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METHODOLOGICAL REVIEW

Temporal reasoning for decision support in medicine

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Temporal reasoning;
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Diagnosis;
Prognosis;
Therapy planning

Summary

Objective: Handling time-related concepts is essential in medicine. During diagnosis it can make a substantial difference to know the temporal order in which some symptoms occurred or for how long they lasted. During prognosis the potential evolutions of a disease are conceived as a description of events unfolding in time. In therapy planning the different steps of treatment must be applied in a precise order, with a given frequency and for a certain span of time in order to be effective. This article offers a survey on the use of temporal reasoning for decision support-related tasks in medicine.
Material and methods: Key publications of the area, mainly circumscribed to the latest two decades, are reviewed and classified according to three important stages of patient treatment requiring decision support: diagnosis, prognosis and therapy planning/management. Other complementary publications, like those on time-centered information storage and retrieval, are also considered as they provide valuable support to the above mentioned three stages.
Results: Key areas are highlighted and used to organize the latest contributions. The survey of previous research is followed by an analysis of what can still be improved and what is needed to make the next generation of decision support systems for medicine more effective.
Conclusions: It can be observed that although the area has been considerably developed, there are still areas where more research is needed to make time-based systems of widespread use in decision support-related areas of medicine. Several suggestions for further exploration are proposed as a result of the survey.

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1. Introduction

Reasoning about the possible order of activities or about deadlines is certainly an everyday matter in our lives. Accordingly, research in Computer Science about time-related issues has been growing steadily for the last two decades. For example, the last decade the TIME symposium series (see for example [1—4] has brought together researchers with different perspectives, aims and backgrounds conducting research on the fundamentals of dynamic systems and its applications.

In this article, we are especially interested in temporal reasoning as related with decision support-related tasks in medicine. Many researchers, especially from the areas of *Artificial Intelligence* (AI) [5] and *Medical Informatics* (MI) [6], have contributed to this area in the last decades and a good amount of research has been published. We are not aiming to be exhaustive. Instead we address key areas and point to the main publications that could provide a good starting point for the reader. When several options are available or when several related works were produced by the same author we cite their latest publication, from which the interested reader will be referred to previous related publications.

The emphasis of this article is on time-based decision support for some of the fundamental stages related to patient care, namely diagnosis, prognosis and treatment. The survey is not restricted to particular diseases, tools or techniques and other related topics will also be included, for example, time granularity or information representation and retrieval as they play a role in the way automated decision support for diagnosis, prognosis or treatment can be realized.

Other publications in the form of surveys and special issues (details are provided in another section below) have considered high level views on the topic of temporal reasoning in relation with the medical domain. Although these were significant steps on raising awareness about a diversity of topics within the community related to the area of application, very few of them actually considered the areas of Diagnosis, Prognosis and Treatment as the concepts around which these information should be organized. Neither they put all the areas together reinforcing the view that these are not isolated steps in patient treatment and mutual influence should be considered in further depth.

The remaining sections are organized as follows. First (Section 2) we introduce some basic concepts in relation with temporal reasoning. Then (Section 3) we explain why time is important in Medicine and we put this article in the context of previous efforts to summarize time-related literature within the area of AI in Medicine. Next (Section 4) we provide a non-exhaustive but comprehensive description of the work that has been done in those key topics identified in the previous section. We first consider several related proposals on issues related to time-based information representation, storing and retrieval (Sections 4.1 and 4.2) and then we provide a survey on each one of the main areas we consider in this work: diagnosis (Section 4.3), prognosis (Section 4.4) and treatment (Section 4.5). We conclude this article (Sections 5 and 6) by providing an analysis of what still can be improved and what is needed to make the next generation of decision support systems for medicine more flexible and effective.

2. Time representation and use in artificial intelligence: some basic concepts

The formalization of temporal reasoning proved to be a great task as the literature in logic, philosophy, linguistics, AI and Computer Science testifies. There are then many perspectives and many options to consider at the stage when one is trying to define what the basic layer of a temporal system should be. We are not aiming here at covering all the aspects and will instead focus very shortly in a subset of them from the perspective of medicine. The reader is addressed to [7,8] for lengthier descriptions of the basic concepts as well as a description of the main trends of temporal reasoning in AI. We will first consider some concepts related to the ways we can define a structure for time-related references. Then we describe some concepts that are usually associated to time references. The final step is to relate the previous discussions about time representations and temporal concepts to characterize one of the key notions for any dynamic system, e.g. change.

2.1. Defining the underlying structure for temporal references

Characterizing the temporal scenario to be assumed strongly influences the theory to be proposed and this, in turn, the tools to be produced. Recently Computer Science and AI researchers (building on previous work from philosophers, linguists and logicians) have considered temporal notions as part of the program to characterize the notion of *intelligence* and as a first step to different goals. See for example [8—13].

One aspect to be considered is what basic "shape" and set of properties the underlying temporal structure is assumed to have. Time is usually conceived as a line where temporal references can be aligned. This conception of time proved to be popular since the Newtonian physics paradigm was adopted and provides the simplest conception and way to arrange temporal references. See [14] for example. Another popular alternative in Computer Science (CS) and artificial intelligence (AI) is a future-branching structure representing past as linear and the present as a distinguished point where the future opens as a bunch of possibilities. The adoption of a future-branching structure could be motivated in several ways. Usually it is the possibility of representing the capability of an intelligent entity to choose between alternatives or a way to provide hypothetical reasoning which is behind its adoption [15]. A past-branching structure could provide a good framework for abductive reasoning and other related tasks as it provides natural representation for the different possible ways of arriving to a present state of affairs. Circular time could be useful when analyzing repetitive patterns, cyclic processes. See [16] for a philosophical background and [17] for a computational perspective. In a distributed system (like a multi-agent system or a distributed database) it could also be useful or necessary to consider that each or some of the participating nodes have their own account of time organized in a specific way. For example such a system can be conceived as an arrangement of parallel lines. In this scenario, coordinating mechanisms and specific protocols should be provided in order to reach agreement on the operations between the interacting parts of the system.

Some tasks may demand consideration of time up to a point. For example, when analyzing symptoms that lead to a particular disease, facts that happened beyond some day will not be of interest. In this context time can be conceived as having a final moment. Reciprocally, when considering a treatment there may only be an interest on facts occurring beyond a specific date. There are other conceptions of time where no specific limits are imposed or to the contrary that conceives time as a limited structure with a beginning and end [18].

Time can be also considered from a "topological" perspective, e.g. discrete, dense or continuous. This led to the so called *topological time* because temporal structures could be analyzed under the light of topology as known in mathematics. Sometimes it suffices to define the time references as a discrete succession, i.e. isomorphic to $\mathbb{N}$ or $\mathbb{Z}$, e.g. height measurements and weight. This characterization is particularly relevant in relation with the notion of time granularity, a topic we will consider in more detail later on. For example, tasks like clinical management, diagnosis, prognosis, and treatment can well benefit of a calendric view where references to years, months, days and hours can be represented. However a realistic representation and modelling of subtle physical, biological or chemical processes, like forecasting sugar and blood pressure levels, may demand a dense or continuous conception of time, i.e. isomorphic to $\mathbb{Q}$ or $\mathbb{R}$. However, these steps could not be given without a price to pay. There exists for example the so-called *dividing instant problem* [19] which warns us about some difficulties in continuous change representation.

The problem of deciding which kind of reference must be considered the basic one has been subject to intense debate. Literature about the philosophy of time provides us with several articles from people sustaining an instant-based view of time [20] while others support a period-based approach [21,22]. Names vary with authors but usually *instants* and *time points* are used to refer to punctual occurrences while *periods*, and *intervals* are used to talk about durative temporal references. Recently some proposals have explored the benefits to allow both kinds of references in the same level of importance [23—27]. See [19] for an analysis of the three alternatives, i.e. to consider instants, periods or both. Both kind of references are certainly useful in medicine where we need to refer to punctual as well as to durative events and happenings of interest. For example, some symptoms are described as occurring at a particular day, like "The symptoms started on 4th of July" while others have a duration associated like in "He already had fever for three days".

Temporal references with a defined place in the temporal axis, e.g. "4th of July", will be sometimes called *anchored* and those which does not, e.g. "the last three days", are called *unanchored*. This terminology is more popular in the literature from specific areas of research like the one associated to Temporal Databases [28—31]. Literature related to temporal logic, e.g. [32], will most probably refer to them as *absolute* and *relative* temporal references.

Usually intervals are assumed to be periods with known beginning and end. This assumption simplifies matters for computation but it could be an unrealistic assumption to assume that knowledge will be always available. Another common assumption in the literature for temporal reasoning in AI is that they are *convex*, that is uninterrupted spans. It is interesting to see that both kinds of references, punctual and durative, can be defined in terms of each other. For example, periods could be seen as sets of instants or the duration denoted by two instants acting as beginning and ending points. Also instants could be defined as the meeting point between two periods. See [12] for a more detailed account of these complementary conceptions of time.

