover, Bayesian Networks are not used to represent guidelines in the strict sense of continuous long-term care [MC07] but punctual decisions in diagnostic and prognostic reasoning, treatment selection, or discovering functional interactions between genes [LvdGAH04]. On the contrary, we propose a process which starts with the data stored either in health care centre databases or in electronic health records, then these data are analyzed by a machine learning methodology to induce health care knowledge structures that represent the health care procedures carried out in the health care centre in the long-term and in a format that health care professionals are familiar with. The final purpose of these knowledge structures is to show health care professionals an explicit representation of the past health care procedures and to use these representations to study their deviations with respect to official and predefined protocols and MAs.

Therefore, this chapter introduces a novel methodology to the automatic generation of MAs for the analysis of the health care procedures followed in health care centres. These health care procedures are represented with SDA diagrams introduced in chapter 4. The methodology has been implemented and tested on the databases of the SAGESSA Group [SAG] for patients with hypertension.

5.2 Automatic Generation of SDAs

Health care databases are a potential source of knowledge on the medical procedures followed in health care institutions. The difficulty of dealing with hundreds or thousands of data can be overcome with the use of intelligent machine learning algorithms that make the knowledge behind these data explicit. We propose a methodology to generate SDA diagrams that generalize health care procedures from health care databases. These SDA diagrams are induced by maximizing the adherence to the data while maintaining its capability of generalization. Figure 5.1 shows a diagram of the proposed methodology.

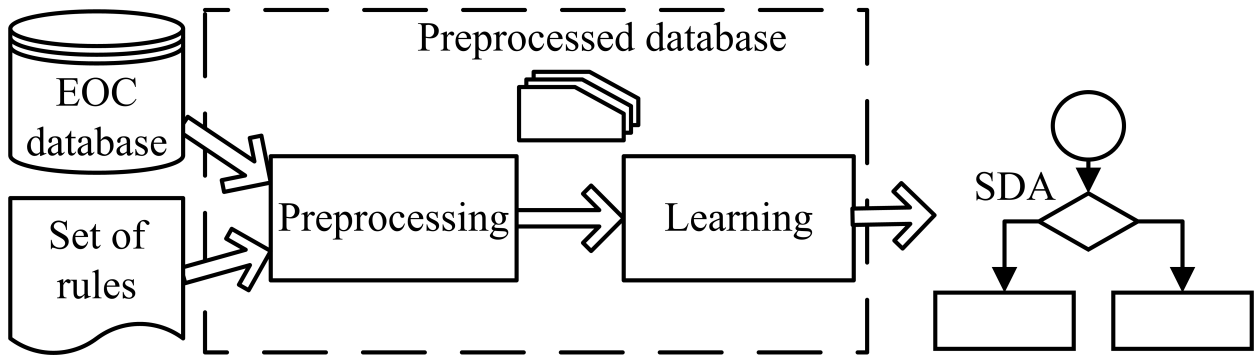


Figure 5.1: Scheme of the automatic generation of SDA diagrams.

This methodology is based on two initial structures, the EOC database and the set of rules, which contain, respectively, patient data from a health care centre whose structure fulfils a predefined *EOC data model*, and some user-defined *translation rules* which are used in a *preprocessing step* to adapt the data of the EOC database to the terminology the final users want the resulting SDA to have. The data obtained after the preprocessing step is used to generate the final SDA diagram by means of a *machine learning* method.

All these elements (i.e., the EOC data model, the translation rules format, the data preprocessing step, and the machine learning method) are described in the next subsections.

5.2.1 The EOC Data Model

An *episode of care* (EOC) of a particular patient is the sequence of encounters aiming at curing, stabilizing, or palliating one or several of that patient's ailments [HHJ85]. Concerning a single *encounter*, the standard behaviour of a health care professional is to observe the current state and antecedents of the patient (i.e., the *patient condition*) and then decide some *actions*. Observe that some *evidence* may exist that justify these actions. Therefore within the same encounter, several *health care measures* may coexist containing, each one, the evidence to a subset of the actions performed during that encounter. For example, in the hypertension domain, for a particular encounter the health care professional may decide both a drug therapy based on the evidence that the patient is at high risk of cardiac disease, and a recommendation to modify the patient lifestyle, due to the presence of cholesterol.

A simplified formalization of the EOC data model can be seen in table 5.1.

Here, the patient condition, the health care actions, and the medical evidence supporting these actions are described as a list of state, decision, and action terms, respectively. For example, the

episode of care	← sequence of encounters
encounter	← patient condition + list of health care measures
patient condition	← list of state terms
health care measure	← evidence + action
evidence	← list of decision terms
action	← list of action terms

Table 5.1: Simplified formal description of the EOC data model.

MA depicted in figure 4.1 [ICS06] (§4.1) to diagnose and treat hypertension, contains the following indications:

- A patient in a encounter can be in one of the following four possible alternatives patient conditions:
 - Screening and identification of elevated blood pressure (BP) in patients with diabetes, chronic kidney disease, heart failure or CAD.
 - Initial assessment completed (i.e., evaluated, accurately staged, and complete risk assessed).
 - Hypertension is suspected to be caused by secondary causes.
 - Hypertension is under control and a continuing care must start.
- The health care actions proposed are:
 - Confirm hypertension on the initial encounter, plus two follow-up encounters with at least two BP measures at each encounter; following standardized BP measurement techniques, including home BP measurements.
 - Consider a thiazide-type diuretic as initial therapy in most patients with uncomplicated hypertension.
 - For many patients, two or more drugs in combination may be needed to reach hypertension goals.
 - Refer to hypertension consultation.
- The medical evidence that support these health care actions are:
 - Is a second cause of hypertension suspected?
 - Is a blood pressure at goal? (i.e., within normally limits).

- In it a resistant hypertension? (i.e., when blood pressure goals are not met despite compliance with a triple drug regimen that includes a diuretic).

5.2.2 Translation Rules

In order to convert the data in a health care centre EOC database to the EOC data model, we use translation rules. The purpose of this conversion process is not only to have a means to adapt any EOC database to a common format (data formatting), but also the way to decide which are the state, decision, and action terms that we want our final SDA be expressed with (data filtering), and the way to transform the data in the EOC database into medical terms (data discretization). The set of translation rules must be provided by an expert whose effort is proportional to the number of terms that we want the SDA diagram to contain and to the number of database columns related to these terms.

Given T a set of terms and C the columns of the EOC database that contain the information about the states, decisions and actions of the health care procedures in a health care centre, a translation rule is an expression of the form $t \leftarrow p$, where t is one of the terms in T and p is a constraint on some of the columns in C . For all the encounters in which the patient fulfils p , the translation rule is triggered generating the output term t .

There are two kinds of translation rules, one for state and decision terms and another one for action terms. In the first kind, t is either a state or a decision term and p is a conjunction of conditions of the form $\{c \text{ } s \text{ } val\}$ where c is one of the columns in C , s is one of the comparison symbols $=, <, >, \leq, \geq, <>$ or the same symbols preceded by an exclamation mark (!) meaning the negation of the symbol or unknown value; and val is either a numerical, multi-valued or Boolean value, or another column. For example, the translation rule 5.1 will introduce the decision term “*Resistant_Hypertension*” in all the encounters of the database in which the observed systolic blood pressure (SBP) of the patient is greater than 140 mm Hg and the current treatment comprises two or more drugs.

In the second kind of translation rules, t is a SDA action term and p is a conjunction of columns of the database. For example, the rule 5.2 will introduce the action term “*Drug_Therapy*” in all the database encounters in which the patient is prescribed with *DIUREX_20MG*.

$$Resistant_Hypertension \leftarrow \{SBP > 140\} \& \{NUM-DRUGS \geq 2\} \quad (5.1)$$

$$Drug_Therapy \leftarrow DIUREX_20MG \quad (5.2)$$

5.2.3 Data Preprocessing

The preprocessing step in figure 5.1 uses a set of translation rules to adapt the data in a EOC database to the terminology that we want for the final SDA. This preprocessing is justified, firstly, by the fact that the database may contain numerical, multi-valued or Boolean values and we may not need such amount of variability in the final SDA. Secondly, from a medical point of view, it may be of some interest to reflect only part of the treatment or different perspectives of the same treatment, instead of the complete treatment registered in the EOC database. For example, if we are only interested in the nursing activities or in the treatment of critical cases. So, part of the data should be left out of the learning process or generalized in a different way. Finally, data preprocessing is useful to integrate data from different health care centres which may use different terminology. In these cases, preprocessing can be used to format, filter and discretize data from different sources and make these data homogeneous before the machine learning process is started.

Translation rules perform operations on the domain terminology such as generalization, extension, removal and replacement. *Generalization* allows a common term to represent different conditions. Formally expressed, generalization is when a unique term t represents several constraints p_1, p_2, \dots, p_n within the database (i.e., $t \leftarrow p_i$ with $i = 1..n$). For example if we consider the rules 5.3 and 5.4, the action term “*Drug_Therapy*” will generalize the prescription of either *DIUREX* or *DILUTOL*.

Extension is the operation of increasing the vocabulary with synonyms. Formally expressed, we may require that different terms t_1, t_2, \dots, t_n represent the same constraint p of the database (i.e., $t_i \leftarrow p$ with $i = 1..n$). For example, the constraints on Systolic Blood Pressure (*SBP*) and Diastolic Blood Pressure (*DBP*) in the rules 5.5 and 5.6 give rise to the decision terms “*Grade_I/II_BP*” related to the blood pressure level of the patient, and “*High_Risk*” related to the cardiovascular disease risk.

Removal is used to avoid the use of some of the columns in the database because they are not of our interest. For example, if none of the rules contain *BILIRUBIN* then the final data will not take into account this information about the treatment, and the final SDA will describe a treatment without considering bilirubin.

Finally, *replacement* consists in substituting a health condition by an equivalent term. Formally expressed, replacement is the operation of using the term t to refer a constraint p in the database

(i.e., $t \leftarrow p$). For example, the state term "*Initial_State*" is used in our tests to refer the encounters whose date is equal to the date in which the EOC started. This replacement is achieved with rule 5.7, *E-DATE* meaning the date of the encounter and *EOC-DATE* the date when the EOC was created during the first visit.

$$\text{Drug_Therapy} \leftarrow \text{DIUREX_20MG} \quad (5.3)$$

$$\text{Drug_Therapy} \leftarrow \text{DILUTOL_10MG} \quad (5.4)$$

$$\begin{aligned} \text{Grade_III_BP} \leftarrow \{SBP \geq 140\} \&\{SBP \leq 179\} \& \\ &\{DBP \geq 90\} \&\{DBP \leq 109\} \end{aligned} \quad (5.5)$$

$$\begin{aligned} \text{High_Risk} \leftarrow \{SBP \geq 140\} \&\{SBP \leq 179\} \& \\ &\{DBP \geq 90\} \&\{DBP \leq 109\} \end{aligned} \quad (5.6)$$

$$\text{Initial_State} \leftarrow \{E\text{-DATE} = \text{EOC-DATE}\} \quad (5.7)$$

5.2.4 The Machine Learning Method

Provided the preprocessed data, once it is structured according to the previously described EOC data model, it is possible to generate a SDA diagram that generalizes the individual treatments as a global treatment. The proposed method is depicted in figure 5.2 and it involves five tasks: detect states, detect actions, determine evolutions, determine actions, and integrate all the components in a final SDA.

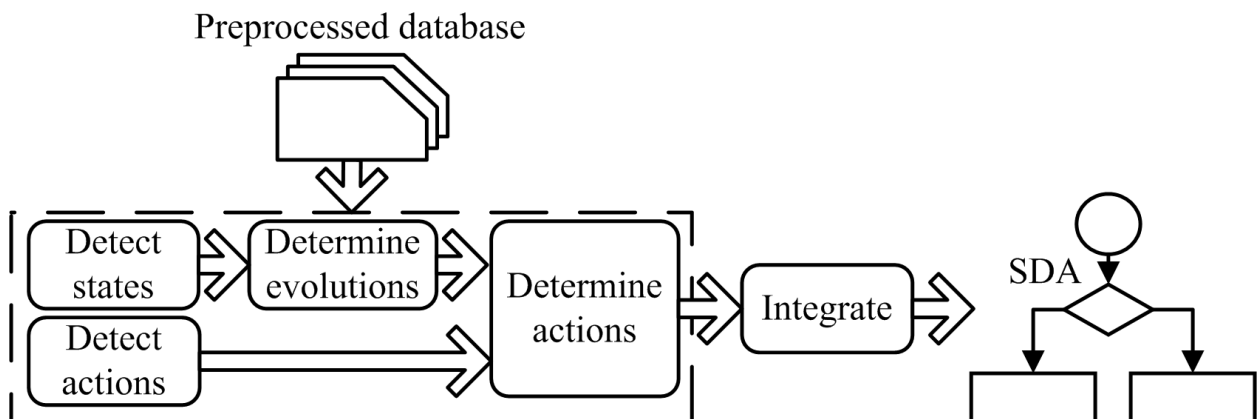


Figure 5.2: Generation of SDA diagrams.

Task 1: Detecting states

After preprocessing the database with the translation rules, the obtained data is used by an inductive learning method to generate a SDA diagram that generalizes all the individual treatments. In order to detect all the states that will be part of this SDA, we apply an automatic method which is based on a function of similarity between states. The method is as it follows. Being $S_1 = \{s_{11}, s_{12}, \dots, s_{1m}\}$ and $S_2 = \{s_{21}, s_{22}, \dots, s_{2n}\}$ the respective sets of state terms of two encounters, each one representing a state, then a similarity function between these states is defined as $similarity(S_1, S_2)$ in equation 5.8. If this value is greater than a predefined threshold $0 \leq \alpha \leq 1$, these two states are considered to be the same. The threshold chosen depends on the level of detail needed for the SDA diagram. With $\alpha = 0$ there will be only one state in the final diagram, and with $\alpha = 1$ there will be as many states as encounters with a different state are in the data.

Alternatively to the automatic detection of states, the user may define the SDA states wished and the state terms that compose each one of these states. For example, the states $S_1 = \{Initial_State\}$ and $S_2 = \{Intermediate_State\}$ in figure 5.4.

$$similarity(A, B) = \frac{|A \cap B|}{|A \cup B|} \quad (5.8)$$

Task 2: Detecting sorts of actions

In order to detect all the sorts of actions that will be part of the final SDA, a similar method to the one to detect states is applied. This is based on a function of similarity between actions. Let $A_1 = \{a_{11}, a_{12}, \dots, a_{1m}\}$ and $A_2 = \{a_{21}, a_{22}, \dots, a_{2n}\}$ be the respective sets of action terms of two encounters, each one representing a sort of SDA action, then a similarity function between A_1 and A_2 is defined as the quotient $similarity(A_1, A_2)$ in equation 5.8. If it is greater than a predefined threshold $0 \leq \beta \leq 1$, these two sorts of SDA actions are considered to be the same. The threshold chosen depends on the level of detail needed for the SDA diagram. With $\beta = 0$ there will be only one sort of action in the final SDA diagram (i.e., the same exact treatment is applied to all the admitted patients), and with $\beta = 1$ there will be as many sorts of actions as encounters with a different action are found in the data (i.e., any difference, small or big, is interpreted as a different treatment).

Alternatively, the user may avoid the application of this process and define the available sort of actions by choosing the action terms that compose each one of the wished actions. For ex-

ample, $A_1 = \{LifeStyle_Modification, Drug_Therapy\}$, $A_2 = \{LifeStyle_Modification, Change_Treatment\}$, etc. in figure 5.4.

Task 3: Separating patients who evolve in a different way from the same state

Once the states and the sorts of actions of the final SDA have been determined, the sequences of decisions that determine the different treatments followed by the patients in the EOC database have to be found. In a first stage, this is done by separating, for all the states S_i obtained in task 1, the encounters E_i of the patients in that state. In the EOC database, all these encounters evolve to a next encounter or they are discharging encounters. The states of the patients in these next encounters define different sorts of evolution that our learning process induces.

This process finds a combination of SDA decisions to partition E_i with a procedure that is inspired in the split criterion used by the C4.5 algorithm [Qui93] for decision tree induction. This procedure is the following:

- A. Let D be the set of all the decision terms that appear in the encounters in E_i . For each possible subset of decision terms D' in D , a SDA decision is created with as many decisional connectors as decision terms are in D' , plus an otherwise connector. Each one of the decisional connectors is assigned a different decision term in D' .
- B. The best of these SDA decisions is the one that, for each one of the encounters in E_i provides a higher information gain [Qui93] about the state of the next encounter.
- C. In the best SDA decision, each connector is related to the subset of encounters in E_i that contain the decision term in the connector. All the encounters that contain none of the decision terms in the SDA decision are grouped in an additional subset which is related to the otherwise connector.
- D. For each one of these subsets, the corresponding connector is linked to the resulting SDA decision obtained after applying this same procedure with E_i that subset. The process is repeated until all the encounters E_i correspond to patients that evolved from an initial state S_i to one same state S_j .

At the end, we have d_i a combination of SDA decisions which partitions the encounters of patients in S_i into several subsets of encounters E_{ij} , each one containing the encounters of the patients who evolved from S_i to S_j . This process is represented as the first step in figure 5.3.

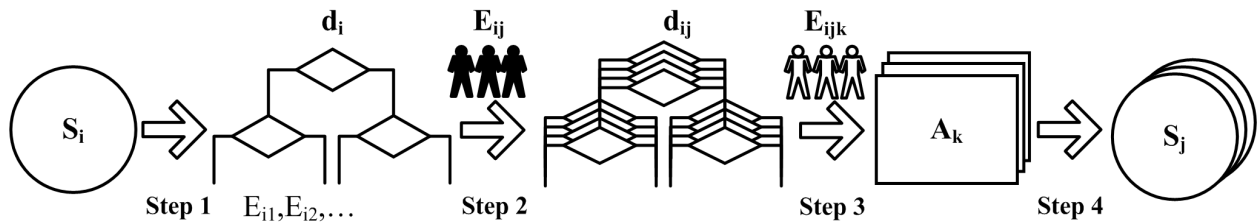


Figure 5.3: Integration of states, decisions and actions in the SDA.

Task 4: Determining the correct action for the patients of each evolution

Once the patients who evolved from the same state S_i to different next states S_j have been separated, each one of the combinations of SDA decisions d_i is extended with other combinations of decisions that decide which is the SDA action that defines the treatment of the patients following this evolution. The same process of task 3 is applied to all the subsets of encounters E_{ij} but, in this case, the selection of the best decision is based on the information gain about the sort of action performed rather than on the expected next state. The process is repeated until all the encounters in a subset correspond to patients that are treated with the same sort of action. We call d_{ij} the combination of decisions which partitions E_{ij} into several subsets E_{ijk} , each one related to patients who evolved from S_i to S_j in the next encounter, receiving the treatment represented by the SDA action A_k . This is represented as the second step in figure 5.3. During this partition process, type-II non-determinism may exist if some encounters in the same subset have the same decision terms but different medical actions. In this case, some of the decisions in d_{ij} may have different decisional connectors with the same decision terms. A pruning process is incorporated to reduce non-determinism. Given a threshold $p\%$, during the whole process, whenever a subset of encounters has less than $p\%$ of encounters with a same action, these encounters are removed from the subset before any SDA decision is generated. If none of the actions appears in more than $p\%$ of the encounters, then only the most frequent action is considered.

Task 5: Integration

The SDA diagram is obtained as an integration of the states, the sorts of actions and the combinations of decisions obtained in the previous tasks as figure 5.3 summarizes. The states detected in task 1 are the states in the final SDA. The root SDA decision of each d_i is connected after each corresponding state S_i . The root SDA decision of each d_{ij} is connected after the last decisional connector of d_i that leads to E_{ij} . Then, a SDA action of the sort A_k is placed after the last decisional

connector of each d_{ij} that leads to E_{ijk} . Each terminal action of d_{ij} is connected to the SDA state S_j . Finally, since the same sort of action can appear several times in the SDA, all the identical actions that lead to the same next state are unified into one single action in order to simplify the final SDA.

5.3 Results

This methodology to generate SDAs from EOC databases has been tested using the patients treated of hypertension in the SAGESSA Group [SAG] and the resulting SDAs analyzed from two points of view: their ability to predict correct treatments and their similarity to already existing official MAs.

5.3.1 Source Data and Preprocessing

The methodology has been tested on the medical domain of hypertension, which is one of the most common chronic diseases. The EOC database was provided by the SAGESSA Group [SAG]. The database contained 1,092 encounters of patients who were treated for hypertension.

