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Temporal reasoning with medical data - A review with emphasis on medical natural language processing

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Abstract

Temporal information is crucial in electronic medical records and biomedical information systems. Processing temporal information in medical narrative data is a very challenging area. It lies at the intersection of temporal representation and reasoning (TRR) in artificial intelligence and medical natural language processing (MLP). Some fundamental concepts and important issues in relation to TRR have previously been discussed, mainly in the context of processing structured data in biomedical informatics; however, it is important that these concepts be reexamined in the context of processing narrative data using MLP. Theoretical and methodological TRR studies in biomedical informatics can be classified into three main categories: category 1 applies theories and models from temporal reasoning in AI; category 2 defines frameworks that meet needs from clinical applications; category 3 resolves issues such as temporal granularity and uncertainty.

Currently, most MLP systems are not designed with a formal representation of time, and their ability to reason about temporal relations among medical events is limited. Previous work in processing time with clinical narrative data includes processing time in clinical reports, modeling textual temporal expressions in clinical databases, processing time in clinical guidelines, and building time standards for data exchange and integration.

In addition to common problems in MLP, there are challenges specific to TRR in medical text, which occur at each level of linguistic structure and analysis. Despite advances in temporal reasoning in biomedical informatics, processing time in medical text deserves more attention. Besides the need for more research in temporal granularity, fuzzy time, temporal contradiction, intermittent events and uncertainty, broad areas for future research include enhancing functions of current MLP systems on processing temporal information, incorporating medical knowledge into temporal reasoning systems, resolving coreference, integrating narrative data with structured data and evaluating these systems.

Keywords

temporal representation; temporal reasoning; natural language processing; medical narrative data

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1. Introduction

Temporal information is crucial in electronic medical records (EMR) and biomedical information systems [1–7]. Healthcare providers normally record the progress of a disease or a hospital course chronologically in text, and procedures and laboratory tests are stored in databases with time-stamps. The EMR is only significant in a certain temporal context. Retrieval of information often relates to time; e.g. "what happened after that operation?" As a fundamental entity, time is intrinsically connected with many medical reasoning tasks. Automatically reasoning about temporal information can help us understand the dynamics of medical phenomena and may potentially improve the quality of patient care.

Temporal information processing in medicine is a task that draws from many fields, including philosophy, artificial intelligence (AI), database management, computational linguistics, and biomedical informatics. During the last two decades, researchers with different backgrounds, perspectives and objectives have attempted to bring together the fundamental methodologies and techniques from these disciplines to conduct research in this challenging area. Several review articles present detailed summarization and analysis of this area [1, 2, 4]. However, research efforts in temporal reasoning in biomedical informatics are predominantly in processing structured data [1, 2, 8], which is the focus of most of these previous review articles. Recently, Augusto [1] argued that in the medical domain, "Natural Language turns into a very fertile area of research where temporal issues are very important."

Nowadays, the most significant impact of computer technologies in medicine is in processing structured data [9]. In general, structured data is information presented in a standard, predictable form (e.g. defined data types and operations) that is easily processable by a machine. By contrast, unstructured data is information that does not have a data structure. Examples include free text, audio and video. The term "natural language" is used to distinguish languages for human general-purpose communication from computer languages (e.g. a programming language or a formal representation). In the medical domain, natural language commonly appears in patient charts, scientific literature, technical and administrative reports, emails, surveys, presentations, etc [10]. Natural language processing refers to any system that manipulates text or speech [11]. In this paper we focus on medical text processing along with associated applications, such as information extraction and retrieval, and we also limit our scope to the English language.

Processing time in medical text is a very challenging area, which lies at the intersection of temporal representation and reasoning (TRR) in AI and medical natural language processing (MLP). In addition to the general difficulties in TRR and MLP, there are many other critical issues that need to be deeply studied in order to handle such information. In natural language, times related to an event are not always stated explicitly. Interpreting this implicit information require complex linguistic analysis and domain knowledge. In addition, temporal expressions are diverse and often vague (e.g. "during that time", "recently") [8]. Another challenge is to determine whether two expressions refer to the same concept. For example, in the statement "The patient was in her usual state of good health one day prior to admission when she developed running nose, fever, cough and respiratory distress. Her symptoms worsened on the day of admission", "Her symptoms" refers to a set of manifestations underlined in the first sentence.

Although many fundamental concepts in relation to temporal reasoning have been extensively discussed in previous publications [1–4, 12, 13], they are inadequately addressed in the context of processing medical narrative data. Thus, this article first examines some of these concepts, specifically focusing on basic time-related notions, theories and models in AI, with emphasis on medical narrative data.