In the medical domain is also very useful to provide some way to handle what some researchers call *semi-intervals*, [33], i.e. intervals for which either the beginning or the ending is not directly known, e.g. "Started yesterday evening and stopped at some point during the night". The lack of precise information about a temporal reference, e.g. when an instantaneous occurrence took place or when a durative occurrence actually started or finished, is called in the area of temporal databases *temporal indeterminacy* [30,31]. It is also important to provide some account for repetitive processes, e.g. "It has headache each time that goes to music class" and frequencies of occurrence, e.g. "It has been taking this medicine three times each day" or "It has been coughing frequently during the night". Rich calendric references should be handled, like seasons, in order to discover potential causes of disease, e.g. allergies.

It is useful to bear in mind that the above considered set of possibilities for defining different aspects of a temporal structure are independent from each other. For example, the decision if the structure is linear or branching does not rule out considering if it is bounded or not neither to consider if it is discrete, dense or continuous. So there are plenty of choices at design time. Each one will have an effect in terms of the balance between expressiveness and the computational complexity needed to handle it.

2.2. Time-related concepts

Another important issue in all temporal theory is to decide what sort of information is subject to change or, in another way, what kind of concepts are considered in the theory beyond time itself. While the information to be associated with temporal concepts can vary from scenario to scenario, some concepts appear repeatedly when we examine temporal reasoning-related literature.

Because temporal reasoning involves solving problems in a changing world, there is a need to represent what *properties* the objects of that world can have or do have at each meaningful temporal reference. These characterize aspects like size, weights, temperature measurements and other distinctive features of each object considered in the intended scenarios. The set of objects and their properties define a *state* of the world. A given state of the world is changed by the occurrence of *events*. These are strongly tied to the notion of time because it is natural to think about time as a mechanism around which we organize reasoning about change in the world. *Actions* are identified with the agents' capabilities of interaction with the world. They are considered event-producers but events could be the by-product of just other event(s) like machine failures, power cuts. Usually the representation of causal relationships will be closely tied to the level of conceptual granularity in which the system is described.

It is usual to assume that properties are *homogeneous* which means that if a property holds in an interval then it holds in each of its subintervals.

For example, if a patient was diagnosed to have been under anesthetic effects from 11 a.m. until 12 a.m. s/he has been on that state at every minute and second between 11 a.m. and 12 a.m. That is, the property can be transferred "downwards" to smaller time references. Instead, events are assumed non-homogeneous. If an event *e* occurs during an interval it is supposed not to occur as such in any part of that interval. It is possible that another instance of the same type of event occurs but not exactly *e*, which is unique. For example, if a patient had surgery from 11 a.m. until 12 a.m. that surgery conducted at that place for that patient is a unique event and although s/he was in surgery from 11:45 a.m. until 11:46 a.m. that surgical intervention as a whole event did not last from 11:45 a.m. until 11:46 a.m. but for a complete hour.

A sketch of event classification was brought by Allen and Ferguson [34] where they grouped occurrences depending on how predictable they are. They classified events into *triggered*, *definite* and *spontaneous*. The first group identifies events provoked by the system being represented and its consequences are supposed to be known as in "When temperature raised to a critical level the alarm was triggered". Definite events are not provoked by the system but are known by it and could be predicted like in "Dr. Harrison arrives everyday at 9:00 a.m.". Spontaneous events are unexpected and the system could not predict where and when they could happen, e.g. "A power cut started at 7 p.m.". Although this is not the only possible classification, grouping events into categories may be useful to prepare the system to react appropriately when critical events occurred.

Actions are a key concept in the formalization of an autonomous system. They provide a way to formalize how a system could interact with its environment. As was said above, actions typically produce events and in that way play a key role in a dynamic environment. They are usually attached to *agents* in a broad sense, e.g. persons, robots, machines and other autonomous or semi-autonomous devices. The reader is invited to see [35] for further analysis on the many aspects involved in the analysis of actions.

Another technical term that usually appears in the bibliography is that of *processes* which denotes repetition or regularly sustained activity as in "the patient has been taking a medicine for the last week", "the patient has been doing exercise the last year" and "the patient has been on dialysis for the last six months". This does not mean that the activity was done continuously throughout the referred period of time, for example for the first case it does not mean necessarily that the patient was taking the medicine each minute of that week. Some authors describe them as a "state of change" as a way to differentiate them from events which could be defined as a "change of state" [12]. If they can be considered as primitive objects in a theory of change or not is still a matter of debate. Allen [14] assumed they must be considered from the very beginning. He characterized processes as those occurring at least in a part of an interval but not necessarily in the entire interval. These assumptions are criticized in [25] and [36]. In general there is no consensus about what sort of concepts this word really involves and some researchers prefer not to include them at the same level as the aforementioned notions [19]. A broader ontology is proposed in [36] where he departs from the vocabulary centered on states/events/processes and instead focus on the basic notion of a "proposition type" for which several different subcategories are suggested. Some of these categories coincides with the notions of states, events, and processes.

There has been many debates about different conceptions of time modelling and temporal knowledge representation in the last decades. Here we considered some basic notions and highlighted that there are several alternative views. See [12,25,37] for some alternatives on how all these concepts can be related with each other. As a summary we can sketch a picture of how these concepts interact with each other and how they can be put together to provide an explanation of the evolution of a dynamic world. Given some conditions, some actions can be applied by agents and this will produce events to occur which in turn will change some properties of the objects affected. This change in the properties of objects will lead to the identification of state changes. This change in the state of the world will eventually allow a possibly different set of allowed actions to be applied and so on. Repetitions of this loop may lead to the formation of higher level entities like processes.

2.3. Modeling change

We can distinguish two main ways to talk about change and to make temporal references. One way is by using absolute time references like "Symptoms started on 1 January 2003". Another common way of making time-related constructions do not make explicit mention of calendric references like in "surgery is advised as soon as possible", "two tablets have to be taken after each meal until further notice" and "the cream has to be applied over the area until the irritation has completely disappeared". In these last examples, time is mentioned as constructions relative to the notion of *present*. This is not to say that each kind of temporal references cannot be recreated in the other approach but instead that they are favored in each case.

The first case is closer to what is called the Newtonian paradigm, favored also in the past by famous philosophers and logicians like B. Russell and W. Quine as the preferred way to talk about temporal notions, where time is conceived as an unbounded line of instants. Time is conceived to have existence from the very beginning and the concepts of states and change are derived from it. Classic first order logic, or variations of it, is usually adopted as the tool to handle temporal references of this kind.

The other conception of time relies heavily on the notion of change, which is directly associated to events. They are assumed to exist from the very beginning and temporal concepts are built from this foundation. A new class of temporal logics based on this conception of time where references are relative to the events occurred and their relative order were offered by the middle of this century (see [38] for a first landmark and [10] for a more modern account). Because of its adequacy to represent the kind of temporal notions and references used in linguistics, these logics may be favored for natural language oriented applications.

Historically these conceptions have been considered as competitors originating a debate lasting decades since Quine's and Prior's work. As the reader will see in the following sections it is still unclear if one must be preferred to the other and in a CS context it probably will be the case that each one will have areas of applications where one will bring advantages over the other but both will coexist. See [12] for more details on this debate. We follow this source on the following explanation on how these different views are related to each other.

Consider two time references i_1 and i_2, for example calendric references like 21/07/2004-18:05:26 and 22/07/2004-18:30:00, and two events e_1 and e_2, for example *weightmeasurment1* and *weightmeasurment2*, associated with each one we could say which occurred before or if they were simultaneous (see Fig. 1).

Two states of the world associated with two different instants are said to be different if a property holds in one of them that does not hold in the second one. Given the situation represented in Fig. 2 we say there was a change between i_1 and i_2 and the world evolved from a state S_{i1} to another S_{i2}. For example, properties p_1, p_2 and p_3 could represent *patient under treatment*, *patient's weight equals to 38* and *patient's weight equals to 37*, respectively. Because there was a change between i_1 and i_2 we could suppose that some events occurred, as for the diagnosis to be realized, events of weighting took place and as a by-product of the conditions established like age, height and difference in weight between two consecutive days, the event of diagnosis also occurred. So the world evolved to a state in which a diagnosis of anorexia was established for that particular patient.

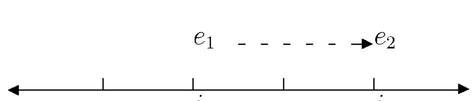

Figure 1 Deriving event order from time order.

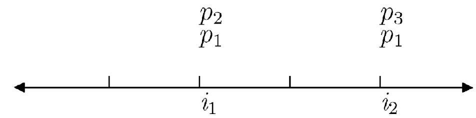

Figure 2 Discovering a change.