With the purpose of studying the differences between the health care procedures of the EOC database and some predefined official MAs, a set of translation rules was developed for each one of the four MAs on hypertension provided by ICSI [ICS06], SIGN [SIG01], NHF [NHF08], and SEH [SEH05]. These official MAs were represented as the SDA diagrams that are provided in figures 5.4, 5.5, 5.6, 5.7, respectively. Each set of translation rules was used to convert the data in the EOC database to the terminology of each one of the respective MAs before the machine learning methodology was applied, so that the SDA diagrams obtained and the MAs in figures 5.4, 5.5, 5.6, 5.7, could be compared. A total number of 379 operations were performed with translation rules. These rules do not contain additional medical knowledge but only the matching between the data in the SAGESSA Group database and the terminology used by the different official MAs.

The number of operations performed with the translation rules are summarized in table 5.2. *Removal* is the most frequent operation because there were several columns in the database that contained information that was not present in the official MAs (e.g., *BILIRUBIN*). All the terms in the official MAs could be found in the EOC database; therefore, operations of the sort *extension* were not necessary. The operations of *generalization* and *replacement* were used in all four cases (e.g., *LOW_SALT_DIET* was replaced by the term "*LifeStyle_Modification*" and "*LifeStyle_Measures*" in ICSI and SIGN, respectively). The main differences are found in the

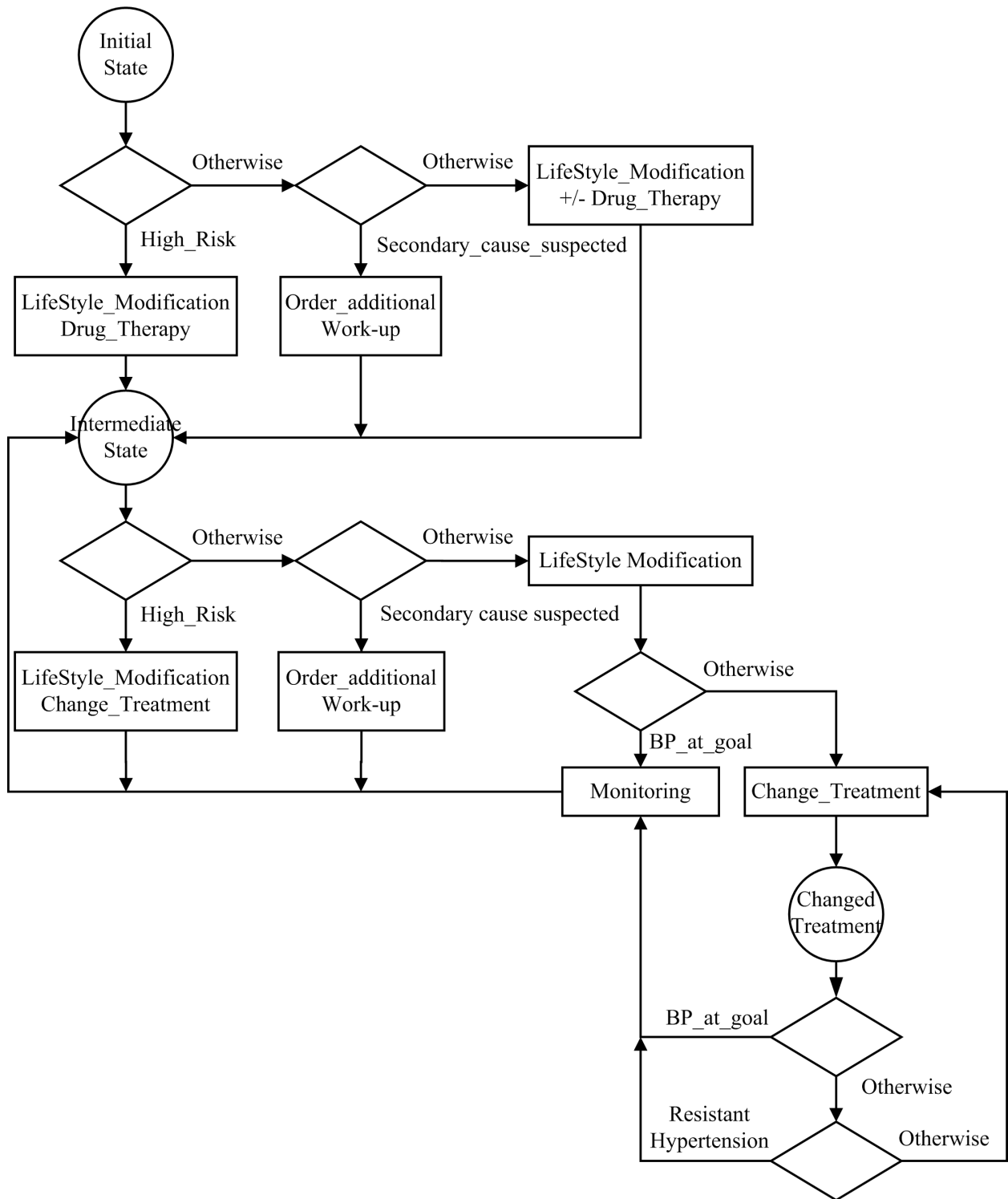


Figure 5.4: SDA diagram obtained from MAs provided by ICSI for the treatment of hypertension.

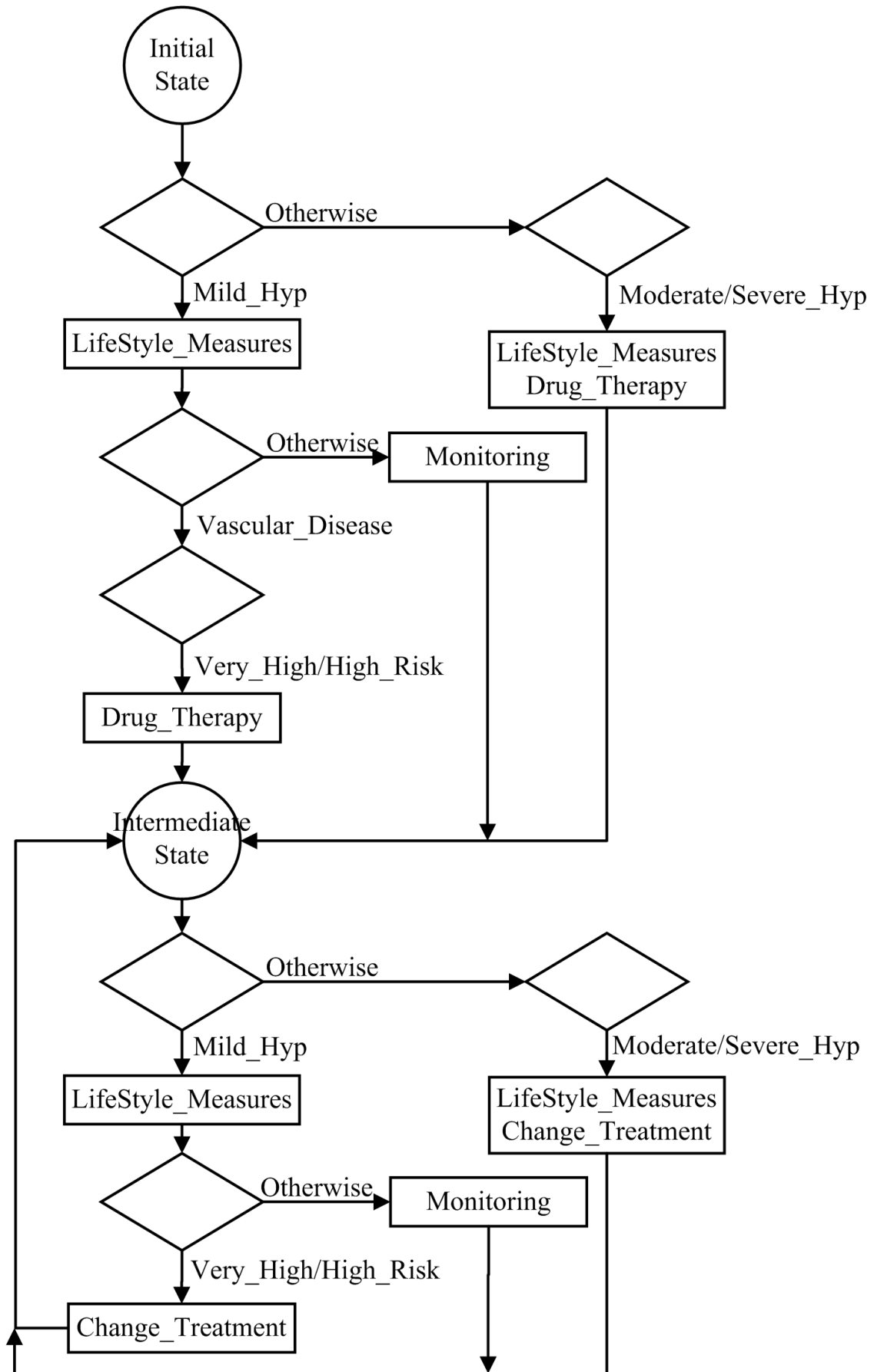
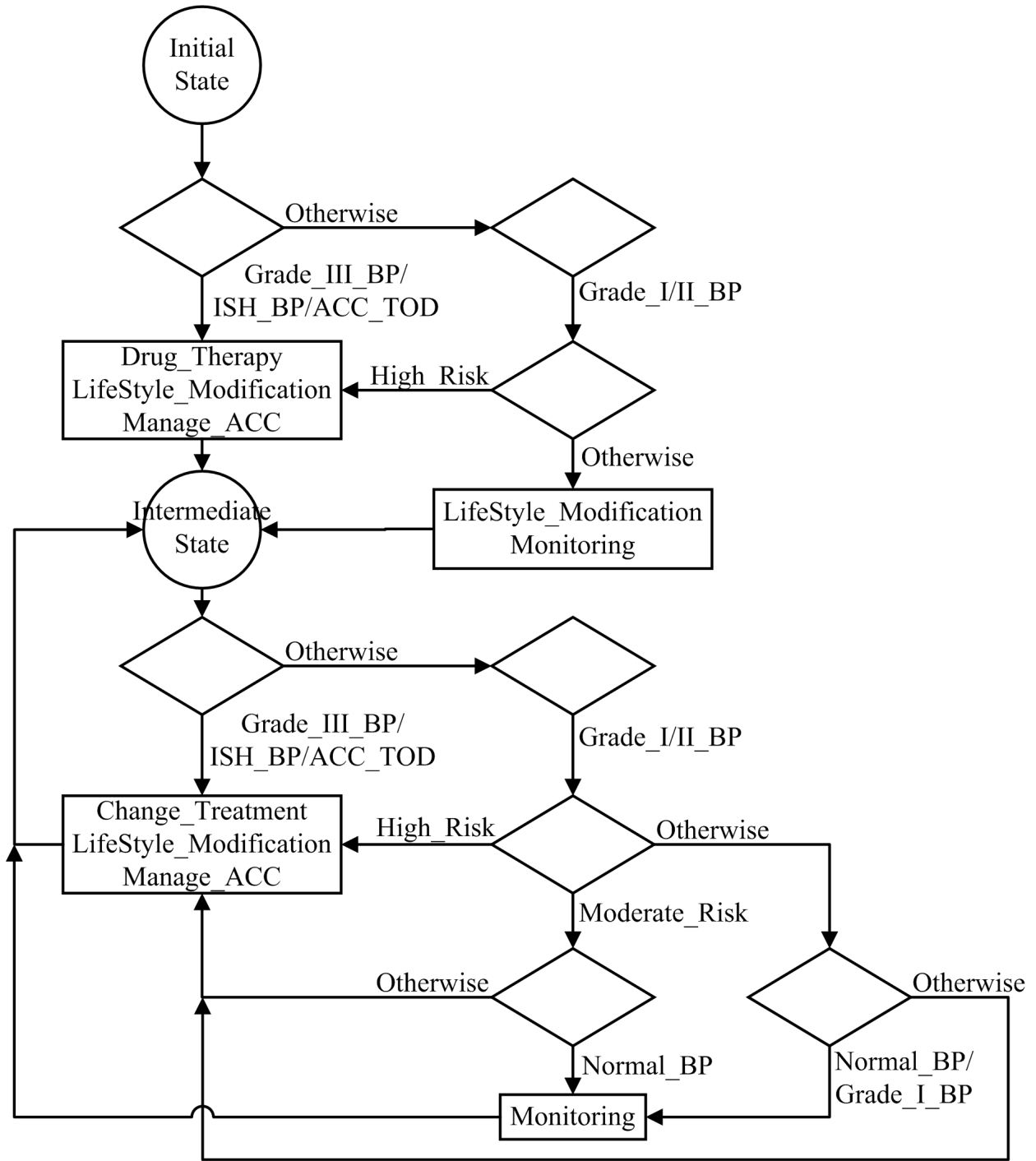
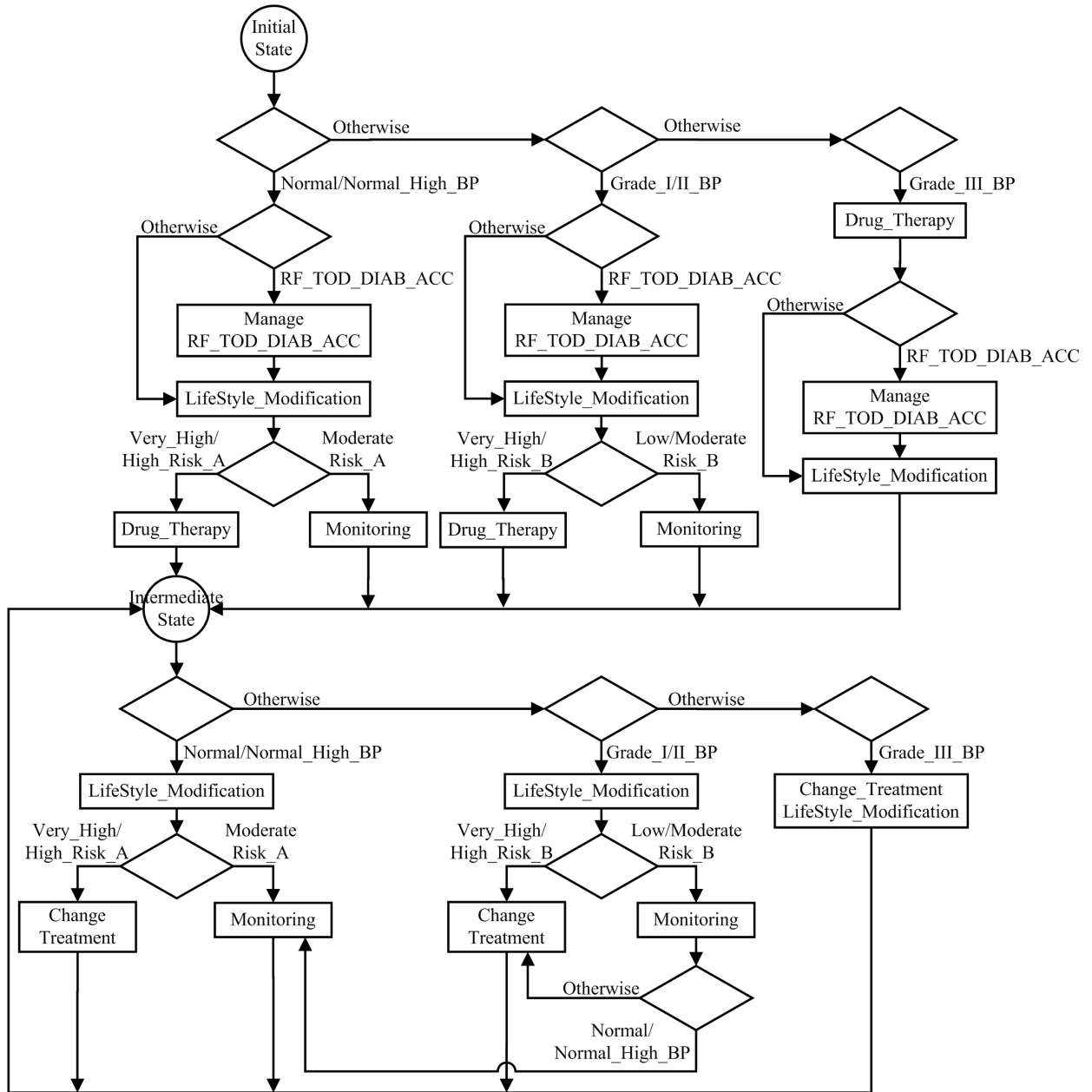


Figure 5.5: SDA diagram obtained from MAs provided by SIGN for the treatment of hypertension.



ISH_BP: Isolated Systolic Hypertension; ACC: Associated Clinical Conditions; TOD: Target Organ Damage

Figure 5.6: SDA diagram obtained from MAs provided by NHF for the treatment of hypertension.



RF: Risk Factor; TOD: Target Organ Damage; DIAB: Diabetes Mellitus; ACC: Associated Clinical Conditions

Figure 5.7: SDA diagram obtained from MAs provided by SEH for the treatment of hypertension.

number of generalization rules, this is so because the number of decision terms in NHF and SEH is higher than in ICSI and SIGN, and more rules are needed to generate these additional terms.

	Terms			Operations				Total
	S	D	A	Gen.	Ext.	Rem.	Rep.	
ICSI	2	4	5	7	0	75	4	86
SIGN	2	4	4	7	0	91	3	101
NHF	2	6	5	9	0	80	5	94
SEH	2	8	5	14	0	80	4	98

Table 5.2: Number of terms (State (S), Decision (D) and Actions (A)) and frequency of the operations (Generalization (Gen), Extension (Ext), Removal (Rem) and Replacement (Rep)) performed with translation rules for each medical algorithm.

5.3.2 The Obtained SDA diagrams

The figures 5.8, 5.9, 5.10, 5.11, depict the SDA diagrams that were obtained from the EOC database after preprocessing the data with the respective sets of translation rules. Due to the reduced number of states the parameter α was fixed to 1, whereas β was recommended by the health care professionals of the SAGESSA Group to be also 1 in order to obtain the most detailed SDA diagrams possible on which these health care professionals performed a validation process. In this process they were asked to assess several aspects of the SDA diagrams: flexibility (i.e., capacity of the SDA diagrams to capture the treatment alternatives), generality (i.e., ability of the diagrams to deal with the variability of patient cases), medical appropriateness (i.e., medical and clinical correctness), common behaviour (i.e., capacity of the diagrams to capture usual treatments), level of detail (i.e., the treatments in the diagrams have the appropriate degree of abstraction), and comprehension (i.e., the diagrams are clear and easy to understand).

After the validation process the health care professionals evaluated satisfactorily all these aspects and they remarked an outstanding performance with regard to flexibility, medical appropriateness, level of detail, and comprehension. So, for example, they argued that all the diagrams describe treatments that are more flexible than the corresponding official MAs depicted in figures 5.4, 5.5, 5.6, 5.7, because they include non-determinism in some of the decisions. For example in figure 5.8, the decision on the left side has three decisional connectors with the decision term "*High_Risk*" leading to different actions. This reflects that some health care professionals of the SAGESSA Group do not always act according to the MA indications, but providing alternative treatments under the same circumstances of the patient. This behaviour was qualified as appropriate and common by

independent health care professionals. Health care professionals also argued that the level of detail of pharmacological treatment in the diagrams was adequate to the treatment of hypertension where many correct drug combinations are possible for the same medical case.