Then, we present a methodological overview of temporal reasoning in medical domain. One motivation is that we consider that these theoretical and methodological studies will in general contribute to processing time in medical text, either in the development of systems which make use of these methods, or in a future direction that integrates processed narrative data with structured data for higher level temporal reasoning tasks.

In the remaining sections, we emphasize NLP and processing temporal information in medical narrative data. We start with an overview of previous work on processing time in NLP in general. Then, we introduce several important studies on processing temporal information in medical text in the field of medical informatics. We provide a discussion of significant issues and challenges on handling temporal information. Finally, we conclude this article by pointing out several key areas for future research.

2. Revisiting Basic Concepts in Temporal Representation and Reasoning

Researchers have been puzzled by fundamental questions about the nature of time. Is time bounded or unbounded? Is it discrete or continuous? There are widely divergent answers for such questions, and thus it is quite difficult to give a clear definition of time. In the discipline of philosophy [14–16], there is a longstanding argument about whether time is a substance or an abstract concept. Modern philosophers in the past century debated the existence of past, presence and future. In physics [14, 15], time is regarded as one of the fundamental quantities (or dimensions) just like mass and length.

Even though time is hard to define or explain, human beings have no difficulty manipulating it in the real world. Psychologists and cognitive scientists [14] have found that time perception changes as the perceiver's environment or age changes. For example, time flies during enjoyable moments while time moves slowly during suffering. In addition, time appears to pass more quickly as the perceiver gets older. Therefore, the measure of time is often fuzzy since different people may judge identical lengths of time quite differently.

For computers, manipulating temporal data is not as easy as it is for humans. Enhancing their capability to process temporal information has been an active area of research. AI forms a vital branch of computer science, and temporal representation and reasoning (TRR) has been a subject of study in AI since 1970's. As a discipline that provides automated solutions to real life problems, studies in AI look for ways to represent and reason about time in an intelligent manner [12, 17–19].

There are two commonly recognized divisions [12] in TRR: reasoning about actions and changes, and reasoning about temporal constraints. The first category studies the changes of the world due to the occurrence of actions and/or events, and is concerned with predicting the future effects of events that occur (forward temporal projection) as well as with inferring explanations of a given situation in terms of possible causes (backward temporal projection). Situation Calculus [20, 21], Event Calculus [22] and Fluent Calculus [23] are perhaps the most influential formalisms in this category. The second category, reasoning about temporal constraints, is concerned with the handling of relations among temporal entities (e.g. points and intervals) for the purpose of performing tasks such as scheduling, planning and natural language processing. The various ways of representing time in this category can be further classified into three subcategories [17]: representation based on dating schemes, qualitative constraint representation, and duration-based representation.

Much of the work in temporal reasoning in medical informatics has used points anchored in absolute time [2, 7, 24–28]. The available data in such work consists of coded events with known times, such as visit information and laboratory test results. Qualitative constraints are usually based upon Allen's interval relationships [29]. In 1983, Allen introduced a set of 13 mutually exclusive binary relations between intervals, including before, meets, overlaps, starts, during, finishes, equals, and the inverses of these relations. He developed a constraint propagation algorithm that can represent any disjunction of these relations. Medical informatics researchers have applied intervals to the abstraction and query process [24, 30–33]. The best known formalisms in AI that address metric relations, which specify durations between pairs of time points, include Detcher, Meiri and Pearl's distance algebra [34] and Dean and McDermott's time map manager [35]. Some of these methods have been applied to the field of medical informatics [36–40], e.g. for the verification of temporal scheduling constraints within clinical guidelines. Each of these methods, however, varies in its expressive power as well as computational tractability. Expressibility and tractability of temporal formalisms tend to be inversely related. A method that achieves a suitable tradeoff will be useful for medical informatics applications.

In the following, we examine some basic concepts and important issues in the field of TRR. We also relate these issues closely to the fields of medical narrative data and natural language processing, which are the focus of this investigation.

2.1. The Categories of Time - How Should Diverse Temporal Expressions be Processed?

Each social culture and each scientific field has its own view on classifying time. A useful distinction was mentioned in [18, 41], where time was classified into three categories: 1) *natural time* is based on natural phenomena, such as the alternation of day and night, and the shift of the four seasons; 2) *conventional time* is based on the social conventions, usually represented by a set of general time-units such as seconds, minutes, hours, days and years, or by a set of special time-units such as epoch and fiscal year; 3) *Logical time* refers to the logical or mathematical structure of time and operations on time. In natural language, mixed use of these variant time-expression styles makes automatic processing of temporal information a difficult task. For example, in the statement "he had a surgery on Christmas

Eve, 2000", according to cultural convention, could span any period from the morning of December 24 through early morning of December 25, 2000.