In this proposal, labelled as the *Newtownian Paradigm* in [12], change is not directly encoded but inferred as a by-product of time. Temporal references are usually numeric and it is easy to represent quantitative temporal relations but also qualitative relations are possible, e.g. if an instant is before another or if two periods have something in common. A state of the world is conceived as a blackboard with a, possibly infinite, set of labels to which information is attached. In this sense information could be said to be *r* eferentially neutral, in the sense it is allowed to be used without care of its relative position with the "present". An example of a proposal for temporal reasoning in AI based in this approach is [14].

In the *Leibnizian paradigm* [12], change is considered the fundamental concept and the concept of time must be built from it. In this case from an ordered succession of events the precedence of two moments of time can be inferred (see Fig. 3).

The usual relations to be used in this framework are *s* imultaneity and *precedence* although others can be also useful such as "to be between two given events". In this case also occurrence is usually considered instantaneous and the structure is assumed to be unbounded and continuous. Durative events could also be considered [14,27,39,40]. Change is represented directly in this approach and not as a by-product of comparing the knowledge in two states of the world. An example of a proposal

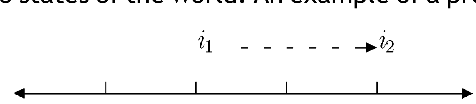

Figure 3 Deriving the order of time references from events occurrences.

for temporal reasoning in AI based on this approach is [39].

One of the areas where this two visions have led to different proposals is in the area of *temporal databases* where extensions to the traditional relational paradigm by explicit handling of time stamped tuples like *TQuel* [41] and *TSQL* [42] coexists with declarative, event-based approaches like *Datalog*$_{1s}$ and *Templog* [43] and the *Event calculus* [44]. In the former new temporal dimensions are introduced to distinguish *valid time*, the time in which the data is supposed to be valid, from *transaction time*, the time in which data arrive and is recorded in the database system. The declarative approach follows the traditional approach based on facts and rules but introducing ways to label information with time-stamps or using temporal operators to introduce temporal order between the inferred data.

3. Time in medicine

Time is so common in our daily thinking and our activities that became of fundamental importance in our lives. So basic that sometimes all this time-based reasoning pass unnoticed. The same can be observed when we consider decision making activities in medicine (see for example [45] for a quick account). It is enough to examine step by step any of the processes carried out during medical diagnosis, prognosis and treatment to quickly discover how some decisions are determined by previous decisions and facts and how important is to project possible scenarios and related treatments. Time constraints are also paramount as sometimes is important to ensure that some process are not carried out in a shorter/longer time than needed or that they are started/ended at some particular times in order to synchronize with other complementary tasks.

During the last decade the role of time in medicine has been brought to the surface and its relevance has been reflected directly in the intense activity of the area. Many articles addressing various topics are now available and in the last years we also witnessed the publication of four special issues dedicated to the topic [46—49] and the dedication of a special session in major conferences of the field (e.g. in AIME the European Conference of Artificial Intelligence in Medicine). Both are signals of the recognition that this area is gaining within the field of application.

A long list of activities were early identified [50] as key initial steps on the process to provide explicit temporal awareness for systems related to medicine: mapping occurrences across temporal contexts, determining bounds for absolute occurrences, persistence derivation, inconsistency detection and clipping of uncertainty, deriving new occurrences from other occurrences, deriving temporal relations between occurrences, deriving the truth status of queried occurrences and deriving the state of the world at a particular time.

As already acknowledged [51], computer-assisted medicine feeds from the multidisciplinary work of many Computer Science-related disciplines. The articles published in [48] reflected that emergent complexity within the particular time-related tasks. An interesting summary was provided in [52] restricted to methodological and theoretical choices. The article highlights the importance of two main research directions: *temporal reasoning* (associated to, for example, temporal abstraction, time-oriented decision support, forecasting and data validation) and *temporal data maintenance* (as related to storage and retrieval of time-related data). A rich agenda was devised: adoption of advanced data models, maintenance of clinical raw data and abstractions, management of different temporal dimensions of clinical data, merging the functions of temporal reasoning and temporal maintenance, handling deterministic versus probabilistic data, handling absolute versus relative time references, provision of standardized and user-friendly temporal-query and temporal-visualization interfaces, resolution of conflicts between temporal-reasoning and temporal-maintenance systems within hybrid architectures and providing efficient storage protocols for hybrid architectures. This is consistent with [53] where two main trends were identified: temporal reasoning (traditionally linked with the AI community) and temporal data abstraction (more identified with the Database community). The interaction of these two areas is highlighted as an important activity for the research agenda as it has the crucial role of bringing together knowledge representation and reasoning. The special issue of [49] presented a range of increasingly sophisticated systems dealing with various subtle topics addressing this integration issues. Still, as the editors made explicit, those were only the first steps to tackle the formidable task of providing flexible and rich integration between time representation and use in medicine.

We share that view and the purpose of this article is then to build on top of that previous work and to unravel further challenges which should be addressed in order to obtain the next generation of intelligent assistants for medicine. That will demand further multidisciplinary interaction between different groups whose knowledge on time-oriented systems may find in the area of medicine a challenging but highly rewarding field of application. Researchers and practitioners from MI, temporal reasoning in AI, temporal databases, active databases, real-time databases, visualization of dynamic systems and real-time systems should have some knowledge and experience to share in this fertile area. In the following sections we highlight some critical activities in medicine, the automated support available up to now and some of the areas demanding further improving or exploration.

4. Decision support for diagnosis, prognosis and treatment

In this section we provide a survey of the latest developments and trends in some of the main areas explored by researchers from AI and MI concerning time-aware proposals for decision support. We start by mentioning some issues about time-oriented data abstraction, representation, storage and retrieval. Then we summarize the main and more recent contributions that have been made in connection with the role of time in diagnosis and therapy planning.

4.1. Representing and retrieving time-oriented data

There is a real need to store time dependent data in medical applications and of course, the purpose is to store this information with the ultimate goal of being able to recover that information later in a useful context. The literature in CS reporting contributions to this problem from a general perspective is rich (see for example, [1—4,28,54]).

There have been other contributions to the topic from within the MI community as early of as in the 1970s with the *time-oriented paradigm* which consisted on adding a time-stamp to the typical parameters of patient identification and clinical parameters.

More recently, [55,56] reported on an attempt to provide services tailored to protocol-directed decision support in medicine which was better prepared to cope with different granularities and with interval-based temporal references in the context of HIV treatment. The proposal was to extend SQL language in three main directions: (a) allowing time-stamps to store the temporal dimension of both instant- and interval-based data (b) providing a set of operations on time points and intervals to manipulate time-stamped data (c) modifying the relational query language SQL so that its underlying algebra supports the specified operations on time-stamps in relational tables.

Granular Clinical History-Object Structured Query Language (*GCH-OSQL*) [57], is an object-oriented and temporally-oriented extension of SQL. It can be used to query a database supporting an object-oriented temporal data model, GCH-OODM. The proposal emphasizes the consideration of granularity and indeterminacy notions as they often appear in clinical data. The authors identify several sources of temporal references based on granularities and indeterminacy related to clinical evaluation of symptoms and therapy prescriptions. The three main aspects which are considered in this proposal are: (a) Seamless management of valid time defined at different levels of granularity or with indeterminacy. (b) Management of uncertainty due to different granularities/indeterminacies of valid times in temporal relationships. (c) Modeling complex temporal clinical information. At a formal level the system is based on a three-valued logic which extends Kleene's [18]. Basic classes for instants and durations allow to define classes intervals and several methods are defined to deal with them. Due to the consideration of extra concepts like granularity and indeterminacy the operations defined over intervals are a superclass of those in the Hamblin's-Allen's framework. GCH-OSQL and GCH-OODM have been used in the definition and development of a clinical database, containing data coming from patients who underwent a coronary-artery angioplasty. The system is capable of handling complex queries like "retrieve the name of all the patients that, after having had normal values of blood pressure (DBP values between 100 and 60 and SBP between 150 and 100) for three weeks and more, suffered from angina, followed by PTCA intervention in 36 months. Only the period starting from Winter, 1988 must be considered".

For the case of modelling medical trials in pharmaco-economics [58] proposed a more radical departure from the relational paradigm for databases including an object-oriented database system where time is considered as one of the basic components. Some issues addressed in this proposal are branching time, granularity and temporal indeterminacy. This proposal was related to the *Tigukat* object model, [59] which aimed to accommodate multiple applications that have different type semantics requiring various notions of time.

The *Tzolkin* system [60], aimed at integrating a general method for temporal-data maintenance with a general method for temporal reasoning capable to allow: (1) the expression of abstract, time-oriented queries, (2) the retrieval of data that satisfy a given set of time-oriented data-selection criteria, and (3) presentation of the retrieved data at the appropriate level of abstraction. This proposal aimed to increase reusability and for that the authors proposed a so called *temporal-database mediator.* A key issue on achieving a higher degree of reusability was the distinction between task-specific knowledge (how to solve a generic temporal reasoning problem) and domain-specific knowledge (e.g. how to infer a particular time-sensitive situation in medicine). The underlying representation for data is the Historical Database model [61] and other related systems connected with its functionality are *Chronus* [56] and *Résumé* [62].