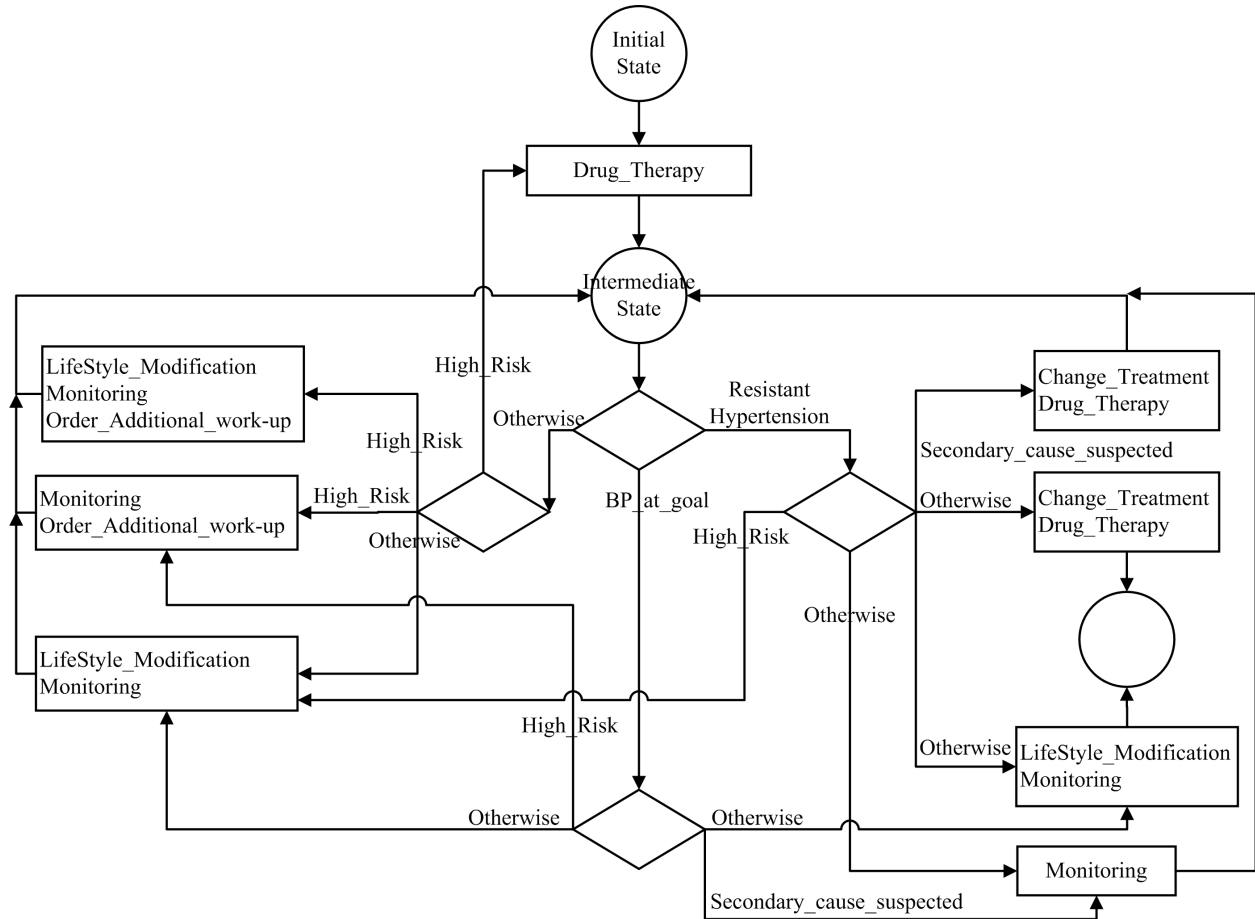


Figure 5.8: ICSI SDA diagram induced from the EOC database for the treatment of hypertension.

Some structural differences can also be appreciated between the standard MAs in figures 5.4, 5.5, 5.6, 5.7, and the obtained SDAs in figures 5.8, 5.9, 5.10, 5.11. According to the EOC database, the procedures carried out in the first encounter are more general than those proposed by the MAs. For example, SEH uses *BP*, the associated clinical conditions (*RF_TOD_DIAB_ACC*)¹ and the risk levels (of types *A* and *B*)² for making decisions in the first encounter (see figure 5.11) whereas the corresponding health care professionals of the SAGESA Group do only consider *BP* in the first encounter (see figure 5.11), and leave the rest of conditions for later consideration. Another difference is that SDAs include a third new state to represent patient discharge, which is depicted

¹RF: Risk Factor, TOD: Target Organ Damage, DIAB: Diabetes Mellitus, ACC: Associated Clinical Conditions.

²Risk stratification according to SEH.

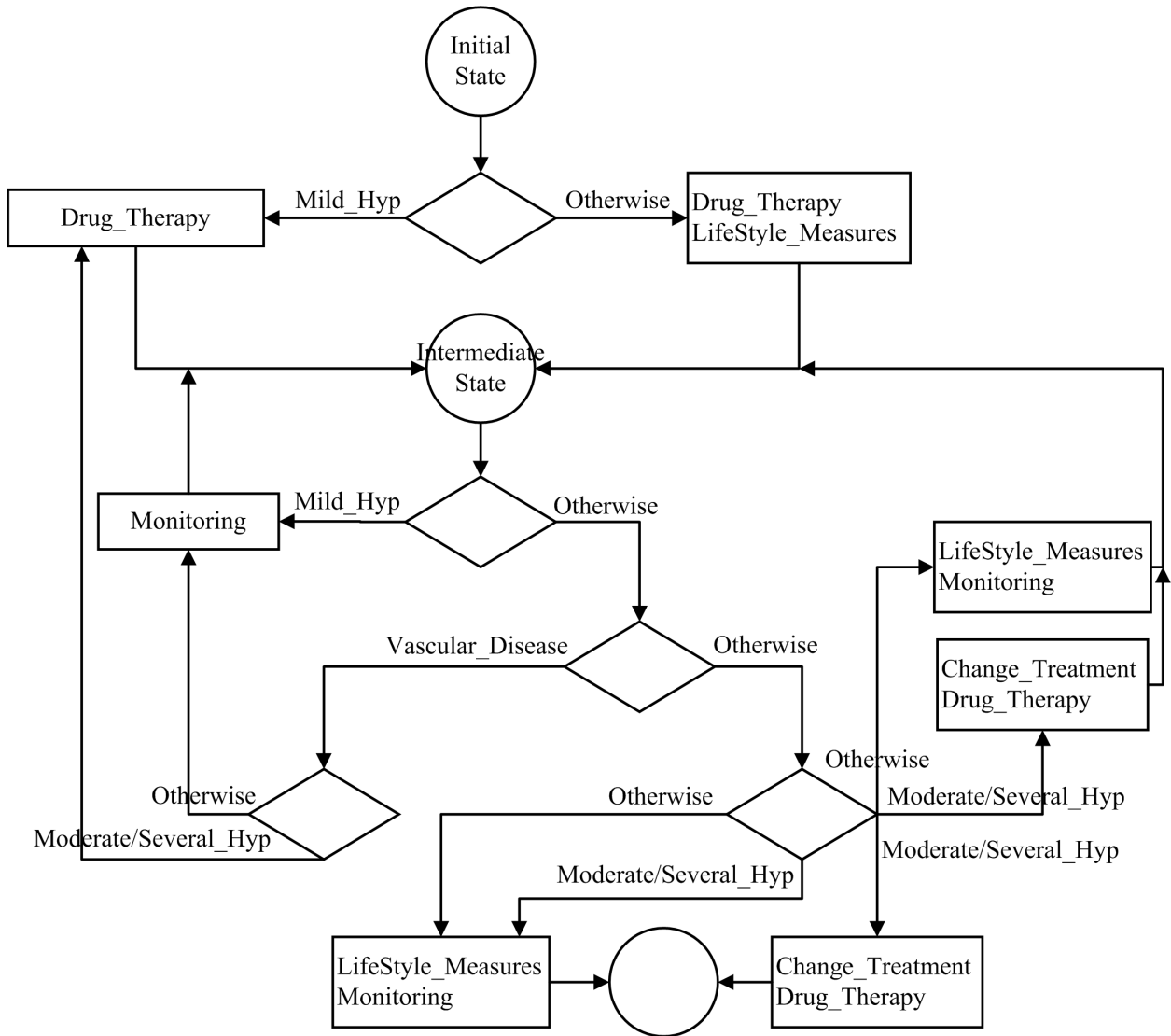


Figure 5.9: SIGN SDA diagram induced from the EOC database for the treatment of hypertension.

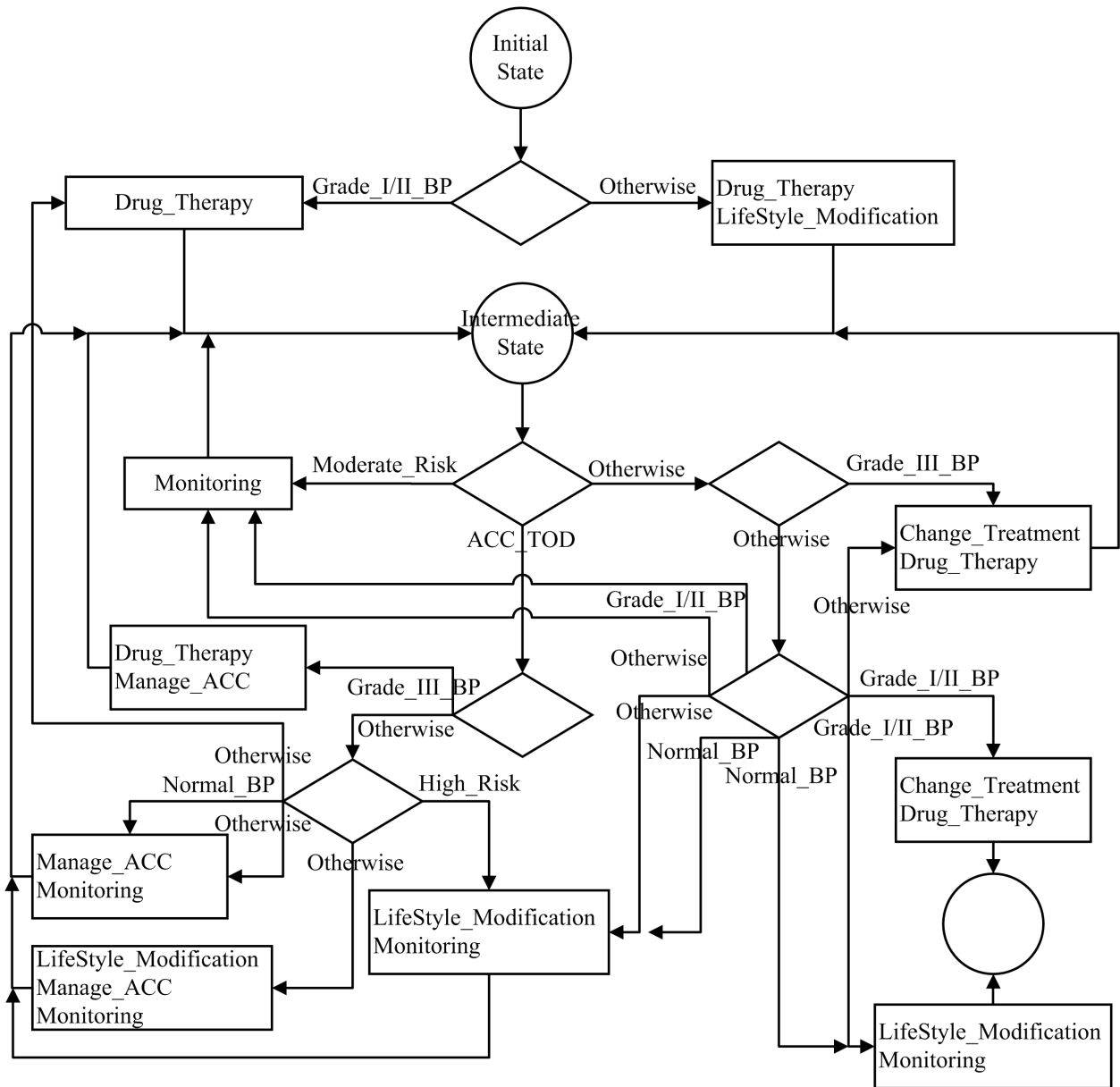


Figure 5.10: NHF SDA diagram induced from the EOC database for the treatment of hypertension.

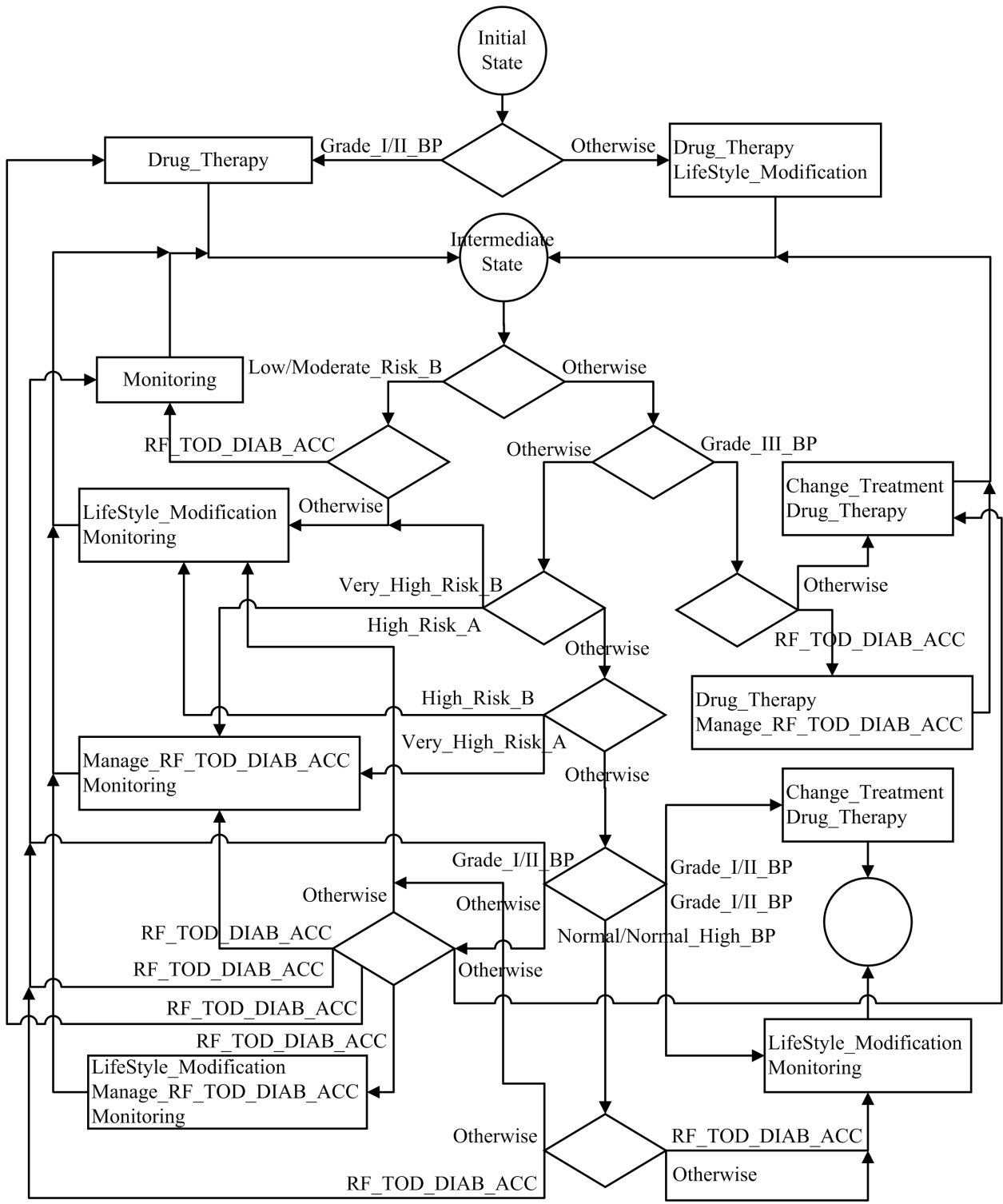


Figure 5.11: SEH SDA diagram induced from the EOC database for the treatment of hypertension.

as an empty state.

Semantically, the treatments described by both MAs and SDAs are similar as it is suggested in the analysis of quality of medical adherence.

5.3.3 Analysis of the Adherence

Medical adherence is defined as the extent to which real medical practices follow the suggestions of medical standards. Here the analysis of the adherence is used both to verify that the methodology introduced to generate accurate representation of medical procedures is correct (SDA-data analysis) and also to validate the SDAs obtained with respect to several predefined standard MAs (SDA-MA analysis). In both cases, the adherence was calculated in terms of type I and type II errors [Doa]. *Type I error* is related to the medical relevance of not taking the correct medical decision (e.g., forgetting a drug prescription when it is completely necessary) and *type II error* is related to the medical relevance of taking a wrong medical decision (e.g., ordering a visit to a specialist when it is not necessary). To calculate these errors in the SDA-data analysis, we register the deviations between the treatment performed in each encounter of the EOC database and the treatment proposed by the induced SDA diagram. In the SDA-MA analysis, for the list of all the possible patient conditions and their probability provided by the health care professionals, we register the deviations between the treatment suggested by the MA and the treatment proposed by the SDA diagram. In both cases, each possible deviation of the treatment is given a certain medical relevance provided by a health care professional. The addition of type I and type II errors is called here the *total error*.

The **SDA-data analysis** was performed to verify the correctness of the methodology, that is to say, the level of adjustment of the SDA diagrams to the health care procedures within the database. In table 5.3, the columns *SDA-Data* contain the weighted-mean of type I, type II and total errors when the health care procedures in the EOC database were compared with those proposed by the SDA diagrams in figures 5.8, 5.9, 5.10 and 5.11. The pruning in tasks 3 and 4 of the learning process is the main reason for type I and type II errors. An average 5,1% of the medical orders in the EOC database are not reflected in the SDA diagrams (type I error), and an average 0,3% of medical orders suggested by the SDA diagram do not coincide with the database (type II error).

The **SDA-MA analysis** determines the adherence of the SDA diagrams to the official MAs in order to study the resemblance of the health care procedures carried out in the SAGESSA Group to some official and predefined standards. This serves as a way to determine which type of health care assistance is rendered in a certain clinical centre. In table 5.3, the columns SDA-MA contain

	Type I Error		Type II Error		Total Error	
	SDA-Data	SDA-MA	SDA-Data	SDA-MA	SDA-Data	SDA-MA
ICSI	0,070	0,160	0,004	0,016	0,074	0,176
SIGN	0,083	0,139	0,002	0,011	0,085	0,150
NHF	0,024	0,078	0,003	0,018	0,027	0,096
SEH	0,027	0,083	0,003	0,014	0,030	0,097
Average	0,051	0,115	0,003	0,015	0,054	0,130

Table 5.3: Average type I, type II and total errors obtained in the SDA-Data and SDA-MA analysis of the adherence on hypertension.

the weighted-mean of type I, type II and total errors when the health care procedures of the MAs were compared with those proposed by the SDA diagrams in figure 5.8, 5.9, 5.10, 5.11. The SDA diagrams have an average type I error of 11,5% and an average type II error of 1,5% with respect to the MAs. This means that the patients of the SAGESSA Group were approximately ten times more under-prescribed than over-prescribed³, respect to official MAs. One of the reasons for this difference is that in this work and for the disease under study health care professionals determined that forgetting a medical action is more critical than performing it when it is unnecessary. For example, the medical error of not doing a necessary monitoring of the patient can imply important health consequences. On the contrary, planning an unnecessary monitoring can be a common practice to corroborate the state of the patient, but with null health implications. Therefore, from a medical point of view, type I error has to be greater than type II error.

Observe also that the health care procedures in the EOC database have a lower total error with respect to the MAs provided by NHF and SEH, than to the MAs provided by ICSI and SIGN. This indicates that the health care professionals in the SAGESSA Group act more closely to NHF and SEH indications than to the ICSI or SIGN MAs. The interpretation of the health care professionals of the SAGESSA Group to these results is related to the fact that health care in Spain is mainly a public service coordinated by the Spanish National Health Ministry. This Ministry watches for the national health care centres to provide an homogeneous assistance in all the Spanish regions and it works together with national health societies, as the SEH, to disseminate health care guidelines. Therefore, it is not surprising that the health care professionals in a Spanish health care centre as the SAGESSA Group treat hypertension as it is recommended by the SEH. On the other hand, the good adherence of the SAGESSA Group treatments to the MA of the Australian NHF was unexpected but it also confirmed the similarities between NHF and SEH MAs.

³A patient is said to be under-prescribed when the received treatment lacks of some actions with respect to the official treatment (i.e., a positive type I error). A patient is over-prescribed when the treatment followed contains actions that are not explicitly recommended in the official treatment (i.e., a positive type II error). The under- and over-prescription values in table III represent qualitative rather than quantitative measures of the medical errors.

Some of the deviations observed in this comparative analysis between official MAs and real treatments have been interpreted and justified by health care professionals as experience-based knowledge which complements official MAs. For example, the MA of SEH (figure 5.7) proposes *LifeStyle_Modification* for patients with *Normal/Normal_High_BP*, while the respective induced SDA (figure 5.11) recommends *Monitoring* in addition to *LifeStyle_Modification*. Health care professionals argue that monitoring is highly recommended also for mild hypertension cases for preventive reasons.

5.4 Discussion

We are not aware of friendly machine-to-man methods in medical informatics available for inducing know-how knowledge from health care databases and electronic health records using explicit medical structures that health care professionals are familiar with. Nowadays this kind of knowledge is represented with CIGs as a result of a knowledge engineering process.