2.2. The Structure of Time – Which Structure is Suitable for a System?

Intuitively, time is usually conceived as a *line* where events are aligned chronologically. *Branching time* is adopted when the future is uncertain: that is, when the future has several possibilities. In order to describe repetitive processes, *circular time* is often the choice. *Parallel time* is considered when handling time among different agents simultaneously. To process a medical narrative report, a system may consider a mixture of these structures to address different situations. For example, to represent the history of illness, we may prefer to use a linear structure, while to represent the future treatment plans, a branching structure may be applied to specify alternative ways of treatments. For repetitive symptoms or medications, like "Procardia XL 60 mg. po bid (two times per day)," circular time is a better choice. If the report also records the effect of a new medication by an automatic monitoring system and with the patients recording their symptoms and feelings, a parallel time may be selected.

2.3. Instant vs. Interval – Which is the Primitive Unit to Model Time?

Whether the temporal primitive unit should be an *instant* (also called a point) or *interval* (also called a period) has been a debated topic among researchers. Early representations of time make use of instant as a primitive unit, such as in McDermott's temporal logic [42, 43]. In this point of view, time points are the foundation of temporal reasoning and time intervals can be constructed out of the points. Allen [44] argued that the interval should be the only temporal primitive since an instant can be represented as a very short interval, and the interval more intuitively addresses issues such as temporal imprecision (e.g. much temporal information is relative but not absolute) and temporal uncertainty (e.g. incomplete knowledge about the relationship between two times). Later on, researchers [45–47] proposed using both instants and intervals with the same level of importance. Medical data include both of these two types. For example, some lab tests are carried out on a particular day and stored in a coded clinical database with timestamps, such as "01/31/2005". In contrast, medical problems and findings that are frequently recorded in textual data may have an associated duration, as in "fever lasted for three hours". Both instants and intervals have been considered in representing temporal information for medical information systems.

In general, a point-based representation is desirable if every event is assigned a date. Unfortunately, in real applications, many events cannot be assigned a precise date. In natural language, time references are rather relative and vague. In such cases, time intervals are convenient.

2.4. Absolute Time vs. Relative Time – Can Temporal References Always be Anchored in the Time Axis?

Temporal references that can be allocated in the temporal axis (e.g. February 26th, 2006) are called *anchored*, while those that cannot are called *unanchored* (e.g. "the rash began before admission"). Some literature refers to these as *absolute* and *relative* temporal references, respectively. An interval is often defined by modeling its endpoints. For example, an interval is an ordered pair of points where the second point is never before the first. In the medical domain, there are many cases where either the beginning or the ending is not directly known. For example, in “the medication is started on the day of discharge”, the exact time when the patient stops this medication is unknown. This phenomenon is also called the semi-interval problem in the literature [48].

2.5. Events, States, Actions and Processes

Time-related technical terms that frequently appear in the literature of this field are events, actions, states and processes [1, 18, 49]. These kinds of concepts are used in the computing field to describe things that take place and to embody changes in the world.

In the literature, changes in the world are usually represented using states and events. An object or a set of objects and their properties (such as size and temperature) define a *state* of the world. A given state of the world is changed by the occurrence of *events*. *Actions* are identified with the agents’ capabilities of interacting with the world. They are considered event-producers; however, events could be the by-product of other events. Allen and Ferguson [49] state that a temporal event “must involve at least one object over some stretch of time or involve at least one change of state.’ *Process* [50–52] denotes a sequence of events, that produces some outcomes. Most processes found in nature are recurrent or periodic: for example, “the patient has taken hydralazine for several weeks.” However, whether processes are as primitive as events and states for temporal reasoning is still in depute.

Sowa’s ontology rests on different assumptions [53]. He states that *processes* can be described by their starting and stopping points and by the kinds of changes that take place in between. The changes are either continuous or discrete. In a continuous process, which is the normal kind of physical process, incremental changes take place smoothly. In a discrete process, which is typical of computer programs or idealized approximations to physical processes, changes occur in discrete steps called *events*, which are interleaved with periods of inactivity called *states* (see Figure 1).

TimeML [54] is a markup language for events and temporal expressions in natural language. In TimeML, all time-oriented information is tagged as “events”. The authors consider “events” an umbrella term for situations that happen or occur. Events can be punctual or can last for a period of time. Furthermore, the authors argue that linguistic analysis can be used to classify events.