The capability of providing a high level view of that data by means of abstractions is a valuable step in recovering and processing data depicting the evolution of a patient. By abstraction we refer to summarization of patient data. Clinicians and care providers in general need to know that some symptoms were recurrent with some particular temporal pattern in some specific context in order to diagnose correctly instead of having the rough data that, after possibly long consideration, would lead to the discovery of such condition. The reader may find in the literature quite a few terms related to this activity, e.g. *Data Analysis*, *Temporal Abstraction* or *Data Interpretation*. Also more general terms denoting areas of Computer Science related to discovery and learning, e.g. data mining, may be included as well. Many systems were proposed to provide different levels of abstraction capabilities for time related information. They extended the first attempts for providing time-aware databases by providing not just retrieval capabilities but also temporal reasoning and other processes that allowed to gather several pieces of data in the form of trends and high level descriptions of complex conditions. As an example of one of the earliest systems on this line we can consider the one reported in [63], which provides alternative criteria that an expert system can use in order to detect clinically relevant temporal changes in insulin therapy from diabetes patient data.

Two different object-oriented systems called *Temporal Network (TNET)* and *Extended Temporal Network (ETNET)* [64], extensions of *ONCOCIN* [65], were used in the oncology domain to provide chemotherapy advice based on context-sensitive temporal reasoning based on relative temporal references as opposed to those using specific dates. The basic difference between these two architectures is that while TNET is more like a traditional database, ETNET have a dynamic set of rules that can be used according to the context, a similar approach to what nowadays is known as active databases [66—68]. *T-Query* [69] was the TNET/ETNET query language. A further evolution of ETNET was *TOPAZ* [70,71] where pair-wise differences among patient observations, population-based predictions and patient-based predictions are used to generate meaningful temporal abstractions.

One of the most comprehensive proposals perhaps being the *K* nowledge-Based Temporal-Abstraction method [62] and much of the exposition that follows is based on the research related to this project. Usually the process of time-related data abstraction is divided in the following stages. First the raw data is filtered, then some abstract episodes are identified from the data available and finally by interpreting these episodes at higher level some of the patient's original data regarding some particular aspect of her/his evolution can be summarized as synthetic knowledge. The importance of the task and the problems likely to be faced in the attempt were clearly summarized in [72]:

Intelligent Data Analysis (IDA) refers to all methods that are devoted to support the transformation of data into information exploiting the knowledge available on the domain. In bio-medical data analysis IDA may play a crucial role, since the "value" of each datum may be higher than in other contexts: experiments can be costly, due to personnel and instrumentation involvement and/or to the patients discomfort; the data set can be small, reporting non-reproducible situations. Nevertheless, the data may also be affected by several sources of uncertainty, from measurements errors to missing data, or from data coding errors to information buried into textual reports.

One system that is focused on this kind of service is Résumé [73,74] where several subtasks are considered:

(1) *Temporal-context restriction*: different contexts require different assumptions, different information and can guide significantly the inferential procedure, e.g. reasoning about intensive care demands different level of assurance than in a routinely consultation visit.
(2) *vertical temporal inference*: obtaining higher level information about an episode based on more specific data obtained from the patient. For example, from separate vital signs sensing it can be inferred that the patient is in a particular stage of a disease.
(3) *Horizontal temporal inference*: provides sound simplification of information referring to the same fact in a complementary way. For example, coalescing two consecutive measurements

readings or two consistent pieces of information coming from different sources.

(4) *Temporal interpolation*: bridges the gap between non-contiguous, but related, pieces of information like two registered periods of the same illness that commonsense will dictate are in fact the extremes of a continuum process. This task is more involved in the sense that demands more hypothetical and inferential work for each step.

(5) *Temporal-pattern matching*: allows the detection of a higher level condition based on other data previously discovered or inferred.

Temporal interpolation is a complex subtask by which a new temporal instance is obtained from other two, obtaining for example an interval-based temporal reference from two point-based ones. The procedure can also be applied to interpolate a point and an interval or two intervals. In these two later cases a discrete notion of compatibility is associated, ranking the operation and having then an effect on the kind of inferences allowed over that abstraction.

The possibility of association is a very context-dependent one as for example, two weeks of pregnancy separated by two years cannot be joined but two weeks within the same month are compatible and, given some other constraints like age, may be joined. Certainly contexts are also given relevance in Résumé as explained in [75]. In fact in that system an ontology of *interpretation contexts* is considered as a hierarchical arrangement where each instant of a context can be associated to an interval where it is active. Many aspects of the process being evaluated can change the context of reasoning, say by turning a previous context into a more specific one. For example, in an intensive care unit, a vital sign approaching a critical threshold can trigger a special protocol of operation. These contexts are not considered necessarily as disjunctive, they can be also combined. Contexts are not only useful for more accurate and realistic inference but also allow consideration of a wide range of situations as the intervals over which they have an effect can relate with each other in, for example, all the different ways two intervals can in Hamblin-Allen's sense [21,14]. Although illustrations of *Résumé* are usually made by referring to its applications on the diabetes therapy domain, the proposal is presented as a general problem-solving technique.

An interesting alternative to the *Résumé* approach on temporal abstraction on time sequences of clinical data is presented in [76] based on an integration of the deductive and object-oriented approaches for clinical databases. The deductive system, more specifically the event calculus [39], is used as a formalism where to specify the temporal ontology, to perform temporal reasoning, and to provide users with a query language. The object-oriented approach, more specifically OODAPLEX [77], provides a versatile and efficient methodologies and tools for data modeling, design and implementation of prototypes. The following issues were considered in the design of the conceptual model: modeling time sequences, modeling the well-known basic abstractions (e.g. increase, decrease and stationary), modeling complex abstractions (obtained by composing abstractions through temporal operators). Although the system was initially designed for its use in cardiology it is also general and extensible. The two major outcomes of the system in terms of clinical decision-making support are: (a) aggregation and abstraction of large amounts of stored data with identification of significant features for each patient, and (b) evaluation of specific relations between clinical findings and trends of numeric parameters on the whole patient database or on selected subgroups of patients.

There are plenty of other interesting issues to consider and contexts that may turn the task of intelligent temporal data analysis difficult. Due to space limitations we just name a few of them below. Applications of these techniques considering both historical and real-time data are considered in [78] for general domains and illustrated over data related to central venous pressure. *RASTA* (RASTA: A System for Temporal Abstraction) [79] enhances *Résumé* with distributed capabilities for problem solving in order to scale-up the system to more complex scenarios. Sometimes data in clinical domains can be vague and imprecise and that includes the time were some critical events happened, e.g. symptoms occurrence. Specially tailored techniques like those presented in [80] to approximate data by using fuzzy categories and applied to anaesthesia monitoring are then meaningful. Some abstraction techniques are better tailored towards a specific area in Medicine. For example, in [81] an application of intelligent data analysis is reported over the Diabetes Mellitus domain. The reader may find in [82] a description of other techniques and applications that however are rather out of date by now, but may offer a good survey of the basic techniques, aims and potential benefits from the area. A more up to date and very comprehensive account on the field is given in [83].

Early developments soon recognized the value of being able to retrieve time-related data and to present the results in a more comprehensible way. For example, in [84] a system based on a temporal structure called *time-line* and a set of related operations to recover and visualize information from different perspectives is presented. At that stage was also recognized the importance of having a flexible system to handle temporal granularity issues, as different events usually have different levels of granularity where they most usually occur. Some of them may correspond with calendar units, some may not. More recently, many other systems with interfaces tailored for medical applications. In [85], a system to record and visualize medical records is presented. Line color and thickness illustrate relationships or significance of the concepts being visualized and rescaling tools and filters allow users to focus on part of the information. The *KNAVE* (KNowledge-based of Abstractions for Visualization and Exploration) system [86], related to the previously mentioned system *Tzolkin*, is a proposal focused on a general knowledge-based framework for interactive visualization, navigation, and browsing of time-oriented data, including visualization capabilities at different levels of temporal abstractions. Semantic-navigation operators allow the user visual navigation through the domain-specific temporal-abstraction (sub) ontologies, thereby leading to reciprocal visual navigation through the multiple levels of temporal abstractions of the particular time-oriented database that is queried. Within the medical domain it has been applied to a series of different areas like guideline-based medical care, monitoring of children's growth and therapy of diabetes. The system *Asbru*, designed for therapy planning and to be considered in a later section, has a special interface, called *AsbruView* [87], to visualize how plans are structured using 3D visualization perspective with a rich repertoire of symbols. Also a 2D view is possible for more detailed and time-specific information about the evolution of a plan in relation to time, these includes qualitative relations called sequential, parallel, some-together, all-any-order, some-any-order and cyclical to describe the different plan types Asbru can handle. Other specific details are also considered like visualizing minimum and maximum constraints to starting and ending of intervals or closed and open interval limits [88]. The metaphors exploited in the proposed visual vocabularies are based on real-world and concrete objects. The visual vocabulary is related to Allen's Interval Algebra and found to be representative of the interval algebra subset termed *conceptual neighborhood* in [33]. A method for mapping queries composed by the visual vocabularies into SQL queries is discussed. A visual temporal pattern specified by the user represents a query on a temporal database which is internally translated as an SQL query. Finally two examples of lately developed systems which offers different approaches to the visualization of time-related information. LinkVis [89], is designed to alleviate the task of tracking and comparing psychotherapeutic processes by using three different visualization techniques: scatterplots, Chernoff faces, and parallel coordinates. LinkVis has been applied to Cognitive Behavioral Therapy treating anorexic patients. Interactive Parallel Bar Charts (IPBC) [90] embeds an approach for visual data mining on temporal data. The system is illustrated on its application to management of hemodialysis. The approach is based on the integration of 3D and 2D information visualization techniques to better visualize collection of time series.