Other approaches as the automatic construction of Petri Nets [vdAvDH⁺03, vdAWM04, MSL⁺08] or causal Bayesian Networks [MC07] from health care data produce knowledge structures that are not as familiar to health care professionals as MAs and they do not represent long-term treatments [MC07] but punctual decisions in diagnostic, prognostic or treatment procedures, or gene analysis [LvdGAH04]. Therefore the methodology introduced here is innovative because it automates the induction of knowledge structures representing the long-term health care procedures carried out in a certain health care centre in a manner that health care professionals may understand. Moreover, the fact that this knowledge is represented using the SDA model (see chapter 4) offers several advantages with respect to the classical MA representation as, for example, the representation of long term procedures, the identification of multiple entry points and the possibility of using multi-term decisions and non-determinism.

All the tests presented in section 5.3 correspond to hypertension because the SAGESSA Group was interested in the analysis of their databases for this particular disease. Hypertension is a controlled well-known medical domain that affects a big percentage of chronic population, it is a common disease of any health care centre and, therefore, the amount of data available in different centres is (1) representative of the different sorts of treatments, (2) usually non-biased, and (3) sufficient to apply the inductive learning methodology introduced in this chapter.

Moreover, on the contrary of other already analyzed diseases as Chronic Obstructive Pulmonary Disease and certain cancers [RLVT07], hypertension is a medical domain with multiple available official MAs and whose treatments are always described at the level of abstraction that avoids the

extreme personalization of medical procedures (e.g., considering drug treatment instead of concrete drugs). Both, having several official MAs and being adjusted to the level of abstraction of the terms in these MAs were compelling conditions satisfied by hypertension but not by other diseases considered.

The results obtained provide evidence on the correctness of the machine learning methodology with an average total error of 5,4% when the generated SDA diagrams are compared with the health care procedures in the source database. According to health care professionals, this percentage corresponds to some atypical cases. Observe that 94% of this error concerns to type I error (i.e., rejecting decisions which appear in the database of the health care centre) and 6% to type II error (i.e., proposing additional decisions which do not appear in the database of the health care centre). So, the learning methodology shows a conservative behaviour with respect to the treatments observed in the database. Furthermore, the methodology has been used to study the differences between the health care procedures registered in the health care database of the SAGESSA Group and four official and predefined standards [ICS06, SIG01, NHF08, SEH05]. These differences represent an average total error of 13% which is below 10% for NHF and SEH. For hypertension, this means that health care professionals in the SAGESSA Group are following more than 90% of the recommendations of official organizations.

5.5 Conclusions

The development of a machine learning methodology to solve problems of the planning activities in diagnosis and medical-clinical treatment, is one of the objectives of this thesis. Therefore, the aspects followed to achieve this objective are exposed as chapter 5 conclusions:

- Based on SDA model introduced in the chapter 4, in this chapter we have proposed a new methodology to machine learn SDA diagrams from the databases of health care centres. These structures represent know-how knowledge on the health care activities of such centres.
- A data model which is based on the concept of EOC is introduced as a means to provide a common design for the health care databases to induce SDAs.
- The proposed machine learning methodology involves five tasks: detect states, detect actions, determine evolutions, determine actions, and integrate all the components in a final SDA.
- A formalism to represent translation rules is also provided. This sort of rules is used to adapt

and to translate the data in health care databases to the terminology that we want the final SDA diagrams to have.

- The machine learning methodology proposed can be used for two purposes. On the one hand, to generate SDA diagrams that serve as graphical representations of the health care procedures carried out in health care centres. In this sense, we have tested it over the database of the SAGESSA Group obtaining a SDA diagram which represents an average 94,6% of the treatments in the database, only excluding some atypical cases. On the other hand, since SDA diagrams are easily comparable to MAs, it is possible to use them to study the adherence of these health care procedures to the official standards. Therefore, we have compared the health care procedures of the SAGESSA Group with the standards defined by ICSI [ICS06], SIGN [SIG01], NHF [NHF08], and SEH [SEH05]. The highest level of adherence has been obtained for NHF and SEH with about 91,4% of treatment coincidence.
- All the results obtained in this chapter have been analyzed and evaluated by medical experts of the SAGESSA Group who have also stated that the SDA diagrams obtained are easy to understand and medically correct. Therefore, the proposed methodology provides a valid tool to automatically induce know-how knowledge SDA diagrams from health care EOC databases.

Chapter 6

Automatic Generation of Know-What Knowledge for Prognosis in Medical Assistance

In this chapter we propose a novel machine learning method to solve problems of the decision activity in medical-clinical prognosis. This method uses an algorithm to induce partial orders on the patient conditions of a disease. The induction process takes the data of the patients that are registered in the hospital databases and that are described in terms of the variables that condition the health state of the patient in the target disease, and produces a partial order that, together with a state-transition diagram that represent the changes of condition of the patients in the health care centre, is able to predict the evolution of new patients.

To describe the induction algorithm of partial orders, this chapter is organized in five sections. Section 6.1 an introduction of the prognosis concept and their antecedents is realized. Section 6.2 formalizes the problem and proposes the structures that the algorithm in section 6.3 uses to induce partial orders on the feasible patient conditions of a disease. Section 6.4 describes the tests and the results of these algorithms on three sorts of cancer. The discussion of the work are exposed in section 6.5 and, finally, the conclusions in section 6.6.

6.1 Introduction

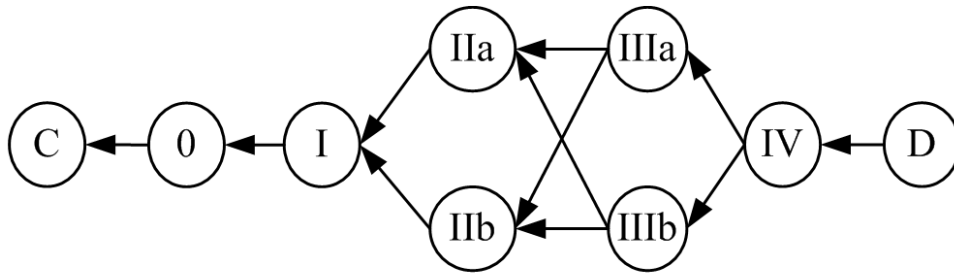
As it was described in the state of the art of this document, medical-clinical prognosis is the process by which the probable course and outcome of a disease is predicted (§2.1.3). Statistics and Artificial Intelligence have traditionally faced this process with several methodologies as survival analysis [Mac01, KM03, Roz06], regression analysis [MR88, KWD⁺91, TMGZ97, PM02, GBF⁺06, LHHGR08], Bayesian networks [GADM02, RBW04, vGJT⁺07, PVTSS⁺07, SDM⁺09, SDBB09],

artificial neural networks [PM02, LWHS03, JAGRRJ+03, MSM+05, GBF+06, BBAM06, KTK08, LHHGR08] (see §2.4 and §3.2.1). All these methodologies have been applied to predict medical facts as survival, relapse, improvement, worsening, or death. These predictions depend on whether there is a temporal restriction related to the prediction or not. Temporal restrictions may be represented as a single point (e.g. probability of suffering a relapse “after one year”) or as multiple independent points in time [Mac01] (e.g., probability of getting an improvement “within the next three months”). Also, prognostic models are classified into those that predict on populations (e.g. patients that are in a similar condition) and those others that predict on individuals [AHL01]. An additional feature of the above methodologies is whether they are able to predict only one fact (e.g. survival) or whether they are able to predict several facts simultaneously.

A feasible approach to obtain predictions on several facts simultaneously is based on the concept of *patient condition* (concept introduced in §5.2.1), which represents the state of the patient concerning a disease. Thus, finding out the probability of a patient to cure, to improve, to worsen, or to die is equivalent to calculate how likely it is that this patient evolves from his current condition to a condition representing cure, a better than the current condition, an equivalent to the current condition, a worse condition, or the death condition, respectively.

All the possible patient conditions (i.e., states) of a disease define an *order relation* that represents the pair-wise comparison of the *severity* of the possible conditions in the disease. So, for instance in breast cancer, stage IV (patients with metastasis) represents a patient condition that is worse than stage I (where the tumour is less than 2 cm across and it is not spread). Unfortunately, the severities of two patient conditions are not always comparable or, if they are comparable, it is not always possible to establish one as clearly better than the other one. Therefore, the relationships among the patient conditions of a disease in health-care are frequently represented with *partial orders* (PO) [DM41] (§3.2.1) which for complex diseases as cancer they are created after an agreement between experts. However, the so created POs are not necessarily designed to represent conditions and relationships from a point of view of the severity of the disease but, for instance, to represent the relationships among these conditions from a practical point of view like the sort of recommended treatment is. This can foster differences between what the theoretical model represents (i.e., the expert-based PO or *standard PO*) and what is really observed at the health-care centres (i.e., the experience-based PO). For example, for the data of the SEER repository [SEE10] describing real breast cancer cases, it is observed that 15% of these cases are in a condition whose severity does not correspond to the severity of the stage indicated by the TNM Staging System [SW02] in figure 6.1.

The reason for that is that the degree of severity of a particular patient condition is not necessarily



TNM BREAST CANCER STAGES

Stage C: no breast cancer observed (Cure). **Stage 0:** Carcinoma in situ. **Stage 1:** The tumour size <2 cm; armpit lymph nodes not affected; cancer not spread. **Stage IIa:** no cells in lymph nodes; cancer in outer covering of the bowel. **Stage IIb:** cancer in outer covering of bowel wall & in nest tissues/organs, lymph nodes not affected; cancer not spread. **Stage IIIa:** cancer in inner layer of bowel wall or in the muscle layer; 1-to-3 nearby lymph nodes contain cancer cells. **Stage IIIb:** cancer through the bowel wall or in surrounding body tissues/organs; 1-to-3 nearby lymph nodes with cancer cells. **Stage IV:** any size; armpit lymph nodes can be affected; metastasis to other parts of the body. **Stage D:** The patient died (Death).

Figure 6.1: TNM staging system for breast cancer.

based on whether this patient fulfills a set of facts or not, but on the combination of the degrees of severity of each one of the variables that define the state of a patient in a particular disease. For instance, it does not seem very wise to admit patients with breast cancers of 2.0 cm in stage II (i.e., severity 2), and at the same time do not consider the possibility of a patient with a 2.1 cm tumour to be in stages with severities below or equal to 2 just because the definition of stage II in breast cancer sets the size upper limit in 2 cm. Following with the example, it could be the case that the first patient with a 2 cm tumour has other complications affecting the seriousness of his disease, making his condition more severe than the one of the second patient, and causing the prognostic of the first patient not to be very accurate.

In order to support the correct joint analysis of the condition of a patient with respect to both the standard PO and the experience-based PO, it is required to develop algorithms to derive POs from the patient records stored in hospital databases. The purpose of this is twofold: on the one hand, these algorithms can be used to generate new health-care knowledge on the feasible stages of a particular disease, and on the other hand, they can be combined with probability theory to increase the accuracy of prognosis on the evolution of a patient.

6.2 Condition-Based Prognosis

In the process of making a prognosis about the evolution of the health of a patient within a probabilistic framework, there are three main questions to be answered: what are the possible conditions of a patient in the selected disease?, what sort of order there is to compare the seriousness of these conditions?, and how the past evolutions registered in the hospital databases can be used to define a probabilistic model to support the prognostic process?

6.2.1 Finding Disease Conditions

For each particular disease D , there is a set of descriptive variables $V = \{v_1, \dots, v_k\}$ with respective domains $Dom(v_i); i = 1, \dots, k$. Each variable v_i represents a property of the disease that is relevant to understand the condition of the patients suffering from that disease. Each v_i defines a *severity function* $s_i : Dom(v_i) \rightarrow [0, 1]$ that provides the degree of seriousness of each one of the values that the variable can take. That is to say, $s_i(v)$ is a value between zero and one representing the severity of the condition of any patient for which v_i takes the value v , zero being the lowest severity (i.e., null), and one being the highest one. *Slightness* is defined as the opposite of severity (i.e., $\mu_i(v) = 1 - s_i(v)$). For the sake of being positive, the rest of the chapter will be based on the concept of slightness rather than on severity. So, Table 6.1 contains the slightness functions for the variables of tumour size (T), nodes (N) and metastasis (M) in the breast, lung and uterus cancer. These functions are derived from the information contained in the SEER repository [SEE10] and may vary from other sources of information.

Given a set of variables V , the condition of a patient p (or patient condition c_p) can be formally described as an element of the set $Dom(v_1) \times Dom(v_2) \times \dots \times Dom(v_k)$ (i.e., $c_p = (a_1, \dots, a_k)$, a_i being the value p has for variable v_i), and the global slightness of c_p in the disease D as a combination of all the slightness functions of the descriptive variables. Many sorts of combinations exist [FGE05], though here only the arithmetic mean is used. So, $\mu(c_p) = 1/k \cdot \sum_i \mu_i(a_i)$ is the function to calculate the global slightness of any patient condition with values a_1, \dots, a_k in the variables of V . This combination is possible since a correlation analysis of the data in the SEER repository shows that T, N and M are mutually independent variables. Although they are not considered here, alternative combination functions should be taken if the variables to combine are not independent.

A patient condition of a disease D (or disease condition C) is defined as a restriction on the domains of the variables of that disease. So, any disease condition can be formalized as $C =$

	Tumor size (T)	Nodes (N)	Metastasis (M)
Breast Cancer			
Lung Cancer			
Uterus Cancer			

Table 6.1: Slightness functions for the variables T, N and M in the domains of breast cancer, lung cancer, and uterus cancer.

(D_1, \dots, D_k) with $D_i \subseteq \text{Dom}(v_i)$, $i = 1, \dots, k$, and represents a common state of a set of patients suffering from D . The set of all the disease conditions C_1, \dots, C_n of a disease D contains the alternative states in which a patient of that disease can be.

For some diseases the set of disease conditions C_i are fixed and well defined, like in cancers where the Tumour Node Metastasis Staging System (TNM) [SW02] was created by the American Joint Committee on Cancer (AJCC) to describe the alternative conditions of diverse cancers; for example, the stages 0, I, IIa, IIb, IIIa, IIIb, and IV in breast cancer that figure 6.1 extends with the extreme conditions cure (left side C node) and death (right side D node).

In other diseases where there is not an agreed criterion on the set of conditions, these can be obtained from the application of a non-supervised clustering algorithm on a representative sample of patient conditions described in terms of the set of variables V . Two alternative sorts of clustering algorithms can be applied: data clustering and conceptual clustering (§3.3.2). *Data clustering* algorithms like kMEANS [Mac67] obtain clusters of similar patient conditions that are dissimilar to the patient conditions in other clusters. On the contrary, *conceptual clustering* algorithms like COBWEB [Fis87] obtain clusters as expressions describing the patient conditions contained in the cluster, in terms of the variables in V .

The application of a clustering algorithm can be made directly on the values of the variables in V (i.e. patient respective values a_1, \dots, a_k) or, alternatively, on the values of the slightness functions of the variables in V (i.e. values $\mu_1(a_1), \dots, \mu_k(a_k)$). Whereas the first option puts patient conditions with similar descriptions in the same cluster, the second group of algorithms gathers patient conditions with similar slightness values in the same cluster.

6.2.2 Sorting the Disease Seriousness

The global slightness function μ defines a complete order relation among the patient conditions that can be described in terms the variables in V . So, for any particular disease, if c_i and c_j represent two patient conditions and $\mu(c_i) > \mu(c_j)$, we interpret that c_i is better than c_j . Nevertheless, this sort of order relation cannot be extended to the comparison of disease conditions where two conditions C_i and C_j of the same disease can not only represent one a worse state than the other, but also incomparable states from the point of view of their respective slightness. This implies that, for any disease D , the order relation of the feasible disease conditions is not necessarily complete.

Based in the definition of PO [DM41] introduced in section 3.2.1 and given a set of elements A , a *PO* $P \subseteq A \times A$ on these elements is a binary relation such that P is reflexive (i.e., $e_i \in A \Rightarrow$

$(e_i, e_i) \in P$), anti-symmetric (i.e., $(e_i, e_j) \in P$ and $(e_j, e_i) \in P \Rightarrow e_i = e_j$), and transitive (i.e., $(e_i, e_j) \in P$ and $(e_j, e_k) \in P \Rightarrow (e_i, e_k) \in P$). PO are typically represented as *directed acyclic graphs* where all the edges that are deducible by transitivity (i.e., weak relations) are omitted.

A set of disease conditions $\{C_1, \dots, C_n\}$ on a disease D defines a PO. This PO can be used to know whether one condition is better or worse than other condition, or if they cannot be compared. For example, figure 6.1 depicts a directed acyclic graph that represents the standard PO of the breast cancer conditions according to the TNM staging system [SW02]. It shows, for instance, that a patient in stage IIa is healthier than one patient in stage IIIa or IIIb (direct edge connection), or IV (connected by edge transitivity), and not comparable in terms of slightness to patients in stage IIb.

The difference between two POs P_1 and P_2 can be measured in terms of the cardinality of the set $(P_1 \cup P_2) - (P_1 \cap P_2)$.

6.2.3 Representing the Cases in Hospital DBs

In the previous section we showed how the conditions of a disease define a PO of their respective slightness. This conceptual structure, however, is unable to represent the evolutions of patients in time which are based on patient improvements, worsenings and stable periods. *State-Transition Diagrams* are directed graphs that model behaviours in terms of states, transitions and actions. Here, *states* stand for the conditions of a disease, *transitions* are the evolutions of the observed patients as their conditions change in time, and *actions* remain unused. Formally speaking, if C is a set of disease conditions of a disease D , a state-transition diagram is a pair (C, t) such that $t : C \times C \rightarrow \mathbb{N}$ is the transition function that, for each couple of disease conditions C_i and C_j in C , $t(C_i, C_j)$ is the number of patients whose conditions evolve directly from C_i to C_j . The *inflow* and the *outflow* of a disease condition C_i can be calculated with the functions $in(C_i) = \sum_j t(C_j, C_i)$ and $out(C_i) = \sum_j t(C_i, C_j)$, respectively.

If this model is used to represent the evolutions of a set of patients across the feasible conditions of a disease, it must be extended with the *admission* and the *discharge functions* $a : C \rightarrow \mathbb{N}$ and $d : C \rightarrow \mathbb{N}$ such that for any condition C_i , $a(C_i)$ is the number of patients arriving in condition C_i , and $d(C_i)$ the number of patients leaving from (or still remaining in) condition C_i . See that, for any disease condition C_i , $a(C_i) + in(C_i)$ must be equal to $out(C_i) + d(C_i)$. Then, if $n_i = a(C_i) + in(C_i)$ represents the number of times any patient has been in condition C_i , and $n_t = \sum_i \sum_j t(C_i, C_j)$ the number of changes of disease condition of all the patients registered in a hospital database, the

probability of a patient to be in condition C_i is $p(C_i) = n_i/n_t$, the probability of a patient p in condition C_i to evolve to C_j in one transition is $p(C_i, C_j) = t(C_i, C_j)/n_i$, and the probability of finding a patient that evolves from C_i to C_j is $t(C_i, C_j)/nt$.

The above function $p(C_i, C_j)$ can be used to compute the probability of a patient to evolve from one set of disease conditions $\mathcal{A} \subseteq \{C_1, \dots, C_n\}$ to another set of disease conditions $\mathcal{B} \subseteq \{C_1, \dots, C_n\}$ in one step as $Pr(\mathcal{A}, \mathcal{B}) = \sum_{C_i \in \mathcal{A}} \sum_{C_j \in \mathcal{B}} p(C_i, C_j)$. In its turn, this function, together with a PO P on the disease conditions, can be used to make prognoses on the likelihood a patient gets cured, improves, worsens, dies, or survives. See equations 6.1 to 6.5, respectively where $Condition(p)$ represents the current condition of the patient, $cure$ is the condition of a healthy patient, and $death$ is the condition representing a deceased patient.

$$Pr(pcures) = Pr(\{Condition(p)\}, \{cure\}) \quad (6.1)$$

$$Pr(pimproves) = Pr(\{Condition(p)\}, \{C : (condition(p), C) \in P\}) \quad (6.2)$$

$$Pr(pworsens) = Pr(\{Condition(p)\}, \{C : (C, condition(p)) \in P\}) \quad (6.3)$$

$$Pr(pdies) = Pr(\{Condition(p)\}, \{death\}) \quad (6.4)$$

$$Pr(psurvives) = 1 - Pr(pdies) \quad (6.5)$$

6.3 Induction of Partial Orders

Condition-Based Prognosis as it was introduced in section 6.2 is a three step process that starts with the determination of the conditions of a disease (here, we will consider the set of conditions already available). Once the disease conditions are fixed, a second step takes the data of the evolutions of patients in a health-care centre to induce both a PO on these conditions, and also a state-transition diagram that contains the probabilities $p(C_i, C_j)$ of evolving from any disease condition C_i to any other disease condition C_j in the context of the selected health-care centre. After that, a third step can be applied that consists on the utilisation of both structures to predict the evolution of new patients: the PO provides the semantic meaning of what "cure", "improve", "worsen", "die", or "survive" means in the context of the patient current medical condition, and the state-transition diagram supplies the probabilities needed to compute the final prognostic value. This section describes the procedures to carry out the second and the third steps.