Questions may arise on how time-oriented medical records should be modeled. Combi and Shahar [2] distinguished two approaches in modeling temporal entities in medical applications. One is the addition of a temporal dimension to existing objects, particularly for the task of managing temporal clinical databases. One example is to add the temporal dimension at the level of a database tuple to facilitate clinical queries that have a temporal component [32]. Another approach is the creation of task-specific entities to meet the need of temporal reasoning tasks. For example, in the HyperLipid Advisory system [55], the temporal representation consists of two lower level objects: point events (e.g. visits) and interval events (e.g. therapies), and higher level abstract objects called phases (e.g. a diet or drug treatment) based on these two lower level objects. Consults were made by combining a rule base with a temporal representation of these objects. Similarly, for Shahar and Musen [56] the temporal abstraction task was defined in terms of inputs and outputs: the inputs include a set of time-stamped parameters (e.g. blood glucose value), events (e.g. insulin injection) and abstraction goals (e.g. therapy of patients who have insulin-dependent diabetes). The outputs include a set of interval-based, context-specific parameters and their values at a summarization level (e.g. a period of 5 weeks of grade III toxicity of the bone marrow in the context of therapy with AZT.).

To model temporal-oriented information in clinical reports, Hripcsak and colleagues [57] adopted a broad definition of medical events to include processes with a start and finish time (e.g. an operation), states over various periods (e.g. the presence of a rash), and instantaneous changes (e.g. death). All of these medical events were represented as intervals, and temporal assertions about events were represented as constraints. For example, in the statement "the rash began before admission," the *start* of rash is constrained by "before admission."

Intuitively, "her weight is 150 pounds" may be modeled as a state, "she had liver surgery" as an event, and "she took ampicillin 250mgs q.i.d. for five days" as a periodic event. However, weight fluctuates, there are many sub-events and states of the surgery event itself, and the repeat patterns of medication taking might not be easy to track (e.g. missing doses). Just as in defining "time," it is hard to give a clear definition for these time-related concepts or to differentiate them. While these concepts are widely discussed and agreement is reached to some extent, modeling temporally related knowledge is sometimes subject to different designs and various needs encountered in the building of a variety of medical systems. For processing time in medical text data, the first step may be to recognize and annotate time and medical situations mentioned in the original text, maybe along with identification and classification of these medical concepts. Afterwards, higher level temporal reasoning tasks such as temporal abstraction (or summarization) can be accomplished by combining medical domain knowledge and computing temporal models. Finally, synthetic knowledge can be used for real time clinical decision making.

3. Overview of Temporal Reasoning with Medical Data

During the last two decades, the literature on temporal reasoning in medical informatics has evolved from a few scattered, unrelated, application-specific accounts, to many articles addressing various topics, to several special journal issues dedicated to the topic [3, 5–7], to a major track in medical informatics conferences and workshops, and to a number of doctoral research theses [58–61] in biomedical informatics. Many studies demonstrate the interdisciplinary nature of this area by connecting technical methodologies with medical applications.

The field of temporal representation and temporal reasoning in medical informatics is thoroughly reviewed and various research directions have been well summarized and analyzed in a few review articles [1, 2, 62]. Combi and Shahar [2] suggested that time-oriented systems in medicine can be classified into two groups: one focuses on applications including different generic tasks (e.g. diagnosis) and clinical areas (e.g. cardiology), another focuses on theories and methodologies. They further reviewed the latter category and divided it into two classes: 1) temporal reasoning, which supports various inference tasks involving time-oriented data, such as planning and execution, and traditionally has been linked with the AI community, and 2) temporal data maintenance, which deals with storage and retrieval of data that may have heterogeneous temporal dimensions, and typically is associated with the temporal database community. In Augusto's review [1], he discussed issues about representing and retrieving time-oriented data and time granularity, and then provided a survey on time-based decision support for some of the fundamental stages related to patient care, namely, diagnosis, prognosis and treatment.

From another point of view, in the field of developing Medical Decision Support Systems (MDSSs), some researchers [58, 60, 63, 64] have suggested that temporal reasoning in MDSSs can be classified into two types: implicit time modeling and explicit time modeling. In implicit time modeling [64, 65], temporal concepts are treated by the MDSS inference mechanism in exactly the same manner as atemporal ones. For example, "significant weight loss during last year" is an example of an implicit temporal statement. By contrast, explicit time modeling [58, 60, 64, 65] has a model of time (e.g. a patient's life time is represented as a series of 1-month intervals) in which various factors are associated to the model of time (e.g. body weight in each 1-month interval). It also has a mechanism to use the association of entities to the time model to draw inferences (e.g. the significant weight loss during last year can be determined by examining the time series of body weight measurements).