4.2. Time granularity

As mentioned in a previous section the concept of granularity (see [91] for an early landmark in the area and [92] for a more recent account illustrated by applications to different areas like temporal databases, AI and data mining) is ubiquitous to any temporal system and decisions taken at such level will affect the functioning of the system. Basically dealing with granularity is about providing ways to safely convert temporal references in provided in different units, e.g. from hours to minutes or from the Gregorian calendar to the Islamic or Chinese calendars.

Using different time units is regular practice in medicine. Either in management, diagnosis, prognosis or treatment, there is always a need to relate processes that develop at a given granularity to those that may happen at a different one. For example a visualization system in a system may allow in a hospital to track the different events associated with a patient during a certain period of time. If the patient has been for, lets say, a month it is probable the patient went through different stages since first diagnosed until the final stages of her/his stay. Views of his evolution throughout one month may focus on the most relevant aspects, like diagnosis, prescription and evolution. A view focused on the activities and significant events of a particular day may focused instead on the patients' response to specific drugs and the results on specific analysis.

On a different kind of application for the concept, sometimes symptoms are identified if a given pattern has been occurring each day for a week or so. Other times an occurring pattern that was present during weeks can be associated to a season, e.g. when diagnosing hay fever. As it can be seen, the problem of handling granularity flexibly and effectively in medicine is more than calendric-related unit conversion.

Although granularity is concerned with decisions taken at the temporal structure level, it will also be reflected in the reasoning mechanisms. Just to mention a simple example, it can be inferred that fever was present as a symptom one day of the week if we previously knew it was present during the whole week but sound inference cannot be drawn the other way round. Hence, a system allowing different level of granularities must supplement that with an accordingly granularity-sensitive inferential system.

Allowing different levels of granularity can also have a computational effect that has to be balanced. On one side some resources should be focused on doing all the granularity-related inferences and that may introduce further computational complexity to the system. On the other hand, all that work can be compensated by the system being able to focus the inferential activities at a more abstract or higher level of granularity. Guiding the inferences by using structured knowledge may bring important computational savings.

In [93], an integral proposal for the handling of time granularity in medicine-related systems is given. Time-objects are the concepts that have a time-related existence in the system. Time-objects can be related either by temporal, structural and causal relationships. Temporal references can be either point-based, that will be assumed as atomic at a given granularity level, or with duration, that can be further decomposable. Different relationships are defined for these two classes. Another distinction made in this proposal is that one of generic and case-specific time-related knowledge which become useful when distinguishing therapeutic guidelines from patient histories. Occurrences in this framework are expressed relative to a conceptual level associated with a particular granularity. Along with the time-objects centered issues of granularity a set of related functions is provided to achieve different higher level tasks like detecting conflicts, clipping or mapping occurrences from one level of granularity to another. The possible applications of the system is illustrated trough the consideration of a scenario of normal evolution of the ossification of cervical spine.

A more recent contribution [94] provides support for granularity handling of both anchored and unanchored temporal references. The proposal is illustrated within the context of diagnosing and monitoring of patients with unstable angina in the broader context of cardiology but it is clear that the kind of temporal information they handle with their proposal is useful in many different scenarios within medical applications. The proposal focuses on providing the basis for a Databases Management System capable to support the following basic activities: (a) representing and storing time instants with different granularities and time spans with different and mixed granularities, (b) handling granularity mismatches in operations between temporal primitives with different granularities (c) converting a temporal primitive from one granularity to another, and (d) considering different interpretations for time labels.

A complementary problem to the adequate handling of granularity was considered in [95]: *temporal mismatches*. Two main sources of information mismatch are identified: *R* epresentational Heterogeneity (the handling of equivalent time values represented differently), e.g. temporal metrics, time-stamp names, and time-stamp structure, and *Semantic Heterogeneity* (handling information that is related in meaning but not equivalent in values), e.g. time-stamp method, time-unit representation, temporal coding, and temporal dimension. A model of time based on a timeline and a set of 12 mapping operators (time-unit validate, time-unit merge, event decode, event duplicate, event restamp, event validate, event conversion, state decode, state duplicate, state restamp, state validate and state conversion) are used to transform information and reduce data heterogeneity in a temporal database.

Important connections can be drawn between granularity and temporal information indeterminacy (partial ignorance on when the information happened). For example, knowing some information related to the evolution of a disease during one particular day does not necessarily mean we know the information at finer levels of granularity like the different parts of the day down/morning/afternoon/evening. See for example [96] for a detailed account. Some works addressed specifically this issue in connection with medical contexts. In [97], a system called *HMAP* is presented as a formal framework which is based in a three-valued logic to handle uncertainty in temporal relationships. The medical scenario is the handling of patient's clinical histories as part of the management of strokes. Some characteristics of the resulting system are: (a) the definition of a temporal data model adopting an interval based logic to manage temporal information at different and mixed levels of granularity or with explicit indeterminacy, and (b) the extension of representation capabilities for intervals. Another proposal, [98], uses a Metric and Layered Temporal Logic as the formal framework in which to deal effectively and flexibly with granularity issues in different medical domains. This work is circumscribed to Gregorian-like calendars, an adequate context for many interesting medical applications.

The proposal is illustrated in the context of therapy plans based on chemotherapy for oncological patients where each plan acts as a specific calendar related to the evolution of the patient.

Meanwhile interesting contributions has been provided from AI and Databases in relation with granularity handling. For example, [99] is centered in a flexible language and a formalization that allows the characterization of temporal objects capable to encompass notions of structured temporal references, e.g. calendars, provided they have a finite number of nested structures. Some concepts of this proposal have been already connected with medical scenarios [100]. Some previous versions of these contributions to the topic have been compared before however it would be an interesting step to have an up to date comparison in terms of flexibility to create new temporal references and in terms of the computational cost needed, both important factors for the successful application of these technologies in medical applications.

Up to now we have considered work which offer valuable support to decision making in medicine. The next three sections will focus on other fundamental applications of temporal reasoning, in the sense that they are more closely linked to the basic steps of diagnosis, prognosis and therapy planning.

4.3. Diagnosis

Diagnosis can be defined as *the determination of the nature of a case of disease* and, as pointed out in [101], there is a rich range of temporal references in the description of symptoms which may be presented associated to explicit time references (e.g. last Tuesday) and sometimes as a collection of inter-related events without explicit mention to time (e.g. "first I felt sick and after that I have severe headache and rush in my stomach"). Usually the degree of uncertainty can be high as precisely when or in which order some of them occurred, e.g. at some moment during the night. Sometimes broad temporal references, e.g. "seasons" or "weekends", may not be very frequent in the technical literature of the associated technologies, e.g. databases. All these features posses interesting challenges for the research in AI and MI. The remaining of this section will focus on what have been done in the area in a broad sense while more specific issues like the relation between granularity and uncertainty are considered in Section 4.2.

Diagnosis has been also an active area in artificial intelligence where the interest were focused on finding explanation for behavior anomalies in different artifacts. Some landmarks coming from that effort are [102—104] while other early contributions which are more relevant to temporal reasoning in medicine are [105] and [106].

A good concise account of model-based proposals for diagnosis in AI and medicine is offered in [107]. There, the importance of considering the evolution of some patient-related indicators over time, e.g. levels of substances in blood, is recognized as one of the important aspects of diagnosis that realistic systems should address.

One of the early proposals on time-related diagnosis was the *RX* project [108], which aimed at extracting knowledge from databases hypothesis to be used as knowledge-based advice-giving systems. A special achievement of this project which is of interest from the temporal perspective was its capability to learn new causal relationships from temporal clinical databases (e.g. the *ARAMIS* database) and the possibility to validate them in retrospective experiments before inserting them as validated hypothesis into the knowledge base. Events observed in the clinical data are recorded into the internal database as interval-based temporal information.