6.3.1 The Data Model

The data model used in the induction of POs is the EOC data model (§5.2.1). Here, an *episode of care* (EOC) contains all the medical information about the treatment of one patient between the date of admission and the date of discharge. Formally, if $V = v_1, \dots, v_k$ is a set of descriptive variables of the patient conditions in a disease D and $A = \{a_1, \dots, a_p\}$ is a set of medical actions, then an encounter e is a pair (c, a) such that c is a patient condition (i.e. $c \in \text{Dom}(v_1) \times \text{Dom}(v_2) \times \dots \times \text{Dom}(v_k)$) and a is a subset of actions in A ; an *EOC* is a sequence e_1, \dots, e_q of encounters, and the database is a list of *EOCs*.

6.3.2 The Statistical Model

According to the data structure described above, for any pair of disease conditions (C_i, C_j) , we can apply a statistical procedure to determine, in a first stage, whether there is an order relation between C_i and C_j and, if there is one, in a second stage, decide which of the two conditions represents a better state of the disease from a health point of view (i.e. the order of the relation between C_i and C_j). Once all the pairs of disease conditions are considered, a statistically significant PO on these conditions is obtained. Here, the above mentioned two stages are implemented as statistical hypothesis Student's t-tests.

In the study of a disease D , with $\{C_1, \dots, C_n\}$ the set of all possible conditions of D , and provided a database containing a representative sample of encounters of all the patients that have been treated of that D , the description of the state of the patient in each encounter e_k in terms of the variables in V defines a patient condition c_k with a slightness value $\mu(c_k)$ (or $\hat{\mu}(c_k)$ in statistics notation). Simultaneously, this patient condition c_k classifies the encounter in one of the disease conditions C_1, \dots, C_n .

Let us call E_k the set of the encounters in the database that are classified in C_k , and $S_k = \{(c_j) : e_j \in E_k\}$ the set of μ -values of their patient conditions. Then, for any pair of disease conditions C_i and C_j , the respective sets S_i and S_j are the two independent samples of a Student's t-test with null hypothesis the means of the slightness values of the elements in C_i and the elements in C_j are equal, provided that the underlying distributions are normal.

Only if the null hypothesis is rejected, C_i and C_j have an order relation whose sense is evaluated with a new Student's t-test with null hypothesis the means of the slightness values of the elements are larger in C_i than in C_j . Both t-tests are based on the t-value (equation 6.6) where μ 's, σ 's and n 's represent the mean, standard deviation, and number of elements of the samples, respectively.

$$\beta = \frac{\bar{\mu}_i - \bar{\mu}_j}{\sqrt{\frac{\sigma_i^2}{n_i-1} + \frac{\sigma_j^2}{n_j-1}}} \quad (6.6)$$

6.3.3 The Induction Algorithm

The algorithm 1 allows the induction of POs under the previously described statistical model. This algorithm realizes the induction process according to the data and the statistical models of sections 6.3.1 and 6.3.2, respectively. The final result of the algorithm is a PO that explains the slightness degree of a disease in terms of the improvement or worsening between the conditions of a disease.

Algorithm 1 Algorithm to make PO

Require: C , data, α

Ensure: PO

{Let $C = \{C_1, \dots, C_n\}$ be a set of conditions on a disease D }

{Let $data = \{EOC_1, \dots, EOC_k\}$ be a list of episodes of care of D }

{ $EOC_i = \{e_{i1}, \dots, e_{iki}\}$ the list of encounters in EOC_i , $i = 1..k$ }

{Let α the statistical significance of the test -e.g. 0.01}

β : float

$PO = \emptyset$; {empty PO on the set of disease conditions C }

for any pair of conditions $(C_i, C_j) \in C \times C$ **do**

$E_i = \{e_{xy} \in \cup_z EOC_z : C_i \text{ is the condition of the patient in encounter } e_{xy}\}$

$E_j = \{e_{xy} \in \cup_z EOC_z : C_j \text{ is the condition of the patient in encounter } e_{xy}\}$

$S_i = \{\mu(c_x) : c_x \text{ is the condition of the patient in } e_x, \text{ for all } e_x \in E_i\}$

$S_j = \{\mu(c_x) : c_x \text{ is the condition of the patient in } e_x, \text{ for all } e_x \in E_j\}$

 Calculate the t-value β according to equation 6.6

if $|\beta| < t_{\alpha/2}$ (first hypothesis test indicates C_i and C_j are related) **then**

if $\beta > t_\alpha$ (second hypothesis test indicates C_i is better than C_j) **then**

 Insert (C_i, C_j) in PO ;

else

 Insert (C_j, C_i) in PO ;

end if

end if

end for

Write the order relation PO ;

6.4 Testing Prognosis on Several Sorts of Cancer

In order to induce POs, we used the databases on the diseases breast cancer (55939 encounters), lung cancer (19491 encounters) and uterus cancer (705 encounters) obtained from the SEER repository [SEE10]. These databases contain information on patient conditions based on three variables:

Tumour Size, Lymph Nodes, and Metastasis classified according to the TNM System [SW02]. Data with unknown or missing values are removed from the databases. The distribution of these data according to each disease condition is described in Table 6.2.

Cancer Disease	Disease Conditions								Total	
	0	1a	1b	2a	2b	3a	3b	4a		4b
Breast	7073	25566		13387	6550	1456	940	967		55939
Lung	11	7298		1338		2629	3022	5193		19491
Uterus	51	242	203	79		45		5	80	705

Table 6.2: Distribution of episodes according to each disease condition.

Two sorts of tests have been performed on these databases: one that is used to compare the difference between the standard POs which are proposed by the TNM Staging System [SW02], and the experience-based POs obtained by the inductive algorithm introduced in section 6.3.3 when it is applied on the proposed databases. The second test is about how these differences affect the process of prediction on the facts of cure, improvement, worsening, death, and survival in breast, lung, and uterus cancers.

6.4.1 Results on the Induction Process

Table 6.3 shows both the standard POs [SW02] and the POs that the proposed algorithm induces from the three databases. The distances between the standard and the induced POs are 2, 1, and 2, respectively. These differences are caused either by the detection of new relations that were not present in the standard PO or by the elimination of relations that do not achieve the statistical significance level required to be part of the experience-based PO. So in breast cancer, the relations IIa-IIb and IIIa-IIIb are statistically justified though they were not in the standard PO. A similar case is observed in lung cancer with the relation IIIa-IIIb, and in uterus cancer with relation Ia-Ib. In this last domain, the SEER repository does not provide enough evidence to keep the standard order relation between stages II and III in the experience-based PO.

These single differences between standard and experience-based POs are cause of new differences when the transitivity property is applied, and the final differences increase to 3%, 2%, and 10% of the total number of binary relations, this meaning that 3, 2, and 10 out of 100 comparisons get different responses whether the standard or the experience-based POs are queried.

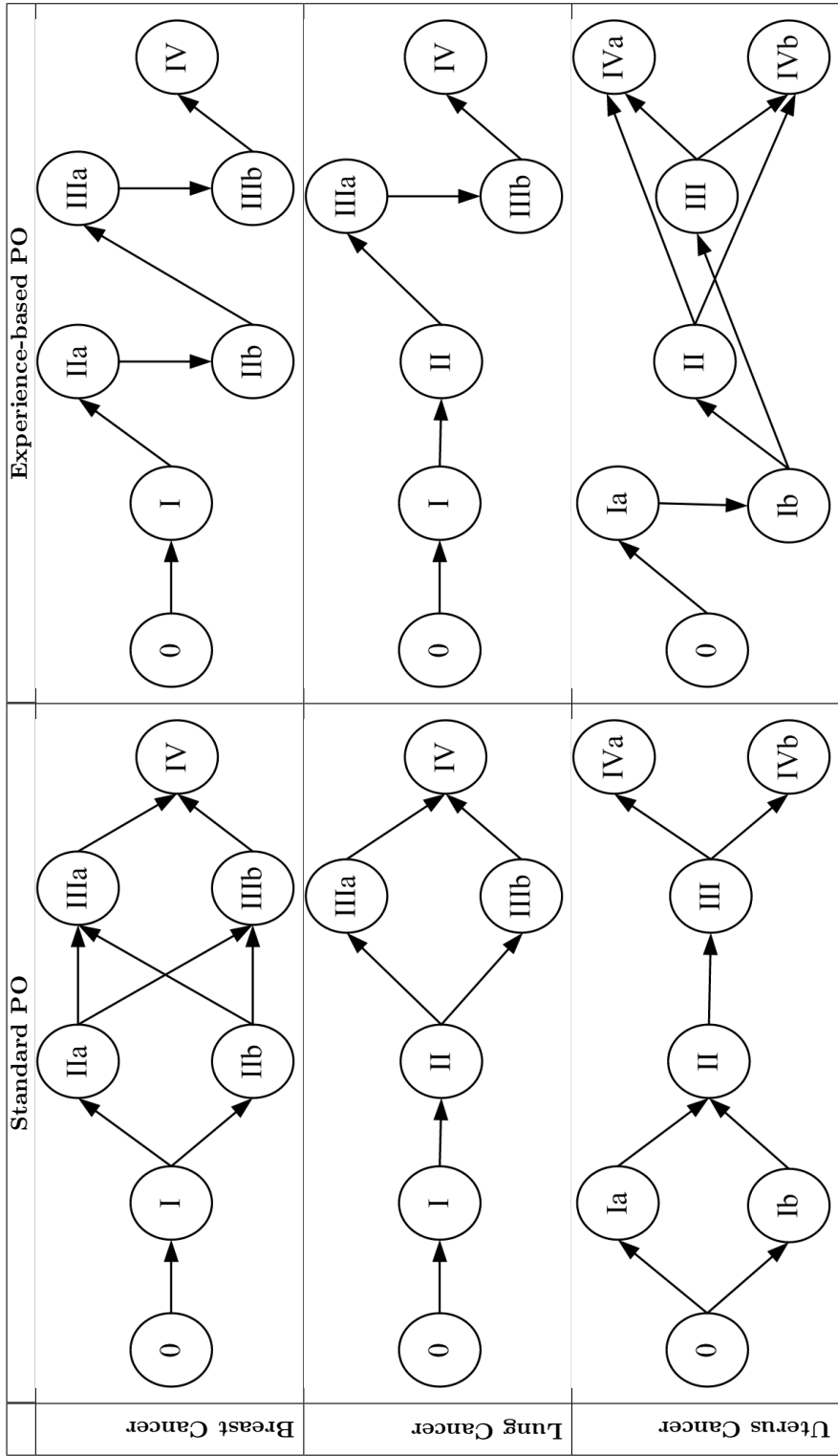


Table 6.3: POs induced.

6.4.2 Results on the Condition-Based Prognosis

Equations 1 to 5 in section 6.2.3 are used to calculate the probabilities of improvement, worsening, cure, death and survival in breast, lung and uterus cancers for both, the standard PO, and the experience-based PO the algorithm in section 6.3.3 obtains for the data of the SEER repository [SEE10], representing real patients.

In order to analyse the differences between the prediction values obtained with the utilization of either the standard or the experience-based POs, the probabilities $p(C_i, C_j)$ that are obtained from the real evolution of a set of patients, are used to define a matrix of patient evolutions. Tables 6.4, 6.5, and 6.6 show the probability matrices employed to analyze these differences in the cases of breast, lung, and uterus cancers, respectively.

	Disease Conditions							STND		EXP	
	0	1	2a	2b	3a	3b	4	I	W	I	W
	0	1	0	0	0	0	0	0	0	0	0
1	0,6	0,2	0,1	0,1	0	0	0	0,75	0,25	0,75	0,25
2a	0,3	0,2	0,1	0,2	0,1	0,1	0	0,64	0,36	0,55	0,44
2b	0,1	0,1	0,2	0,1	0,1	0,2	0,2	0,36	0,64	0,44	0,55
3a	0	0	0,1	0,1	0,3	0,2	0,3	0,39	0,61	0,29	0,71
3b	0	0	0	0,2	0,3	0,1	0,4	0,25	0,65	0,55	0,44
4	0	0	0	0	0	0	1	0	0	0	0

Table 6.4: Probabilities of evolution among disease conditions in breast cancer

	Disease Conditions						STND		EXP	
	0	1	2	3a	3b	4	I	W	I	W
	0	1	0	0	0	0	0	0	0	0
1	0,8	0,1	0,1	0	0	0	0,88	0,11	0,88	0,11
2	0,1	0,3	0,1	0,2	0,2	0,1	0,44	0,55	0,44	0,55
3a	0	0,1	0,2	0,1	0,2	0,4	0,39	0,61	0,33	0,66
3b	0	0	0,1	0,3	0,1	0,5	0,24	0,76	0,44	0,55
4	0	0	0	0	0	1	0	0	0	0

Table 6.5: Probabilities of evolution among disease conditions in lung cancer

	Disease Conditions							STND		EXP	
	0	1a	1b	2	3	4a	4b	I	W	I	W
	0	1	0	0	0	0	0	0	0	0	0
1a	0,4	0,3	0,1	0,1	0,1	0	0	0,68	0,32	0,57	0,43
1b	0,4	0,4	0,1	0	0,1	0	0	0,75	0,25	0,88	0,11
2	0,1	0,1	0,1	0,1	0,2	0,2	0	0,33	0,67	0,58	0,42
3	0	0	0,1	0,1	0,1	0,2	0,5	0,22	0,78	0,32	0,68
4a	0	0	0	0,1	0,1	0,2	0,6	0,25	0	0,25	0
4b	0	0	0	0	0	0	1	0	0	0	0

Table 6.6: Probabilities of evolution among disease conditions in uterus cancer

6.5 Discussion

The probabilities of cure, death, and survival are identical for the standard and the experience-based POs, as expected, since the conditions of cure and death are the same in both POs. However, the predictions on improvement (I) and worsening (W) differ if we use one or the other POs, as the numbers in bold indicates. Some of these differences cause the prognostic with the standard PO to provide excessive “hope” (e.g., in uterus cancer, patients in stage Ia are given 68% of improvement, whereas the experience says that only 57% will improve), or excessive “despair” (e.g., in uterus cancer, patients in stage II get 67% of worsening, when reality shows that it is only 42%).

6.6 Conclusion

The development of a machine learning methodology to solve problems of the decision activity in medical-clinical prognosis, is one of the objectives of this thesis. Therefore, the aspects followed to achieve this objective are exposed as chapter 6 conclusions:

- In this chapter, we have introduced a new machine learning method to support decision activities in medical-clinical prognosis.
- This method is based on partial orders and state transition diagrams to predict the evolution of new patients.
- This method is able to predict several facts simultaneously (improvement, worsening, cure, death and survival) unlike current methods based on statistics and artificial intelligence (§2.4 and §3.2.1) which, generally, they predict only a particular fact.
- The partial orders induced are built from real experiences happened in health-care centres this showing the gap between the criteria to assess the patient condition proposed by medical experts (standard partial order), and the criteria coming out of the medical daily situations (experience-based partial order).
- Based on the tests realized in the section 6.4, we can conclude there are clear structural differences between the standard POs proposed by the health care professionals and those others that are induced from the data of the SEER repository [SEE10] about real patients. A direct implication of these differences is that the prognosis about the evolution of patients may change drastically. This effect has been confirmed with the results of the tests performed which

may drive the health care professional to incorrect predictions of patient future improvements and worsenings.

The work introduced in this chapter has been presented and published in the 11th Conference on Artificial Intelligence in Medicine (AIME2007) [BR07].

Chapter 7

Integral Modelling of Know-What and Know-How Knowledge for the Medical Assistance Activities of Diagnosis, Treatment and Prognosis

In this chapter we propose a integral, computable and knowledge based model that automate the medical-clinical procedure for the decision and planning activities in the diagnosis, treatment and medical-clinical prognosis.

To describe the novel medical-clinical procedure model, this chapter is organized in six sections. In section 7.1 an introduction to the concept of medical-clinical procedure is realized. In section 7.2 a novel medical-clinical procedure model (MPM) is described, the sorts of AI problems in MPM are determined and the MPM Knowledge Structures are defined. In section 7.3 the automatic induction of MPM Knowledge is introduced. In section 7.5 the medical application of MPM is shown. This application is tested on four real Clinical Cases. A discussion of the work is exposed in section 7.6 and, finally, the conclusions appear in section 7.7.

7.1 Introduction

In medicine, the concept of *medical-clinical procedure* (§2.1.4) is used to refer to a course of action aiming to achieve a result in the care of one or more patients. Some of the most important medical procedures are diagnosis (i.e., identification of a patient's illnesses), treatment (i.e., health care given to a patient), and prognosis (i.e., prediction of the probable evolution of a patient or disease). All the evidence found about the medical procedures of one disease or syndrome is gathered together in clinical practice guidelines (§2.3.1) and put into practice by means of specific protocols which are

disease-driven plans implementing concrete medical procedures.

In the last decades, modern medicine has been influenced by several social and technological changes that have affected the way that medical procedures are considered and modeled. Based on the increment of life expectancy, one of the most important social changes is in the sort of average patient arriving at the health care centres who can be described as a chronic comorbid elderly patient. This sort of patient has forced a change of perspective of medical procedures that have shifted from a disease-driven approach to a patient-driven approach, in order to be able to deal with all the variability of the patient with a single holistic procedure. Currently, this change of perspective is widely accepted by the health care community [Har09] and poorly addressed with methodologies for merging and personalizing some specific procedures like medical treatments. In this chapter, based on the Harrison's principles [Har09], we propose a broader approach which integrates the medical procedures of diagnosis, treatment, and prognosis in a Medical Procedure Model (MPM) that provides a holistic management of chronic comorbid patients. The MPM contains internal loops that allow not only a continuous adaptation to the patient evolutions but also the possibility of reconsidering wrong or incomplete diagnoses, treatments, or prognoses.

The practice of medicine is sustained in a medical knowledge that combines scientific evidence and past individual experiences. Scientific evidence is primarily accumulated in clinical practice guidelines (§2.3.1), while past experiences can be found registered in the data of the information systems of the health care centres (§5.2.1). Converting this knowledge into computer-interpretable knowledge structures has been argued to be a difficult task [WPT⁺02, WTSR10]; for this reason, developing mechanisms to automate this process is seen as one of the grand challenges in clinical decision support for the future [SWO⁺08]. Here, the MPM represents the effort for identifying the medical decision problems appearing in the combination of diagnosis, treatment, and prognosis procedures for the medical management of patients. For each subproblem a computer-interpretable knowledge structure to solve it is proposed. If knowledge structures exist for all the MPM subproblems, then their integration defines a knowledge-base architecture of a decision support system towards a holistic management of patients. If some of these knowledge structures do not exist, then we also propose both the minimal data structure required to induce such knowledge structures, and also the induction algorithm to transform those data structures into knowledge structures (some of these algorithms are outcomes of this thesis).

The result is a computer model which is equivalent to the MPM, but exclusively based on computer programs.

7.2 The Medical-Clinical Procedure Model

Medical decisions making (§2.2) are made during the diagnostic and medical-clinical treatment phases. These decisions are based on factual tests (i.e., based on evidence) so patients can obtain maximum benefit from the scientific knowledge available to health care professionals [Mar07]. Proposing the diagnostic possibilities, the execution of a plan or venturing a possible prognosis, not only forces to consider a wide background knowledge, but also to evaluate the relative possibilities within the progress of some diseases and to know the importance of some signs and symptoms that appear with less frequency. In this sense, health care professionals apply a *standard medical procedure* (§2.1.4), that allows to collect data, to propose hypothesis and to obtain objective conclusions about whether a particular diagnostic must be accepted or rejected, to design and execute a treatment plan or to determine the disease progress through a prognosis.

However, this medical standard procedure (see 2.1) does not have the functional detail level to be formalized in a computable way. So, we propose a novel model that solves this problem allowing to integrate the decision and planning activities of medical assistance for diagnosis, treatment and prognosis. This model, which we have called medical-clinical procedure model (MPM), is shown in figure 7.1.

MPM begins with the *elicitation* process (1.1) where the patient information which is relevant for the current medical process is gathered. This information can be obtained by direct observation or by consultation of the patient medical record. The information constitutes the set of signs and symptoms that describe the current health condition of the patient. With this information, a decision (1.2) is made on whether the patient requires a diagnosis, a treatment of their signs and symptoms (symptomatic treatment), or both. Symptomatic treatment can be performed in parallel to the process of finding out the patient diagnosis.

The relevant signs and symptoms are employed to *generate the feasible hypotheses* (1.3) which are the possible causes of the patient health conditions. Signs and symptoms can identify a single disease (i.e., hypothesis), a comorbidity or alternative hypotheses. The diagnostic process aim is the reduction of feasible hypotheses in order to achieve a concrete diagnosis for the patient. The first step consists in deciding among a set of *diagnostic tests* (1.4), where the results may help the health care professional to discard or to confirm some of the available hypotheses. Sometimes these results are organized in a *diagnostic test plan* (1.5) that describes the medical logic about how these tests must be deployed. Once the diagnostic test plan is chosen, it is *executed* (1.6) in order to obtain additional information. The results of the test are used to *modify/adjust the hypotheses*

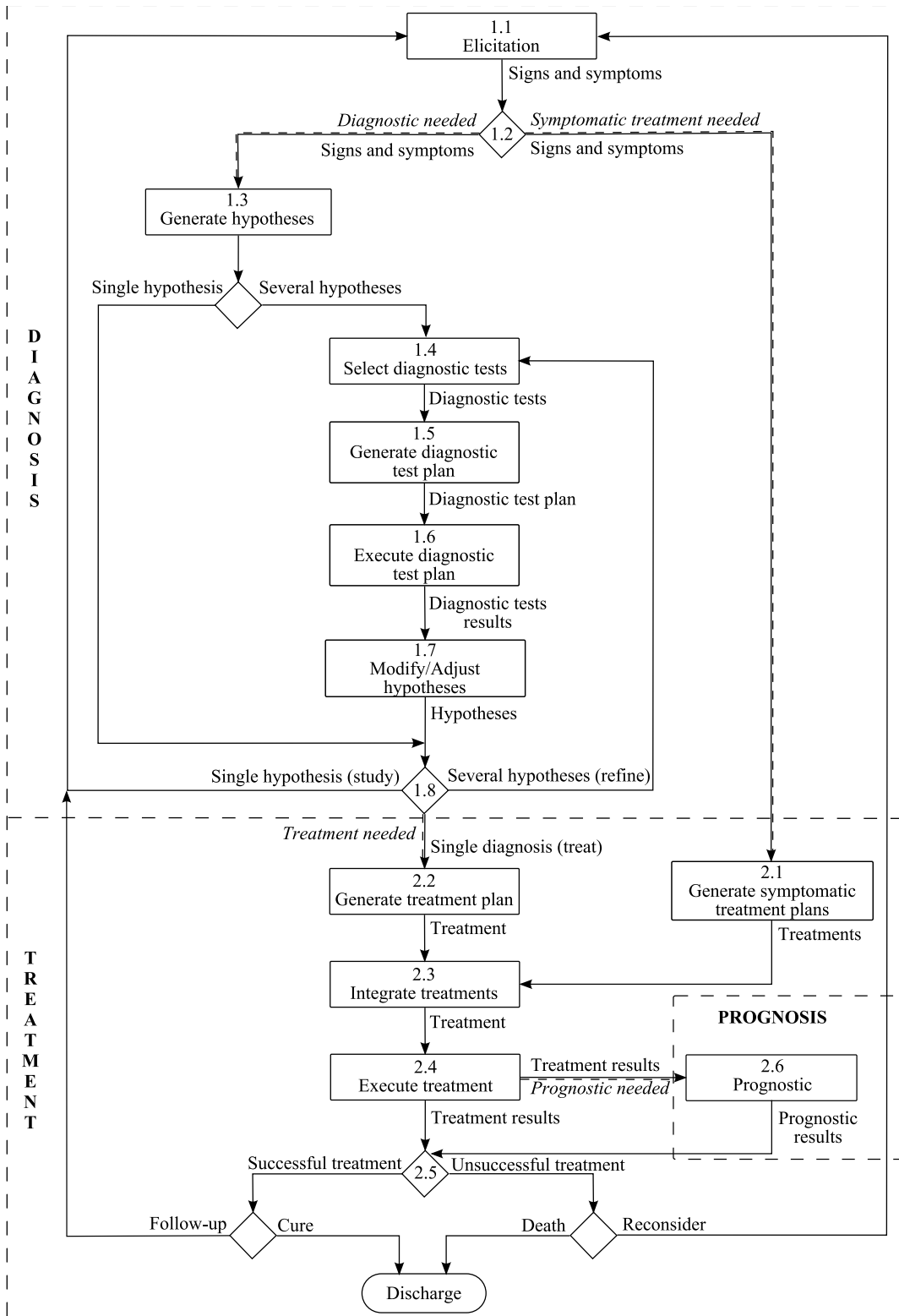


Figure 7.1: Medical Procedure Model.

(1.7) extracted from the elicitation process.

If *several hypotheses* are still possible, the diagnostic process must iterate from step 1.4 in order to keep refining until there is a unique hypothesis (1.8). Even if only a *single hypothesis* remains, the confidence of the patient can be low, and the health care professional may decide to continue studying the case from step 1.1. When there is a single confident hypothesis, the health care professional accept it as the patient diagnosis and the treatment process starts.

Some of the signs and symptoms detected during elicitation may need symptomatic treatment. In this case, the *symptomatic treatment plan* (2.1) must be chosen. Similarly, the patient diagnosis must be treated, so a treatment plan (2.2) must be performed. Symptomatic treatment and diagnosis treatment are combined in a single treatment (i.e., *merging*) (2.3) in order to smooth feasible undesired interaction. Once the unified treatment has been determined, it is *executed* (2.4). Simultaneously, a *prognosis* process (2.5) of the patient evolutions according to the treatment begins.

The treatment results, along with the prognostic results (if it is the case), allow the health care professional to determine whether the treatment followed by the patient was successful or not (2.6). If the *treatment is successful* and the patient has been cured, the patient will be discharged of the health care centre. In the case of chronic disease, the patient will have a follow up to keep his health stable. On the contrary case, if the *treatment is unsuccessful* the whole process must be reconsidered from step 1.1.

7.2.1 Sorts of AI Problems in MPM

The tasks in MPM can be expressed according to four AI problems: binary and multiple decision, planning and prediction. Table 7.1 describes these problems according to each medical activity of MPM (i.e., diagnosis, treatment and prognosis). First, the *binary decision problem* is used to represent tasks where any medical decision in MPM depends only of two possibles alternatives. For example, in the task 1.2a is necessary to decide if a patient requires a diagnostic or not, or in the task 1.8b the decision depends of the number of hypothesis obtained after a diagnostic process (single hypothesis or several hypotheses). Secondly, the *multiple decision problem* is used when solving a task in MPM implies a set of possible alternatives and it is necessary to decide which of these alternatives are better in the solution of this task. For example, in the task 1.2b if a patient needs symptomatic treatment, it is necessary to decide which signs and symptoms of this patient require a treatment. A similarly situation occurs in the task 1.3 (generate hypotheses) where the

decision problem is to determine which are the feasible diagnostic hypotheses, or in task 1.4 (Select diagnostic test) to decide which are the diagnostic test to perform, or in task 1.7 (Modify/Adjust hypotheses) to decide, which hypothesis are still feasible after modify/adjust the initial hypotheses with the results of diagnostic tests.

Third, the *planning problem* is used when, solving a medical task in MPM, requires to define and to execute a logical sequence of medical actions. For example, to solve tasks 1.5 (generate diagnostic test plan) and 1.6 (execute diagnostic test plan), it is necessary to define how the diagnostic tests are organized and how these are applied, respectively. Also, the planning problem can be applied in tasks 2.1 (generate symptomatic treatment plan) and 2.2 (generate treatment plan) to define the sequence of medical actions necessary in the treatment of the patient. Once these plans are observed, the planning problem is used in task 2.3 (integrate plans) to obtain a unique treatment plan and its subsequent application in task 2.4 (execute treatment plan). Finally, the *prediction problem* is used in task 2.6 (Prognostic) of MPM to determine the patient evolution.

7.2.2 MPM Knowledge Structures

The AI problems previously discussed can be represented through computer-interpretable knowledge structures. These structures are summarized in table 7.2. The binary and multiple decision problems are represented by decision trees (§3.2.1) and decision tables (§3.2.1), respectively. The planning problems are represented by SDA structures (§4.2), and the prediction problems are represented by partial orders and state transition diagrams (§6.3).

7.3 Automatic Induction of MPM Knowledge

The basic structure used in the automatic induction of MPM knowledge is the EOC database. This database contains patient data from a health care centre whose structure allow to build supervised data matrix and to fulfil EOC data model to solve the AI problems of decision, planning and prediction in MPM, as it is indicated in table 7.2. To decision problem, a *supervised data matrix* M is building through of queries, SELECT-FROM, to the EOC database according to the decisional questions that have to be solved in the MPM, for example, the question “*is a diagnosis needed?*” (task 1.2a). To solve this question it is necessary to know, for all patients P , the signs and symptoms $S\&S$ of each patient p_i and if each patient p_i has been diagnosed of c . Therefore, the query would be:

Medical Activities	Tasks	AI Problems	Solved Medical Question
Diagnosis	1.1 Elicitation	Not applicable	Not applicable
	1.2a	Binary decision	Is a diagnosis needed?
	1.2b	Multiple decision	Is a symptomatic treatment needed?, which S&S require symptomatic treatment?
	1.3 Generate hypotheses	Multiple decision	Which are the feasible hypotheses?
	1.4 Select diagnostic test	Multiple decision	Which are the tests to perform?
	1.5 Generate diagnostic test plan	Planning	How are diagnostic tests organized?
	1.6 Execute diagnostic test plan	Planning	How are diagnostic tests applied?
	1.7 Modify/Adjust hypotheses	Multiple decision	Which are the feasible hypotheses?
	1.8a	No AI	are there several hypotheses available?
	1.8b	Binary decision	If a single hypothesis is available: is necessary to continue studying the single hypothesis? or proceed treating the patient?
Treatment	2.1 Generate symptomatic treatment plans	Planning	How is the symptomatic treatment organized?
	2.2 Generate treatment plan	Planning	How is the treatment of a single diagnostic organized?
	2.3 Integrate treatments	Planning	How are the treatment plans integrated?
	2.4 Execute treatment	Planning	How is the treatment plan applied?
	2.5	No AI	Is successful treatment or not?
	2.6 Prognostic	Prediction	Which is the patient evolution?
Prognosis			

Table 7.1: Tasks, AI problems and solved medical question in MPM.

AI Problems	Knowledge Structure
Binary decision	Decision tree
Multiple decision	Decision table
Planning	SDA structures
Prediction	Partial orders and state transition diagrams

Table 7.2: Knowledge structures in MPM.

SELECT S&S, diagnosed-Y/N FROM patients

Once the data are obtained after the queries execution, these data are used to induce the structures of knowledge representation which solve the decision problem in MPM. This induction process is based on *machine learning* methods described in section 3.3.1.

For the planning problem, the *EOC data model* (§5.2.1) is applied which adapts the data from EOC database and by means of a set of translation rules to the terminology the final users want the resulting SDA to have (§5.2.2). This adaptation process is realized according to the planning questions that have to be solved in the MPM, for example, the medical question “*how is the symptomatic treatment organized?*” (task 2.1), to solve this question it is necessary to know the data of all the patients that received a symptomatic treatment, and to organize these data in state-terms (terms on the health conditions), decision-terms (*S&S*) and action-terms (terms on the medical actions <treatment>). The data obtained after the preprocessing step are used to generate the final SDA diagram by means of a *machine learning* method introduced in section 5.2.4. Likewise, for the prediction problem, the *EOC data model* 6.3.1 is used to adapt the data of patient evolutions from EOC database and to induce both a partial order on patient conditions and a state transition diagram which contains the probabilities of evolving from any disease condition to any other disease condition in the context of the selected health-care centre. The induction procedure of partial orders is based in the inductive algorithm introduced in the section 6.3.3.

All the data structures, based on supervised data matrix and EOC data model, used in the automatic induction of MPM knowledge are described in table 7.3.

Tasks	Knowledge Structure	Data Structure
1.1	Not applicable	Not applicable.
1.2a	Decision Tree	Supervised data matrix ($M1 = \{P \times S\&S \times c\}$). Where P is the set of all available patients for the study, $S\&S$ the set of signs and symptoms available for each patient p_i , and c the boolean value which indicate if a patient p_i have received a diagnostic process.
1.2b	Decision Table	Supervised data matrix ($M2 = \{P \times S\&S \times Tr\}$). Where $P = \{p_1, \dots, p_k\}$ set of all available patients for the study, $S\&S = \{s\&s_1, \dots, s\&s_n\}$ set of signs and symptoms available for each patient p_i , and $Tr = \{tr_1, \dots, tr_m\}$ set of boolean value which indicate if a patient p_i received a symptomatic treatment.
1.3	Decision Table	Supervised data matrix ($M3 = \{P \times S\&S \times H\}$). Where $P = \{p_1, \dots, p_k\}$ set of all patients which followed a diagnosis process, $S\&S = \{s\&s_1, \dots, s\&s_n\}$ set of signs and symptoms available for each patient p_i , and $H = \{h_1, \dots, h_m\}$ set of hypotheses.
1.4	Decision Table	Supervised data matrix ($M4 = \{P \times H \times T\}$). Where $P = \{p_1, \dots, p_k\}$ set of all patients which have some hypothesis, $H = \{h_1, \dots, h_n\}$ set of hypothesis for each patient p_i , and $T = \{t_1, \dots, t_m\}$ set of diagnostic test.
1.5	SDA Structure	EOC data model (patients receiving some diagnostic test). State-terms (e.g., being and end), decision-terms (terms on the test result realized to the patients) and action-terms (terms on the diagnostic test)
1.6	SDA Structure	Data available for the current patient.
1.7	Decision Table	Supervised data matrix ($M5 = \{P \times S\&S \times H\}$). Where $P = \{p_1, \dots, p_k\}$ set of all patients which followed a diagnosis process, $S\&S = \{s\&s_1, \dots, s\&s_n\}$ set of signs and symptoms available for each patient p_i , and $H = \{h_1, \dots, h_m\}$ set of hypotheses obtained in 1.3.
1.8a	Not applicable	Not applicable.
1.8b	Decision Tree	Supervised data matrix ($M6 = \{P \times S\&S \times d\}$). Where $P = \{p_1, \dots, p_k\}$ set of all patients which have been diagnosed correctly, $S\&S = \{s\&s_1, \dots, s\&s_n\}$ set of signs and symptoms available for each patient p_i , and d the diagnostic realized to the patient.
2.1	SDA Structure	EOC data model (patients receiving a symptomatic treatment). State-terms (terms on the health condition), decision-terms (terms on the S&S of patients) and action-terms (terms on the medical actions <treatment> followed by the patients)
2.2	SDA Structure	EOC data model (patients treated of single diagnostic). state-terms (terms on the health condition of patient), decision-terms (terms on the S&S of patients) and action-terms (terms on the medical actions <treatment> followed by the patients)
2.3	SDA Structure	SDA Structures.
2.4	SDA Structure	Data available for the current patient.
2.5	Not applicable	Not applicable.
2.6	Partial Orders and State Transition Diagrams	EOC data model (Data about the evolutions of the patient conditions in a health care centre). State-terms (terms on the disease condition of patient), decision-terms (not applicable) and action-terms (not applicable).

Table 7.3: Data structures used in MPM.

7.4 Integrated usage of the MPM

Figure 7.2 shows the functional model of the MPM. This functional model uses computable procedures P_i (represented by circles) based on the knowledge which is provided after a knowledge engineering process or induced by a machine learning algorithm from data contained in data structures M_i or EOC (represented by squares), to be applied in the MPM tasks T_i , as it is described in table 7.3. In this process, new knowledge (represented by arrows) is generated. The generation of new knowledge can start the activation of other MPM procedures. These procedures can be grouped into blocks that allow to solve a single MPM task, such as 1.2 task where the $P1.2a$ and $P1.2b$ procedures, based on a decision tree and a decision table, solve the AI problem of binary and multiple decision, respectively. A similar situation occurs to task 1.8, where the computable procedures $P1.8a$ and $P1.8b$ must decide what to do if there is a single hypothesis or if there are several hypotheses at the end of the diagnosis process.

7.5 Application of MPM in Four Clinical Cases

Based on the model of figure 7.1, the figures 7.3, 7.4, 7.5 and 7.6 show the behavior of MPM according to four real clinical cases published in the medical literature [FIS]. The medical situations described in these cases are suggested by Dr. Collado, a senior GP of the SAGESSA Group [SAG], that qualified these cases as diverse and representative of primary care.

- *First case* (figure 7.3): 34-year-old male who comes to a health care centre by feelings of dysthermia, general ailment and arthromyalgia with 24 hours of evolution. In the last 48 hours he has been suffering from: dysury, pollakiuria and mictional urgency (**A**).

Initial Physical Examination:

- Temperature: $38^{\circ}C$
- Otorhinolaryngology: mild hyperemia of the oropharynx
- Cardiopulmonary auscultation: normal
- Abdomen: normal
- negative Goldflam's sign bilaterally (**B**).

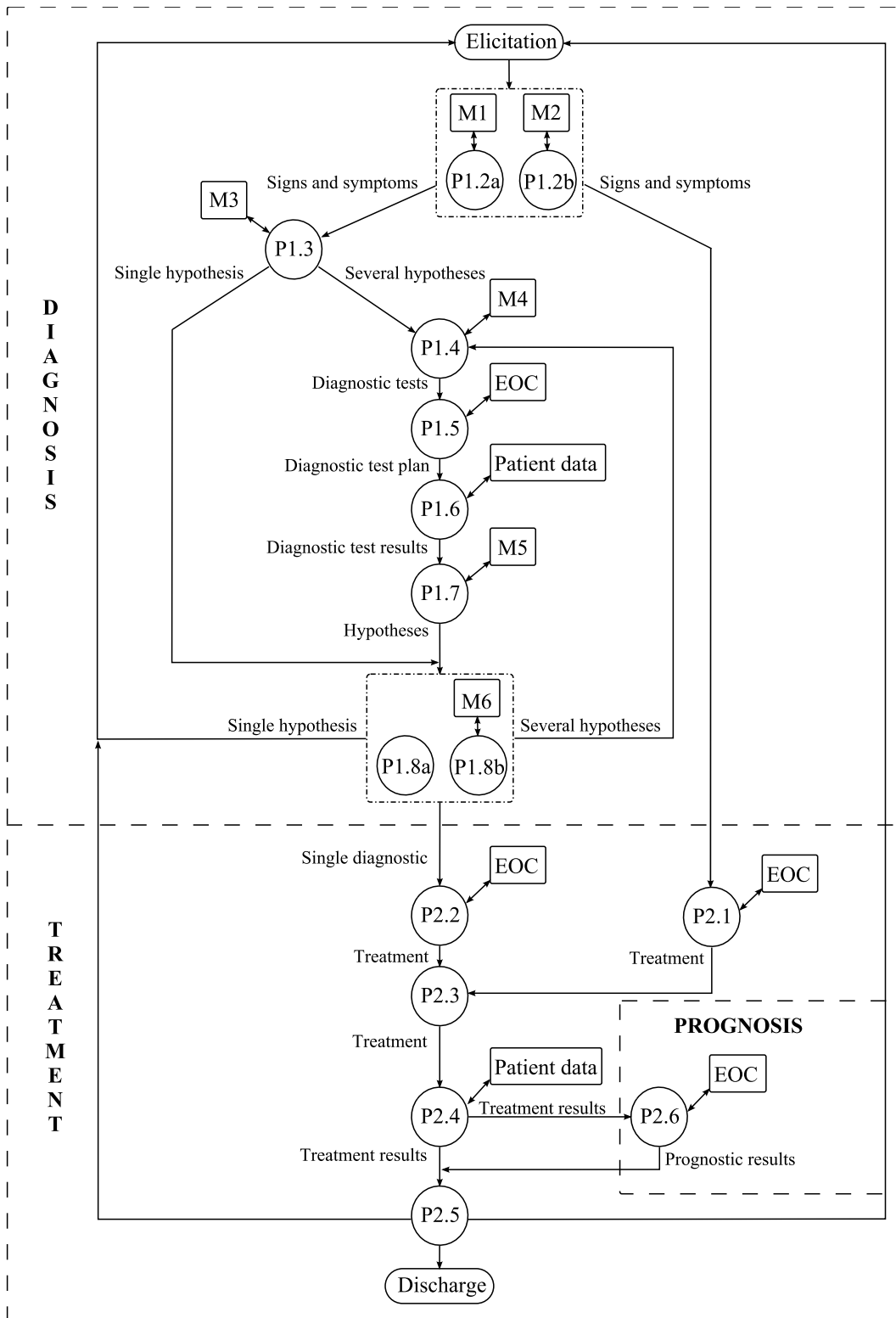


Figure 7.2: MPM functional model.