In [109], a system called Heart Disease Program (HDP) is extended with temporal reasoning capabilities to enhance the diagnosis accuracy by taking advantage of the time constraints inherent to cardiovascular-related reasoning. The use of Bayesian probabilistic networks is used to represent time durations of cause and effects associated with heart diseases diagnosis. For example, to differentiate the cases in which a heart attack occurred before or after the last 4 h as the procedures to follow in each case differ.

Another work focused on causality issues applied to medical diagnosis was reported in [110]. There an interval-based algebra is used to model possible qualitative relationships of symptoms for Hepatitis B. First-Order logic with special dedicated predicates for interval-based time references is used to model the causal relations of the described disease. For example for the case of Hepatitis B, four rules are used to link the description of causes with the temporal relationships that should hold for the effects and for the relations between the effects and the causes. Other rules focus on how the possible patterns of occurrence relate to each other, which is useful for example, if we want to express that all possible forms of manifestation are mutually exclusive. In this approach abnormal observations are explained abductively, and it is required that an explanation is consistent with both normal and abnormal observations. An important feature in this proposal is that they provide abstraction mechanisms that may increase significantly the efficiency of the system depending on the nature of the input data. A contemporary development [111] presents a theory of diagnosis which allows one to complement causal associations with time intervals to denote the durations associated with the manifestations observed. This in turns allow this causal associations to be related by a precedence order between them. The causal relationships are represented by a directed acyclic graph, i.e. without recurring events. Links between two neighbor manifestations do not made explicit how much time elapsed between them, instead each node *n* of the graph will have a set of functions associated which will define for how long each manifestation lasted and also what is the temporal distance between the manifestations represented in *n* and the other manifestations represented in the nodes *n* is linked to. Another interesting feature of the proposal is that both necessary and possible causal connections between disorders and manifestations can be represented. The proposal is exemplified with its application to the food-born disease domain.

Knowledge updates are inevitable if a system is aiming to keep a precise account of a patient's state. Temporal Control Structure (*TCS*) is presented in [112] to supports reasoning with data changing over time. A key aspect in this proposal is the notion of *hindsight*, i.e. the use of newly available information to revise decisions made earlier. The domain of application is cardiology and a typical scenario is described where, as a result of a misleading initial diagnosis, a patient is given a medication designed to overcome the symptoms but as the expected effects are not achieved over time, the validity of the data used for the initial diagnosis and their evaluation is re-examined.

Lack of precision of the information is also present in medical contexts as not always the temporal references are precise enough as demanded. Fuzzy sets theory is used in [113] to model the lack of precision on the temporal occurrence of symptoms, e.g. started around midday, or adjectives used on their description, e.g. intense, in order to match a set of observations developing in time with a disorder model. The proposal is illustrated to diagnose intoxication by ingestion of poisonous mushrooms cases.

Déjá Vu [114] provides scenario recognition facilities during a patient's examination so that when a session is in progress, it can be related to the expected structure of the process. This capability allows anticipating events and detecting possible deviations so that the appropriate actions can be taken to prevent any undesirable condition. Sessions are modeled by using *Constraint Satisfaction Networks* [115] and the task is reduced to comparing two networks: the general description of the process, called "a scenario", and the one describing a session, i.e. the proposed particular instance of the general process. Other standard techniques from graph theory are used as the basis for graph comparison. The system is based on a temporal representation of the sessions that may have precise and imprecise temporal information. Recognitions can be done in two modalities: *on the fly* or a posteriori. The proposal is illustrated on the authors' experience with a simplified ventilation management unit (see [116] for an early system devoted to this domain).

Trend detection is an important feature of time-evolving systems. *TrendDx* [117] is a general trend diagnosis system but specific prototypes have been built to study pediatric growth disorders and hemodynamics. It diagnoses trends by matching patient data to patterns of normal and abnormal trends called 'trend templates'. These patterns consist of a partially ordered set of temporal intervals with uncertain endpoints. Bound to each temporal interval are value constraints on real-valued functions of measurable parameters. The temporal uncertainty in trend templates requires the system to consider alternate temporal worlds in monitoring patient data. The number of possible worlds can grow polynomially in the number of time slices of data. To manage the competing temporal worlds, TrenDx employs special techniques and temporal granularity in the trend template definitions. The system will match trend templates to trend-related observations and using a temporal consistency criteria relativized by one of the possible contexts of interpretation will determine if the observations match a particular generic trend. A component of uncertainty is considered on the temporal occurrence so a relative accuracy criterion is used to discriminate between competing trends.

Temporal reasoning can be used for on-line monitoring and detecting trends of behaviour, in this case applied to an intensive care unit [118]. There a system is proposed as an intelligent alarm system. Evolution trends of the data being monitored, e.g. blood pressure, are classified into nine possible temporal shapes: "steady", "increasing", "decreasing", "positive step", negative step", "positive step + slope", "negative step + slope", "concave transient", and "convex transient". These are in turn broadly grouped into three major cases: "steady", "decreasing" or "increasing", in a spirit close to Résumé's trends detection. According to the trends detected and the type of information that is being monitored the system will provide real-time detection of potentially dangerous developments.

Another approach to patterns of evolution abstraction is offered in [119]. A research project that explores the definition of methods and tools for the assessment of clinical performance of a hemodialysis service is summarized. One of the main time-related tasks developed in the system is detection of temporal patterns. Basic and complex temporal abstractions are considered. By *basic* temporal abstractions it is meant numeric or symbolic unidimensional time series while *complex* temporal abstractions refers to specific temporal relationships between basic temporal abstractions, in Hamblin's [21]—Allen's [14] sense.

Related to systems based on temporal abstraction techniques is *Idan* [120], a distributed temporal-abstraction ''mediator'' for medical databases which can answer abstract, time-oriented queries by adequately handling the queries to the various key modules in a distributed system. An added feature to previous similar approaches like *RASTA* and *Chronus* is that Idan is capable to handle temporal constraints in a uniform way between the system level and the interface level.

4.4. Prognosis

By *prognosis* we refer to those activities related to the forecasting of the probable evolution and outcome of a disease. Clearly the benefit obtained is that by this means it may be possible to anticipate important events and hence to avoid undesirable situations as well as increasing the chances of success of different health care-related tasks. For example, if a patient is being treated we can use the information obtained at this stage to ensure that the drugs, equipment and personnel s/he needs will be available at the time they are required. It has not been until relatively recently that research on this subject started to emerge as a special area of consideration. Prognosis-oriented activities can be inter-related with either the diagnosis or the therapy stages. However the difficulties offered by the subject and the importance of this step to potentiate the value of the knowledge gathered during diagnosis and to influence positively the following steps during treatment, makes it worth considering on its own.

An important step given in this direction was the work presented at a workshop dedicated to prognosis in medicine [121], which later on gave place to a special issue on the topic [122]. Some of these proposals considered time as a important factor in the prognostic task. These works resort to some frameworks suited for reasoning under uncertainty, like statistics, evidence theory, naive Bayes classifier, genetic algorithms, case based reasoning and fuzzy logic to formulate predictive models about specific diseases and conditions (cardiovascular risk, breast cancer, colorectal cancer, hip arthroplasty, acute trauma, intensive care, diabetes and anaesthetics). Although all of these models are considering the trends that some processes are expected to develop in time, hardly any of them considers time explicitly. The more explicit of the articles in the above mentioned special issue regarding the temporal dimension is [123] where a prognostic model is offered that focuses on predicting the long-term outcome after femoral neck fracture with implantation of hip endoprostheses. Domain knowledge is encoded as a hierarchical decision model which mixes inferred knowledge with experts provided knowledge. As there is strong evidence suggesting that the patient's condition stabilizes after approximately one year, the system has to be aware of the development of the patient's condition through time in order to predict the continuation of that condition beyond that period. Other proposal which is based on handling of uncertainty is the work developed on Dynamic Network Models (DNM) [124] to diagnose apnea using a synthesis of Bayesian Belief Networks and time-series models. One characteristic of DNMs is that, by exploiting causal dependency between variables, they can dynamically adjust their inferences at different times in which observations are made. Prediction models are built for chest volume, heart rate and oxygen saturation levels, important indicators in the process to predict sleep apnea. Another system using uncertainty representation and reasoning is *DiaMon-1* [125] which uses fuzzy sets theory for trend detection, also tracking of disease histories, by interpreting data from an on-line monitored case in critical care.

Between the latest contributions in the field we can consider the following two works reported in a prominent conference in the field. *TeCoMed* [126] is a prognostic system designed to anticipate epidemics of influenza. Temporal abstraction techniques are combined with case-based reasoning to match the current pattern of evolution with previous patterns where early warnings were successful. The *NEONATE* project [127] uses sub-optimal decision procedures to alert clinical and nursing staff about potentially concerning situations in a neonatal intensive care unit.

Many contributions to the general field of AI can be identified with the task of prognosis; however, there the concept is most usually referred with the label of ''temporal projection'' (see for example [128] for an important landmark and [5] for a more recent account). It is expected that as a longer-term interaction between the fields develops, these two approaches will be better integrated and the benefits of the mutual experiences will lead to a fully exploitation of the potential that explicit temporal reasoning can bring to prognosis.

4.5. Therapy/treatment

Therapy can be defined as *the treatment of a disease* and also refers to predefined general courses of action to be applied to a patient on the process of treating a disease. Even when having a general pattern to be followed, there are many possibilities and combinations of events that can occur and the possible plans, or variations, to be followed are greater than expected. However planning in advance may help to identify possible unforeseen courses of development.

From the AI perspective planning can be defined generally as devising the course of action to be taken towards achieving a goal. Part of the classical approach to planning in AI will include considering: (i) a description of the world as it is at the moment of the plan being applied, (ii) a description of the available actions as well as the conditions in which they can be applied and the effects they would provoke in the world once applied, (iii) a goal to be achieved. The description of the world may also include the resources available as they can play a decisive role in a realistic plan.

Time in the context of therapy planning can be of paramount importance. The community has been working actively on this area, see for example a good summary in [129]. Work in the area has been usually organized around the concepts of the so-called *care-protocols* or *clinical guidelines* that are specialized to particular domains and can be instantiated accordingly to the context. These descriptions may involve description of actions to be applied, resources needed, activities, intentions, roles, and more. Some of this work has already addressed the importance of time as one of the important resources to be considered in therapy planning. The following ones are some of the main related proposals made in the last decade following their order of development.

For example *TraumaTIQ*, [130] and [131], a real-time critiquing interface, that allows one to improve plans given a problem scenario, for trauma care considered the importance of planning ahead the availability of critical resources and preventing staff to carry out wrong actions when the context changes.

The work presented in [132] focuses on the use of dynamic decision problems using *Influence Views* [133] a graphical framework based on Markov Decision Processes [134], in order to solve decision problems in which the optimal choice has to be revised periodically in accordance to the evolution of the patient's conditions. The proposed methodology is applied to the plan of the prophylaxis in patients affected by a Hereditary Spherocytosis (a production of red blood cells with membrane dysfunction).

An interesting combination of temporal reasoning capabilities have been already incorporated in the *Asgaard* project [135,136]. On a broad scale this work considered two different levels of time: *design time*, encompassing tasks such as plan generation, plan verification and plan validation, and *execution time*, including tasks such as plan selection, plan adaptation and plan execution. On a more specific level, the language *Asbru* which is used as the basis for the planning process incorporates a variety of temporal features. For example, it supports the use of different granularities and reference points to represent multiple time lines. Considers durative actions, and time associated to events, actions, plans and world states with uncertainty in their appearances. Asbru also provides some general temporal relations between sub-plans like "do-some-any-order", "do-some-together". It is also worth to be emphasized that a distinctive feature of the *Asgaard* project is that they explicitly aim at providing a framework where diagnosis and treatment are linked [137].

In [138], a mixed-initiative approach is described that allows user and system to interact to solve typical problems in clinical management as conflicting resources and change of constraints over time. The medical domain is characterized in this proposal as a constraint satisfaction problem [139]. A central hypothesis in this work is that the medical domain is over-constrained and as it usually may happen, constraints found in this area of application are usually opposed: e.g. patient's safety, staff satisfaction, use of limited places and material. The temporal representation of the scenario is made by using constraint networks corresponding to *Simple Temporal Problems* [115]. To resolve this tension on the system they classify constraints into *relaxable* and *n* on-relaxable. Non-relaxable constraints are explicitly visualized and the user is offered the possibility to interact with the system to solve particular critical conflicts, to do that the user can ask from the system descriptions of the causes for the conflicting resources and consult a solution repository to reorganize the protocol in a non-conflicting way.

Planning and scheduling patient's requests for examination tests minimizing patient's stay in hospital and maximizing laboratory resources utilization is considered from a planning perspective in

[140]. Sequential, parallel and periodic activities can be considered over shareable, non-shareable and consumable resources. The planning activities are carried out by the TRL-Planner and the temporal reasoning activities by one of its specialized modules, TRLi [141], that can consider properties and events associated to two basic temporal entities: points and intervals. The importance of temporal scheduling constraints for therapy management is also recognized in [142]. Here a method is proposed with the following characteristics: (1) it checks whether temporal scheduling constraints are consistent with scheduling constraints contained in a guideline (2) it provides suggestions for an equivalent but more explicit representation of non-minimal constraints (3) it can be used to assemble feasible time intervals for the execution of the prescribed activities. The language used to write the guidelines is *Asbru*. The implemented algorithms run in polynomial time.

Clinical Guidelines Knowledge Representation Manager (CG_KRM), see [143] and [144], also considers an interesting range of actions-centered concepts. They distinguish between *atomic* actions and *composite* actions. The qualitative relationships between these actions can be: sequential, concurrent and alternative (e.g. when if-then-else like decisions are made). Temporal reasoning is made more sophisticated for sequential actions by the introduction of boundaries for the time elapsed between the ending of an action and the next one in the sequence. Another useful temporal feature for the area of application is the possibility to express the frequency of actions to be repeated within a time window, useful for example when a drug has to be applied a given number of times within a definite period of time. The proposal is illustrated with an application to the scenario of a treatment applied to a patient with Non-Hodgkin lymphoma.

GUIDE project, a component-based multi-level architecture designed to integrate a formalized model of the medical knowledge contained in clinical guidelines and protocols. Quaglini et al. [145] gives details about a three layers, knowledge representation, model simulation and implementation, methodology within a health care organisation. An initial representation of the guideline (including the necessary human and technological resources) is translated into a high-level Petri net. This translation includes the use of time constraints to include in the model how long it may take for a task to be executed. The simulation allows to validate the careflow model and to suggest the optimal resource allocation before the careflow system is installed. For example simulation runs allow to detect if there will be times during which some resources will be at low or high demand and also time spent by patients in the different phases of their management. The proposal is illustrated with guidelines for the management of patients with acute ischemic stroke.

The *ATHENA Decision Support System* (*DSS*) is based on guidelines for hypertension using Stanford Medical Informatics' *EON* architecture [146]. ATHENA-DSS encourages blood pressure control and recommends guideline-concordant choice of drug therapy in relation to comorbid diseases. ATHENA-DSS has an easily modifiable knowledge base that specifies eligibility criteria, risk stratification, blood pressure targets, relevant comorbid diseases, guideline-recommended drug classes for patients with comorbid disease, preferred drugs within each drug class, and clinical messages. The DSS can generate a message to sequence addition of the drugs over time and to adjust the dose of each drug to avoid hypotension [147].

The Guideline Acquisition Representation and Execution (*GLARE*) system [148,149] is a domain-independent manager of clinical guidelines. The representation language allows the user to specify temporal constraints in several ways, particular attention was paid to the role of periodic events. Between the temporal concepts considered are: (a) the specification of temporal bounds on differences, e.g. the time between two successive intakes of a specific medicine should not exceed 8 h during the first two days of the treatment, (b) constraints between actions of a same plan, e.g. the intake of liquid has to precede a scanning, (c) constraints in different plans, e.g. the time schedule of the plan to prepare for endoscopy must be fully contained within the time schedule of surgery, and (d) constraints on repeated actions, e.g. a specific medicine has to be taken twice a day until body temperature returns to normal. Constraints are solved here as an instance of *Simple Temporal Problems* [115].

The clinical management of therapy's time-related information during long-term chronic diseases contains different temporal may contain information from many different sources and as such be incomplete and inconsistent. In [150], a domain-based temporal abstraction mechanism relying on a simple qualitative and heuristic approach to handle temporal indeterminacy on period bounds. Hamblin's [21]—Allen's [14] interval relationships are considered when some information is missing, in the sense of Freksa's [33] work, and according to the particular combination of "semi-intervals" being considered, concepts like uninterrupted continuation, possible disruption, possible simultaneousness are inferred. The algorithms are strongly influenced by heuristic knowledge obtained from the domain application in order to simplify the potential cases to be considered.

Although we focused on some of the latest developments, there is more interesting research aiming to provide time-related support in guidelines centered languages which is worth to look at. Other previous proposals with explicit inclusion of temporal constraints, are: the previously cited *Asbru* language, Sherman et al.'s proposal [151] based on the Arden syntax, DILEMMA [152] and its successor the PRESTIGE project [153], the GuideLine Interchange Format (GLIF) [154], and PROforma [155].