A radioactive tests is done (**D1**) where main results are: $Ph = 5,5$, density > 1030 , leucocytes $+++$; blood $+$; resting $-$ (**E**). A genitourinary examination is completed with normal results, and it is performed a rectal exam that shows an enlarged prostate, soft, hot, painful on palpation and with effacement of the central sulcus. We ask for a blood test, urine test and uroculture, and we begin an empirical treatment with ciprofloxacin 500 mg/12h. After 48 hours, the patient is asymptomatic and has no fever, hence we complete the antibiotic guideline during 28 days (**I**).

Complementary tests results:

- Immediate blood test: leukocytosis with predominance of polymorphonuclear, urea and creatinine within normal.
- Immediate urine test: $Ph = 5,5$, density ≥ 1030 , total protein = 0,3 g/l, blood $+$, leucocytes $+++$.
- Sediment (cytometry): leucocytes 1772(0 – 20), red blood cell 6(0 – 15), epithelial cells 48(0 – 25), cylinders 1(0 – 1), bacteria 4443(0 – 2,5).
- Sediment (manual): abundant leukocytes/field and abundant bacteria/field.
- Uroculture: > 100000 ufc/ml. E. coli sensitive.

Once the medical treatment is finished, another uroculture is realized. The result is negative (**J**).

- *Second case* (figure 7.4): 59 year-old male, controlled at the health care centre by presenting a pulmonary edema secondary to paroxysmal atrial fibrillation recent and by her diabetes mellitus type 2 (DM2). He explains that he has had throatache and earache with no suppuration, fever or expectoration in the past few days (**A1**).

We revise the patient's medical record and we find that:

- Personal antecedents: smoker (1,5 pack/day from 20 year ago), no other toxic habits, DM2 no dependent of insulin, paroxysmal atrial fibrillation, without family history of interes.
- Regular treatment: Metformin, Amiodarone, Acenocoumarol and Furosemide.

During the physical examination it is observed a slightly hyperemic pharynx, whitout exudate plaques. There are no submandibular lymphadenopathy. The otoscopy and the cardiopul-

monary auscultation are also normal. The rest of the examinations results are normal (**B1**). It is established a treatment with anti-inflammatory (ibuprofen 600 each 8h), antibiotics (amoxicillin/ac. clavulanic 500/125 each 8h for 7 days) and plenty of fluids, by suspect of acute pharyngitis.

A few weeks later, the patient attends to the health care centre indicating that have pain throat and left otalgia alter the treatment. Besides, he has found a small lump to left submandibular level since a few days. He does not have dysphonia, hemoptysis nor general symptoms (**A2**). In the physical examination it is shown a normal pharynx, with no oropharyngeal injuries. shows an adenopathy of 2 cm to left submandibular level. The ear examination (otoscopy) is normal. No lymphadenopathies are observed. There is no goiter nor hepatosplenomegaly. The rest of the examination is normal (**B2**). Alter the examination, a blood test and a thorax radiography are requested. The results of the hemogram and biochemistry are normal; Epstein-Barr virus (EBV) negative; toxoplasmosis negative; erythrocyte sedimentation rate (ESR) and C-Reactive Protein (CRP) normal; thorax radiography normal and Mantoux less of 5mm.

The patient experiences an increase of odynphagia and the appearance of an associated dysphagia. He is sent to the medical emergency, where he is attended by an otorhinolaryngologist. Indirect laryngoscopy was performed, in which lesions were observed at the supraglottic level suspicious of neoplasia, and a biopsy is programmed. While the patient is waiting for biopsy results, he goes to consultation due dysphonia, that had not been present yet (**C**).

The biopsy is informed as supraglottic neoplasia (**D**) with glottic affectation whitout metastasis to distance. The following decisions are taken: first, practice total laryngectomy (by glottis affectation) with tracheostomy and radiotherapy. Second, definitive tracheostoma and starting the voice rehabilitation.

- *Third case* (figure 7.5): 19 year-old female who comes to the health care centre suffering from occipital headache of oppressive way and progressive intensity, whitout vomit, whitout increase (when applied Valsalva test) and no other symptomsy. The profile was preceded by neck and back pain of mechanics characteristics. There was no traumatic precedent (**A1**). The neurologic examination was normal and there was no alteration on the rest of the physical examination, except obesity. There were neither personal nor familiar record of interest (**B1**). Possible triggering socio-familial factors are investigated and the patient recognises

couple problems (**C**). An analgesic treatment is established (**D**) and the patient is to be cited in consultation scheduled to deepen into her personal problems, her clinical record and the physical examination.

In consultation, 10 days after the first encounter, the patient shows an increase in intensity of the headache (**F**), despite the scheduled treatment. Besides the patient has suffered two morning vomiting, and blurred vision with a sensation of double vision (**A2**). The patient is conscious and oriented, but because of the appearance of alarm symptoms a new neurological examination is done. The results are normal, with no oculomotor paresis or other alterations (**B2**). Ophthalmoscopy was performed and displays an image of papilledema (**G**). It was done a lumbar puncture (**G**) that was diagnostic: output of fluid pressure. The patient was admitted in the neurological service with the diagnosis of benign intracranial hypertension associated to obesity. It is rejected that the hypertension was secondary. The patient was referred to ophthalmology for assessment of campimetry and visual acuity. Currently, the patient is asymptomatic, has not suffered similar episodes, and her weight is being controlled by nursing (**H**).

- *Fourth case* (figure 7.6): A 45-year-old female with precedents of extrinsic bronchial asthma goes to consultation, she is a former smoker without clinical record of chronic obstructive pulmonary disease (COPD), she has dyspnea of three days of evolution, with fever of 38°C and clinical non-productive dry cough, myalgia, headache, and pleuritic right subcostal pain (**A**). She has an O₂ saturation of 92% (**C**) and a heart rate of 113 bpm (beats per minute). Cardiopulmonary auscultation is normal and the meningeal signs are negative. There are no other significant findings (**B**). The health care professional asks a blood test and a thorax radiography, which provides normal results. She is sent home with an antibiotic (amoxicillin and clavulanic acid) and asymptomatic treatment, and she is scheduled for a revision in a few days if there is no improvement (**D**).

After a week, she returns to persisting fever and resting dyspnea (**A2**). In the analysis done the previous week it can be noticed: hemoglobin, 11; absence of leukocytes; High-density lipoprotein (HDL), 876; C-Reactive Protein (CRP), 14, and the rest is normal. A new examination is done and it is found oral thrush, decreased vesicular murmur with scattered wheeze (**B2**) and O₂ saturations of 88 (**C2**). She is repeatedly asked about her personal antecedents and she explains that she suffered herpes zoster, weight loss of 15 kg in the last 2 years and that she's been parenteral drug addict (PDA) until 17 years ago (**A3,B3**). A

new thorax radiography is requested (**C3**) where emerge a bilateral interstitial pattern. The patient was referred to the hospital urgency service with a diagnosis of suspicion of atypical pneumonia (**H**) by pneumocystis jirovecii in possible immunosuppressed. The suspicion was confirmed and she was also diagnosed AIDS (**H**).

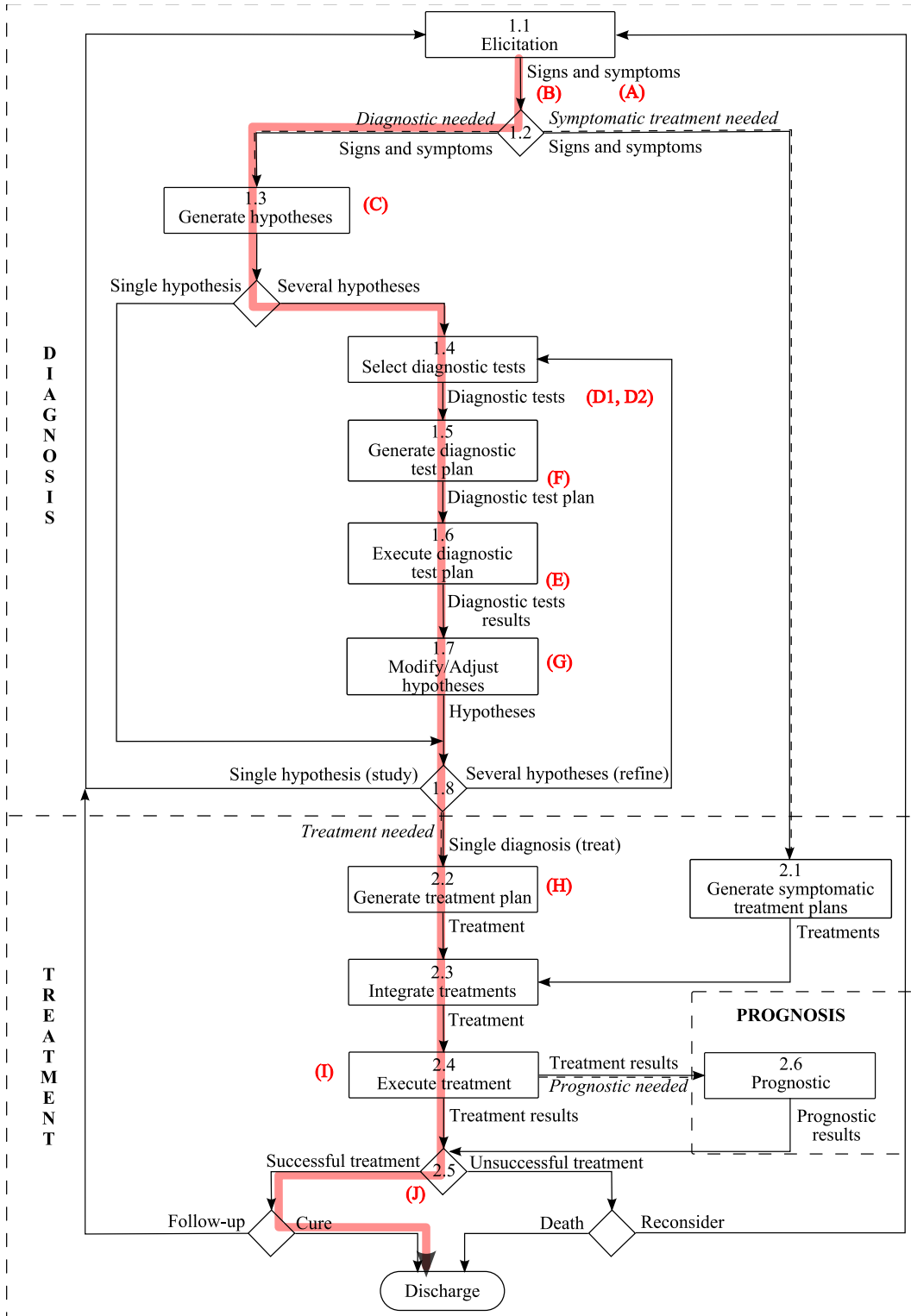


Figure 7.3: Behavior of first real clinical case.

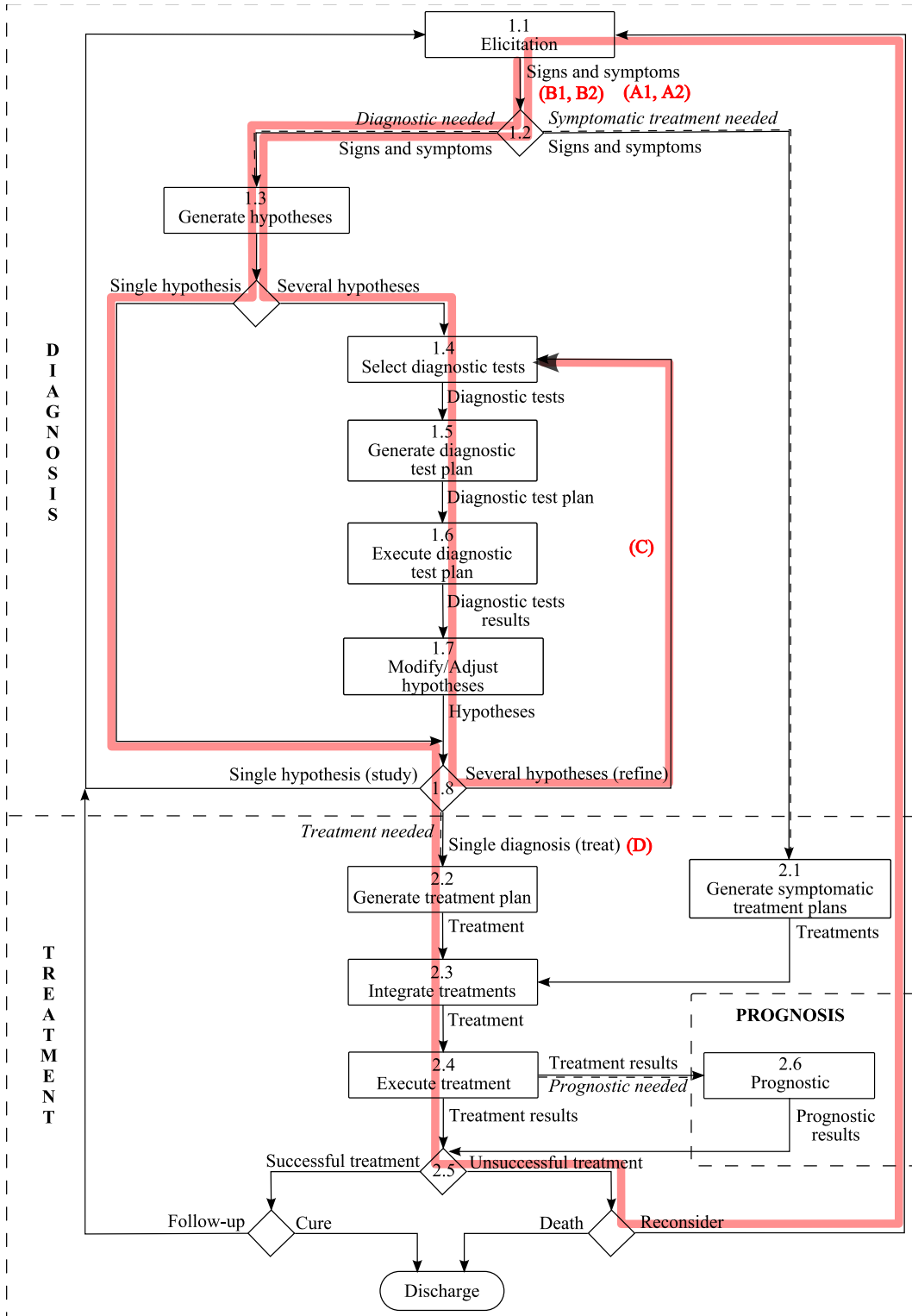


Figure 7.4: Behavior of second real clinical case.

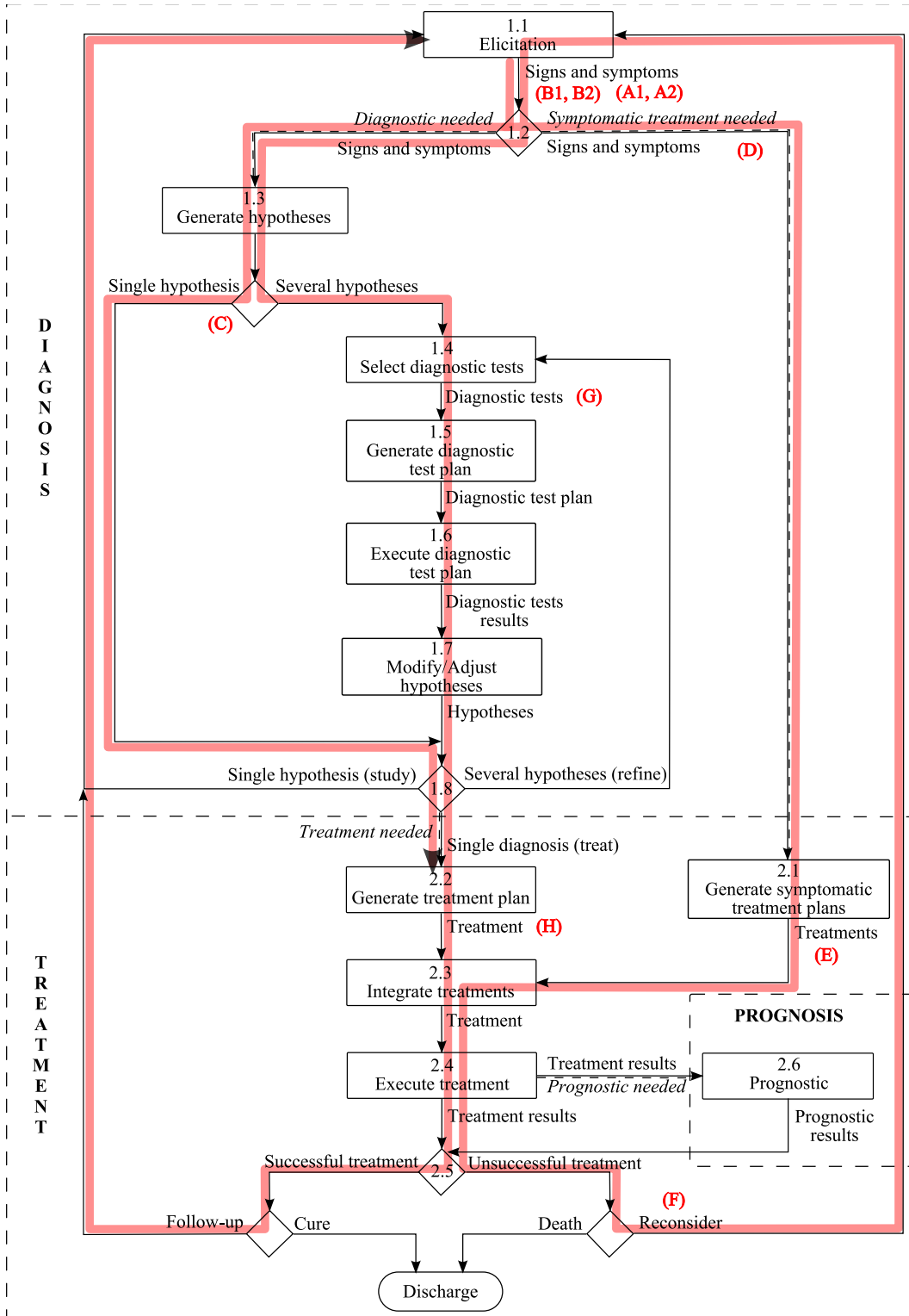


Figure 7.5: Behavior of third real clinical case.