Despite the work that has been done in planning and in particular in the medicine-related applications, much progress has yet to be done in order to successfully incorporate this technique to the everyday process of medical care. Planning from an AI perspective [5] is a very hard problem, even over simple domains, in terms of the computational resources that demands. So the planning tasks are usually restricted to choosing or combining predefined plans (see for example [156] Chapter 5) and the exploration of planning in the broader sense of AI is still very little exercised. As medical procedures are continuously evolving by adapting existing treatments to new findings in the specific area or finding treatment procedures for new diseases, new problems will be added to the already existing ones. This will certainly promise to provide a rich source of challenges for the AI community.

5. Future work and proposed agenda

Although some advances have been made, it is clear that many things still can be done to make the human-machine collaboration even more successful than what have been up to now for this particular area of application. A simplified historical evolution of some of the systems and proposals reviewed is given in Table 1. A summary of the particular fields of medicine where time-related techniques have been applied to is provided in Table 2.

In the classical sequence of steps: diagnosis, prognosis and therapy planning, research into *prognosis*-related topics, still has not generated as much interest within the AI in Medicine research community as diagnosis and therapy planning did. Although some work has been done, see for example [157] for a system that uses the Cached Event Calculus [158] for patient classification, evolution assessment and therapy prescription in ventilation management for intensive-care units, still much can be investigated on the consideration of time-related concepts on using AI symbolic deductive approaches at this stage. It seems this step in the decision-making process deserves further consideration as it is a very important link between diagnosis and therapy as temporal knowledge gathered during diagnosis can be fruitfully exploited when forecasting the evolution of a patient. Equally useful would be to export these already foreseen outcomes to the therapy planning stage. Having this information at

Table 1 Some of the latest contributions to time-aware decision support systems

Year	*Diagnosis*	*Prognosis*	*Therapy/treatment*
1991	TNET/ETNET [64], Topaz [64], (Cousins et al.) [84]		
1992			T-Helper [55]
1993			
1994	Chronus [56]		TraumatIQ [130]
1995	Tigukat [59]	DNM [124]	DILEMA [152], (Sherman et al.) [151]
1996	TrendDx [117], HDP [109], Résumé [62]		EON [146] Prestige [153]
1997	t-PCT [111], (Gamper et al.) [110], (Goralwalla et al.) [58]		
1998	DejaVu [114]		CG-KRM [143], GLIF [154], PROFORMA [155], (Magni) [132]
1999	Tzolkin [60], (Wainer et al.) [113], (Lowe et al.) [80]		Abru-Asgaard [136]
2000	(Bellazzi et al.) [81]		Hostess [140], GUIDE [145], ATHENA-DSS [147], (Oddi et al.) [138], (Terenziani et al.) [144]
2001	RASTA [79]	(Zupan et al.) [123]	
2002			(Seyfang et al.) [137], (Duftschmid et al.) [142]
2003	*Idan* [120], (Bellazzi) [119], (Charbonnier) [118]	TeCoMed [126], NEONATE [127]	

Table 2 Some areas of medicine with time-related techniques mentioned in this article

Area of application	*Related work*
Acute ischemic stroke	[145]
Anaesthesia monitoring	[80]
Assessment of clinical performance of a hemodialysis service	[90,119]
Blood pressure	[147]
Clinical management	[138,140,150]
Diabetes therapy, diabetes mellitus domain	[63,74,81]
Epidemics prediction	[126]
Femoral neck fracture with implantation of hip endoprostheses	[123]
Food-related	[111,113]
Heart diseases diagnosis	[57,76,97,109,112]
Hepatitis B	[110]
Hereditary spherocytosis	[132]
HIV	[55]
Intensive care	[78,114,116,118,125,127,157]
Management of hyperbilirubinemia in the healthy term new-born	[137]
Medical trials in pharmaco-economics	[58]
Non-Hodgkin lymphoma	[144]
Oncology	[64,70,167]
Sleep apnea	[124]
Therapy management	[142]
Trauma care	[131]

the initial steps of the planning process can influence and focus it in many beneficial ways, for example providing valuable information for the initial steps and concentrating the resources on the most critical issues. For example, carrying patient centered information gathered during the different stages of diagnosis like allergic predispositions, can influence the kind of medications to choose from. Equally this information can influence the therapy planning stages as extra safety precautions may have to be taken in order to ensure allergic episodes caused by the administration of drugs. It could be argued that some prognosis activities are embedded in the therapy planning process but, as a planning task demands a great deal of computational efforts, this should not be the case. For example, as a result of the prognosis activities, planning can be discarded altogether. For example, some treatments have to be completely avoided as options to be considered if the patient is pregnant. If therapy planning can be provided by the system, then the prognosis stage, as a result of the interaction between the clinicians and the system, can deliver a better informed description about the initial assumptions, previous cases to consider, and the goals to be achieved.

Causality is a very important notion to AI and Medicine and certainly can be one of those concepts to be considered during prognosis. It is expected that recent proposals coming from AI to automate causality-based simulations, see for example [159], will allow to predict hidden effects in complex interactions.

Natural language is a very challenging area as a general problem in AI (for some time-related work consider for example [160—162]. Suitable restrictions given by the requirements of an area can turn the problem feasible at the time it retains its advantages, namely making the communication between humans and assistant machines more flexible, realistic and useful. Given some appropriate restrictions allowing computational tractability, it may turn into a very fertile area of research where temporal issues are very important. Although explicit references to events, states and processes are important to identify with precision significant developments in the evolution of a patient, also implicit temporal references to time-based activities should be considered (see [163] for an interesting related work). The latest ones are relevant, for example, for the relative order of tasks in a plan for which, before application, no particular date can be attached to and the relevant notions are order and duration of tasks.

Argumentation can be very useful as a way to structure different lines of reasoning and providing consequent explanations for each of the considered alternatives. Some work has been already done in relation to structuring explanations in medicine from an atemporal perspective [164]. Allowing these explanations to include the temporal hypothesis that underlies the reasoning tasks [165] to identify a disease or to support a therapy plan may be an important step towards making this explanations more precise and realistic. An interesting proposal has been made in [156] on this line. Still, a good deal of research and development is needed to successfully ground this proposals into real life use.

Active databases [66—68] are based in a set of rules, called ECA rules, that will apply some action when a given combination of events occurred under certain specific conditions. This kind of systems has been extensively explored in CS in relation with different contexts where they can be used for monitoring the occurrence of events and reacting in a context-sensitive way. Still little or almost no attention has been given to the topic in the literature on how artificial intelligence can contribute to make the detection of complex event detection [166] in medicine-centered contexts soundly and efficiently. This research into complex event specification and languages allowing flexible constructions on event-based references may be also a useful vehicle to characterize the specific patterns of evolution that are sought during intelligent data analysis, other stages of diagnosis or prognosis, as well as to specify goals and conditions during therapy planning. An interesting recent development, the *m* omentum system, is reported in [167]. It is a temporal mediator integrating temporal reasoning tasks with temporal maintenance tasks. A variation of an active database framework described as *active time-oriented database* is used. Although its use is illustrated in the oncology domain, it is a domain-independent system. Lately [168] another application has been reported as the underlying technology in a smart home which can increase living standards of elderly people with cognitive impairments while retaining their privacy. In this context a set of ECA rules allowing the specification of complex-events can be used to anticipate possible undesirable scenarios, specially related to safety issues, leading to preventive actions.

Finally, *verification and validation of protocols* (in the generic sense of the word that denotes a set of rules enabling communication between two or more entities) has been extensively studied in Computer Science [169,170]. Any specification of steps to be followed which can be specified in some formal notation can be analyzed to check if the possible models captured by the specification are the expected ones. Although it is not an application of temporal reasoning in the typical sense of the term from an AI perspective, it is certainly centered on reasoning about the possible evolutions in time of a system. However, verification in medical protocols has not yet received as much attention. An interesting development has been reported [142,171] in relation to protocol verification frameworks specifically related to the guidelines specification language *Abru*. Still it seems that much work should be done on this line. For example, it seems that no systematic work has been done on verification of dynamic behavioral properties, in the software engineering sense. However, because of the importance of the application area and the safety-critical character of the activities involved, verification and validation issues should be in the list of important projects of the area.

6. Conclusions

Research in the previous decades already identified several key issues and gave the important step of providing better access to time-oriented data in medicine. The field seems to have reached maturity as to allow other goals in relation with temporal reasoning as studied in the AI field.

On the other hand time has been also extensively considered as a general topic in AI for the past two decades. Research in temporal representation and reasoning also has their own well-established events (see for example, [1—4]. Although there is awareness throughout the research community that have actively participated in these events, still many developments have not been transferred/adapted from the more general field to the more specific one. Also the feedback from the more specialized field to the more general one is not either fluent or high in quantitative terms. It seems that an interesting topic for a future agenda would be to increase and foster this interaction as it certainly will be beneficial for both communities.

One step has been given in this article by summarizing previous contributions in the field and highlighting some possible continuations for the community to explore. Certainly, there is a valuable experience gained in the last decade both within the temporal reasoning and the MI communities in this interaction. This should provide a firm departing point for the next generation of intelligent and time-aware assistants in medicine.

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