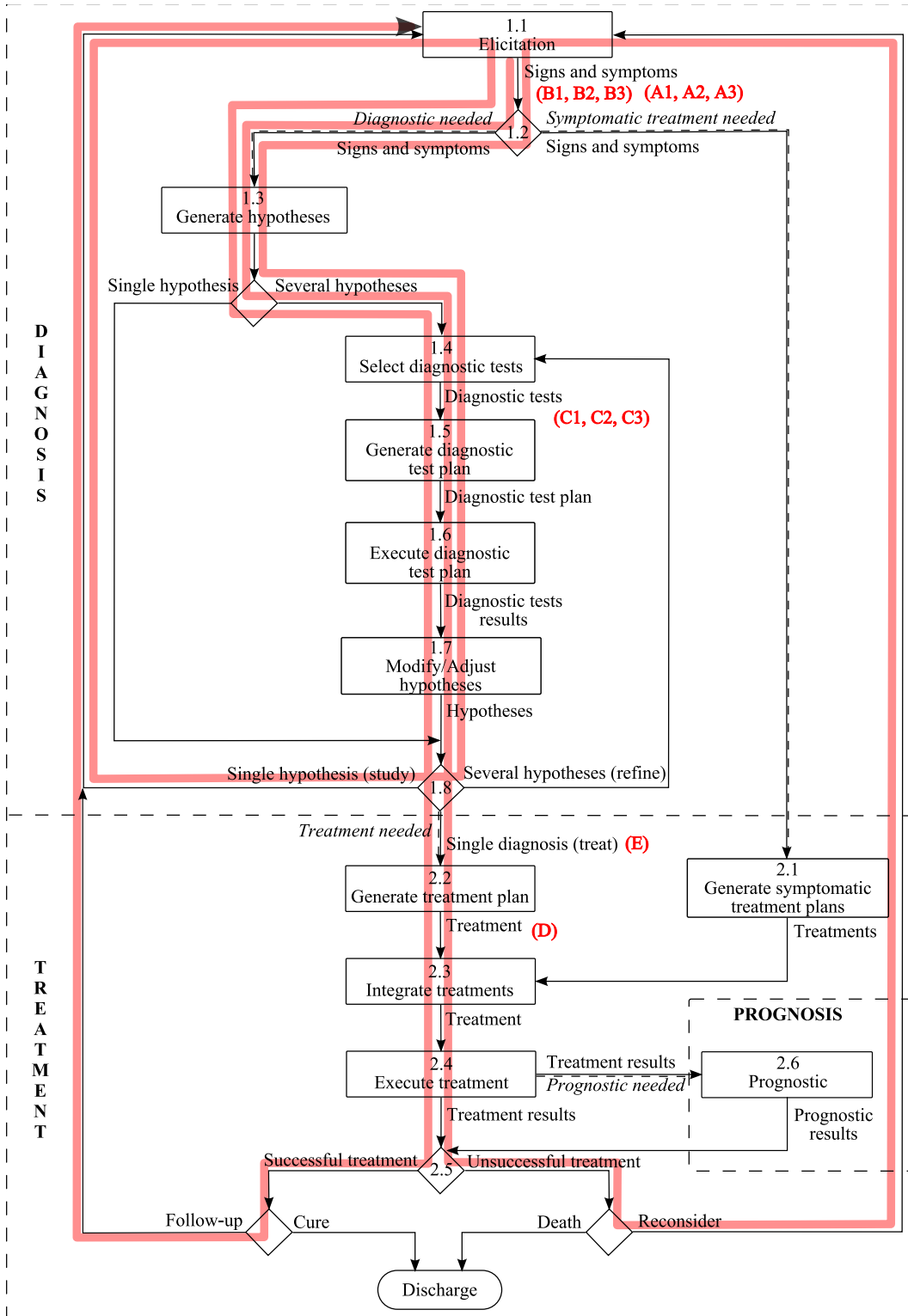


Figure 7.6: Behavior of fourth real clinical case.

7.6 Discussion

Integrating the medical assistance activities of decision and planning for the diagnosis, treatment and prognosis, in a single computable model, allows that a great diversity of medical situations can be represented and solved by this model, as it was shown for four representative clinical cases whose management is depicted in figures 7.3, 7.4, 7.5 and 7.6. So, the implementation and use of MPM can be used to help to improve the medical-clinical processes of decision making.

7.7 Conclusions

The development of an integral, computable and knowledge based model that automate the medical procedure for the decision and planning activities in medical-clinical diagnosis, treatment and prognosis, is one of the objectives of this thesis. Therefore, the steps followed to achieve this objective are exposed as chapter 7 conclusions:

- Based on standard procedure model introduced in the chapter 2, in this chapter we have proposed a new formal medical procedure model, called MPM, that integrates the decision and planning activities to the diagnosis, treatment and medical-clinical prognosis.
- We Propose a computable architecture based in knowledge that automates the formal model MPM.
- In MPM, the main AI problems in the medical assistance activities have been identified as binary and multiple decision, planning and prediction problems.
- The formalisms of decision tree, decision table, and partial orders plus state transition diagrams were proposed to represent the sort of know-what knowledge required to solve the AI problems of binary decision, multiple decision, and prediction problems, respectively.
- The SDA structure to represent know-how knowledge was proposed to solve the AI problem of planning.
- To validate the MPM, this model was applied to four real clinical cases. These medical situations described in these cases are suggested by Dr. Collado, a senior GP of the SAGESSA Group [SAG], that qualified these cases as diverse and representative of primary care cases.

Part IV

Conclusions

Chapter 8

Contributions, Limitations, Future Work, and Final Comment

8.1 Introduction

This chapter concludes the thesis. In section 8.2 we provide a summary of the main contributions. In section 8.3 we discuss general limitations of our results. Finally, in section 8.4 we present the final comment of this thesis.

8.2 Summary of Main Contributions

This thesis has contributed to the development of a computable model based in knowledge that integrates all the decision and planning activities for the medical-clinical diagnosis, treatment and prognosis. To accomplish this, first, in chapter 2 we did an analysis of the background in medical informatics, referring to medical assistance. The results obtained (§2.5) allowed us to reveal a series of events which defined and directly conditioned this thesis. Second, in chapter 3 an analysis of antecedents in the scope of formalizing knowledge about medical assistance was realized. This analysis showed (§3.4) the importance of proposing new alternatives of representation and induction of know-how and know-what knowledge. Therefore, in chapter 4 we propose the state-decision-action (SDA) knowledge model to represent health care procedures as SDA diagrams which are similar to medical algorithms. This novel model presents an alternative to the current languages of know-how knowledge representation in medicine. In chapter 5 we propose a novel methodology to automatically induce state-decision-action (SDA) diagrams from health care databases and electronic health records in order to show health care professionals an explicit representation of the past health care

procedures and to use these representations to study their deviations with respect to official and predefined protocols and medical algorithms. In chapter 6 we propose a novel machine learning method, based on partial orders and state transition diagrams, to solve problems of the decision activity in medical-clinical prognosis.

Finally, in chapter 7 we propose a novel and broader approach which integrates the medical procedures of diagnosis, treatment, and prognosis in a Medical Procedure Model (MPM) that provides a holistic management of chronic comorbid patients.

8.3 Limitations and Future Work

The SDA model to represent know-how knowledge in medical assistance, introduced in chapter 4, permits two sort of time constraints in the diagrams [KRRW07]: micro and macro-temporality. *Micro-temporality* is used to attach temporal restrictions to the terms in the SDA diagram (e.g., durations, frequencies, deadlines, etc.), while *macro-temporality* is used to attach temporal restrictions to the connectors in the SDA diagram (e.g., delays, waits, schedules, etc.). In this thesis, we have not considered these time features given its complexity [KRRW07, KRW08, KRW09], however, the SDA model is prepared for the introduction of time knowledge.

The methodology of automatic generation of know-how knowledge in medical assistance, reported in chapter 5, has a limitation respect to the lack of medical background knowledge involved in the learning method which may be particularly useful to detect states and actions. Here, the similarity between states (and actions) is done manually by health care professionals or using an approach which is based on the coincidence of terms (see equation 5.8 and parameters α and β in tasks 1 and 2 of section 5.2.4). This approach is mathematical rather than medical, which may affect the medical quality of the SDAs obtained. In the future, we aim to incorporate background knowledge represented by means of ontologies in the machine learning method.

The methodology of automatic generation of know-what knowledge for prognosis in medical assistance, introduced in chapter 6, is based on the concept of *patient condition* (5.2.1), which represents the state of the patient concerning a disease. The tests realized in this methodology, was based on diseases where the set of disease conditions are fixed and well defined, such as cancers (Tumour Node Metastasis Staging System (TNM) [SW02]). However, for other diseases there are is an agreed criterion on the set of conditions, in this case, we propose the use of a non-supervised clustering algorithm to obtain the set of disease conditions in 6.2.1.

All these limitations are the starting point of alternative works that are left out of the current

thesis and considered as future improvements.

8.4 Final Comment

As it is previously evidenced, the research work of this thesis contributes to formalize and to automate medical assistance with the support of a knowledge-based model. In order to accomplish this, we have proposed knowledge models for all the medical-clinical activities that can be induced from medical data, we have raised inductive learning solutions for all the medical-clinical activities and we have proposed an integral model that formalizes the concept of medical procedure. These contributions allow to improve the processes of medical-clinical decision that health care professionals have to face in their daily work.

Finally, in spite that the research work has been fully concluded, there are some minor issues that should be improved before finalizing this PhD thesis. These are twofold, on the one hand we're currently working together with Dr. Colomé and Dr. Collado from SAGESA Health Group (Tarragona, Spain) and Dr. Roca and colleagues from Clinic Hospital (Barcelona, Spain) testing our algorithms with additional databases. The current results are promising, though medical analysis and the consequences of this analysis are still not concluded. On a second hand we expect to introduce the new results within the sections about conclusions at the end of several of the current chapters and in chapter 8, which may cause a slight restructuring of some parts of the current document.

Part V

Appendix

Appendix A

Publications

List of articles realized as part of the development of this PHD thesis.

A. Journal Publications

1. *MPM: A Knowledge-Based Model of Medical Practice*

David Riaño, John A. Bohada, Antoni Collado, and Joan A. López-Vallverdú, (submitted to) Journal of Biomedical Informatics. February 2012.

abstract. Medical practice (or the practice of medicine) is a varied and complex discipline that involves medical tasks as diagnosis, therapy providing, and prognosis which are supported on intelligent acts such as intelligent search, decision making or knowledge merging and deployment. The application of artificial intelligence technologies in medical practice has been a continuous research area since the early 1970's, but usually restricted to specific medical tasks and not as a solution to medical practice as a whole. We think that one of the reasons for that is that there is not a formal model describing the interactions among diagnostic, therapeutic and prognostic tasks in medical practice. In this paper, we introduce a medical practice model (MPM) resulting from the analysis and integration of partial models surveyed in specialized literature. The integrated model is described, together with the health care data involved, the functionality of the model, and the sorts of knowledge to support such functionality. The validity of the model is tested against 93 medical cases, but also in comparison to other models and some published clinical decision support systems. The limitations and capacities of the model are also discussed.

2. *Automatic Generation of Clinical Algorithms within the State-Decision-Action Model*

John A. Bohada, David Riaño and Joan A. López-Vallverdú, (submitted to) *Journal of Expert Systems with Applications*. January 2012.

abstract. Objective: To propose a methodology to automatically induce state-decision-action diagrams from health care databases and electronic health records in order to show health care professionals an explicit representation of the past health care procedures and to use these representations to study their deviations with respect to official and predefined protocols and clinical algorithms.

Materials and Methods: The methodology is based on two initial models giving rise to the data and knowledge structures episode of care database and set of rules. These two structures contain, respectively, patient data from health care centres and the translation rules which are used to adapt the data of the episode of care database to the terminology we want the resulting state-decision-action diagram to have. The data expressed in the new terminology is used to generate the final state-decision-action diagram by means of a machine learning method. We have performed several tests on the treatment of hypertension with data from the SAGESSA Health Care Group. The state-decision-action diagrams obtained have been analyzed at the level of their ability to predict correct treatments and at the level of their adherence to the clinical algorithms published by four official health care organizations.

Results: The state-decision-action diagrams obtained represent an average 94.6% of the treatments in the database, only excluding some atypical cases. Moreover, these diagrams show a high level of adherence to the treatment proposed by the National Heart Foundation and the Spanish Society for Hypertension with about 91.4% of coincident treatment.

Conclusions: A new methodology has been developed which automatically induces state-decision-action diagrams which can be used as a graphical representation of the health care procedures carried out in health care centres. The methodology is also a tool to study the adherence of these health care procedures to the official standards.

3. *Improving Medical Decision Trees by Combining Relevant Health-Care Criteria*

Joan A. López-Vallverdú, David Riaño and John A. Bohada, (submitted to) *Journal on Knowledge and Information Systems*. November 2011.

abstract. Through the years, decision trees have been widely used both to represent and to conduct decision processes. They can be automatically induced from databases

using supervised learning algorithms which usually aim at minimizing the size of the tree. When inducing decision trees in a medical setting, the induction process should consider the background knowledge used by health-care professionals to make decisions in order to produce decision trees that are medically and clinically comprehensible and correct. Comprehensibility measures the medical coherence of the sequence of questions represented in the tree, and correctness rates how much irrelevant are the errors of the decision tree from a medical or clinical point of view. Some algorithms partially solve these problems pursuing alternative objectives as reducing the economic cost or improving the adherence of the decision process to medical standards. However, from a clinical point of view, none of these criteria is valid when it is considered alone, because real medical decisions use to be taken attending to a combination of them, and also other health-care criteria, simultaneously. Moreover, this combination of criteria is not static and may vary if the decision tree is made for different purposes as screening, diagnosing, prognosing or drug and therapy prescription. In this paper, a decision tree induction algorithm that uses combinations of health-care criteria is presented and used to generate decision trees for screening and diagnosing in four medical domains. The different criteria have been selected from internal quality studies performed at the Clinical Hospital in Barcelona (Spain) and the SAGESSA Health Care Group (Spain). The mechanisms to formalize and to combine these criteria are also presented. The results have been analyzed from both a statistical and a medical point of view, and they suggest that our algorithm obtains decision trees that physicians evaluated as more comprehensible and correct than the decision trees obtained by previous approaches as they keep an equivalent accuracy.

B. Congress Publications

1. *Induction of Partial Orders to Predict Patient Evolutions in Medicine.*

John A. Bohada, David Riaño and Francis Real. 11th Conference on Artificial Intelligence in Medicine (AIME2007), Amsterdam, The Netherland, 2007. Participation and Presentation.

Abstract: In medicine, prognosis is the task of predicting the probable course and outcome of a disease. Questions like, is a patient going to improve?, what is his/her chance of recovery?, and how likely a relapse is? are common and they rely on the concept of state. The feasible states of a disease define a partial order structure with extreme states those

of 'cure' and 'death'; improving, recovering, and survival meaning particular transitions between states of the partial order. In spite of this, it is not usual in medicine to find an explicit representation either of the states or of the states partial order for many diseases. On the contrary, the variables (e.g. signs and symptoms) related to a disease and their normality and abnormality values are broadly agreed. Here, an inductive algorithm is introduced that generates partial orders from a data matrix containing information about the patient-professional encounters, and the normality functions of each one of these disease variables.

2. *Automatic generation of Formal Intervention Plans based in the SDA* representation model.*

Francis Real, David Riaño and John A. Bohada. 20th IEEE International Symposium on Computer-Based Medical System (CBMS07), Special Track on Machine Learning and Management of Health-Care Procedural Knowledge, Maribor, Slovenia, 2007. Participation.

Abstract: Clinical practice guidelines are important in the work of physicians. These guidelines are manually created by experts using their knowledge and experience. This work gives an approach to automatically develop the clinical guideline charts with the SDA* representation model. In addition, this paper details an example of application of the methodology proposed with the treatment of Hypertension.

3. *Knowledge production and integration for diagnosis, treatment and prognosis in medicine.*

John A. Bohada, David Riaño. 20th Catalan congress of Artificial Intelligence, Alguer, Italy, 2005. Participation and Presentation.

Abstract: Diagnosis, treatment and prognosis are three of the most frequent labors of physician in health care institutions. In decision making, these activities can be tackled from two approaches: decision and planning. Decision structures are designed to help physician in their task of taking atemporal decisions. Planning structures are designed to guide physicians in the time-dependant complex medical procedures. The goal of this article is to present a model that integrates several learning tools to develop decision and planning structures in the medical domain, specifically in the support of decision making.

4. *Data modelling for medical knowledge production.*

John A. Bohada, Aida Kamisalic, David Riaño, Tatjana Welzer. The Tenth International

Symposium on Health Information Management Research (ISHIMR2005), Theme: Improving the quality of health information - an international perspective Thessaloniki, Greece, 2005. Participation.

Abstract: Current medical information systems are designed to support practitioners and managers in their activities in healthcare centres. However, from a cognitive point of view, the power of the data stored in huge hospital databases is not only in the storage or daily use, but on the embedded medical knowledge that they contain and that can be made explicit with artificial intelligence techniques. In contrast to the traditional approach of electronic patient records this paper describes a database structure model aiming, on the one hand, at hosting all the information required about the medical processes of diagnosis, treatment follow-up, and prognosis as they happen during the consecutive appointments of doctors and patients in a healthcare centre, and on the other hand at easing the artificial intelligent processes of making medical knowledge explicit.

5. *A CPG-based CBR model to offer the best available medical Therapy.*

John A. Bohada, David Riaño. 2nd European Starting AI Researcher Symposium (STAIRS 2004), Valencia, Spain, 2004. Participation and Presentation.

Abstract: Therapy assignment is one of the most frequent labours of physicians in healthcare institutions. A Clinical Practice Guideline (CPG) is the way that the medical knowledge about a particular therapy is represented with the purpose of defining standards in clinical assistance. The assignment of a therapy to a concrete patient requires the combination of theoretical and empirical medical knowledge to propose the most convenient CPG according to the situation and also to adapt it to the particularities of the patient. Even though CBR seems the natural artificial intelligence paradigm to deal with therapy assignment, there are still some difficulties to overcome. Here, we describe the first steps towards the definition of a CBR model based on clinical practice guidelines and oriented to the search, proposal, and adaptation of medical therapies. The model has been tested on two cardiopathies: atrial fibrillation and hypertension.

6. *The DTP Model: Integration of intelligent techniques for the decision support in Healthcare Assistance.*

David Riaño, John A. Bohada, Tatjana Welzer. Fourth International ICSC Symposium on ENGINEERING OF INTELLIGENT SYSTEMS (EIS2004), Madeira Island, Portu-

gal, 2004. Participation.

Abstract: The paper introduces a new model, called the DTM model, that uses Artificial Intelligence techniques to obtain health-care knowledge that can be applied in a combined way to support the decision making in some relevant medical activities as diagnosis, treatment selection, and prognosis. The DTP model applies inductive learning techniques to hospital data and obtains action rules, clinical guidelines and belief networks. These knowledge structures are respectively exploited by an inference engine, a case-based reasoner, and a probability propagation system to automatically propose a Diagnostic-Treatment-Prognostic (DTP) sequence that the new patients should follow. The model and its implementation has been tested with data concerning cardiopathologies of the patients assisted in the Hospital Joan XXIII in Tarragona.

C. Technical Reports

1. *Temporal Aspects in Database Modelling for Medical Knowledge Production.*

Aida kamisalic, David Riaño, John A. Bohada, Tatjana Welzer. Report de recerca DEIM-RR-05-006, Juny 2005. Universitat Rovira i Virgili.

Abstract: The document gives an overview of existing temporal aspects and their implementation in TIMEER model considering their usage over specific constructs (entities, attributes and relationships).

Appendix B

Projects Participation

Lists of research projects in which I participated as part of the development of this thesis.

- A. *Project:* K4CARE: Knowledge-Based HomeCare eServices for an Ageing Europe (FP6-026968), 2005-2009.

Funded by: European Union

Description: In eHealth it is increasingly necessary to develop tele-informatic applications that can support everyone involved in providing basic medical assistance (doctors, nurses, patients, relatives, and citizens in general). The care of senior citizens, chronically ill and disabled people, and people with mental illnesses involves life long treatment under continuous expert supervision. Moreover, health care workers and patients accept that being cared for in hospitals or social centres may be unnecessary and even counterproductive. From a global view, such patients may saturate national health services and increase health related costs. The debate over the crisis of financing health care is open and is a basic political issue for old and new EU member countries and could hinder European convergence. To face these challenges we can differentiate medical assistance in health centres from assistance in a ubiquitous way (Home Care model); the latter can undoubtedly benefit from the introduction of ICT. This project will develop a platform to manage the information needed to guarantee an ICT Home Care service.

- B. *Project:* HYGIA, 2006-2009

Funded by: Ministerio de Educación y Ciencia (España)

Description: In this project we propose the use of Intelligent Systems in the processes of acquiring, formalizing, adaptating, using and assessing knowledge models that describe Care

Pathways (CPs). This project sets out that CPs are not generated directly from the clinical practice guideline (CPGs), but from electronic protocols, that represent versions of the adapted guidelines when they are made specific to the particular healthcare circumstances. The CPs obtained could be used by intelligent computer science distributed systems to facilitate the decision making that allows the e-care in the context of a new Information Society. The project considers in a frame of convergence of diverse technologies developed in diverse work groups and European and national R+D projects of which the present investigators have been or are co-ordinators (PROTOCURE I, PROTOCURE II, K4CARE, HeCaSe, PalliaSys, AgentCities Working Group on Health Care Applications, AgentLink III Technical Forum Group on Applications of Agents in Health Care). It is defined, therefore, like a project that integrates compatible and complementary groups that at the moment have obtained financing of independent way, with the purpose of forming a group of national and international reference in the area of the management of the medical knowledge.

C. *Project*: Knowledge and exploitation in wholistic medical treatments, 2004-2005.

Funded by: This project is an integrated action between the Rovira i Virgili University (Spain) and the University of Maribor (Slovenia).

Description: This project aims to define the appropriate information systems to store medical requirements in order to automatically generate diagnosis, treatment and prognosis knowledge; develop Data Mining and Machine Learning techniques to exploit the data in the above information systems, and define knowledge structures suitable to store the results of the data exploitation.

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