A wide range of topics in the area of temporal reasoning in medicine have been recognized including: adoption of advanced data models, management of time-oriented clinical databases, temporal-pattern matching and temporal queries, abstraction and summarization of time-oriented medical data, management of temporal-reasoning knowledge (including knowledge acquisition, maintenance, sharing, and reuse), handling temporal granularity, handling fuzzy and uncertain temporal references, visualization interfaces and implementation of time-oriented medical information systems.

We review theoretical and methodological studies in biomedical informatics by classifying them into three main categories (see Table 1). These theories and methods, which have been predominately applied to structured medical data, can be applied to medical text. Furthermore, they will serve in a crucial role for the future of integrating processed narrative data with structured data. As shown in table 1, category 1 applies theories and models from the temporal reasoning in the AI field. Category 2 defines frameworks that satisfy needs from different clinical applications. Category 3 deals with universal issues such as temporal granularity and temporal uncertainty which should be addressed in Category 1 and 2.

Temporal reasoning is involved in a number of major medical reasoning tasks. Applications of temporal reasoning that support time-oriented decision making can be grouped into each one of these fundamental stages of patient care [1, 60]: 1) *Prevention*, which predicts risk factors using methods such as time series analysis [130, 131]; 2) *Diagnosis*, which discovers patterns of temporal evolution of diagnostic evidence [33, 36, 59, 67, 103, 128, 132–134]; 3) *Treatment*, which administers a therapeutic protocol (e.g. chemotherapy) over several predetermined periods [37, 135–137]; and 4) *Prognosis*, which forecasts the effects of health care on the problems of the patient over a period of time [71, 138–140]. Researchers have also summarized the field according to particular medical specialties to which time-related techniques have been applied: cardiology [141–149], oncology [150–152], psychiatry [153], intensive care [83, 139, 154–156], infectious disease [138], pediatrics [157], and diabetes [30, 105, 158, 159].

4. Processing Temporal Information in Clinical Narrative Data

Up to this point, our review has discussed the nature of time, basic issues on modeling time, and methods for time inference. Now, we focus upon the linguist's viewpoint. Representing and reasoning about temporal information in text has drawn increasing attention in the area of computational linguistics. The text corpus used by research groups in this area was usually outside of medicine (e.g. everyday English and news articles), so the adaptability of these systems to process temporal information in medical data has not been assessed. Nevertheless, the progress that has been made in this field is very valuable and worth delivering to MLP researchers. We organize this section as follows: First, we give a brief overview of previous work on processing temporal information in natural language in general, with a central focus on the field of computational linguistics. Second, we introduce and classify some important studies on processing time in medical text in the field of medical informatics. Third, we discuss critical concerns and challenges in the area. Our analysis associates the related work closely with the different levels of linguistic knowledge and their corresponding linguistic analyses.

4.1. Processing Time in Natural Language

4.1.1. Linguistic Knowledge and Linguistic Analysis—Linguists and computer scientists agree that in order to build a system that intelligently understands and thus is able to process human language, linguistic analysis must be broken into several levels. Figure 2 shows the different layers of linguistic knowledge and corresponding analyses that have been applied to NLP systems [160, 161]. As a result, most current NLP systems are designed with separate modules, with each module handling a different level of linguistic structures. The third column in Figure 2 discusses major challenges encountered in each layer in processing time in medical text. These challenges will be introduced in section 4.3.

Morphology and lexical analysis relates to morphemes (roots, prefixes and suffixes) of a language and are used to determine the sequences of morphemes into words. Syntax relates to combing multiple words and is used to determine the structure of phrases and sentences. Semantics relates to the meaning or interpretation of the words, and how they combine to form the meaning of phrases and sentences. One word can have multiple meanings. For example, consider the word "discharge" in "he was discharged from hospital" and in "a discharge of pus." Pragmatics studies the language as it is used in a social context and is concerned with how sentences combine to form discourse and how this context affects the interpretation of the sentences. In other words, pragmatics tries to fill the gap between the interpretation of the sentence and the speaker's actual meaning [162–164]. An NLP system acquires and represents the aforementioned knowledge as well as applies computational techniques including symbolic formalisms (e.g. finite state machines and context-free grammars) and statistical formalisms (e.g. Markov models) [9]. We do not attempt to enumerate all the methods and techniques in detail here, since they have been introduced elsewhere in many text books [11, 165–167].

4.1.2. Analyzing and Handling Time in Natural Language—In the past half century, different methods have been proposed to handle effects of lexical knowledge, syntax, rhetorical relations, discourse structure, domain knowledge, pragmatic conventions and other aspects for determining the temporal relationships of events in text. A comprehensive edited collection of papers on the topic can be found in Mani et al [168]. Though a timeline may not be efficient enough to describe all the endeavors, to some extent a gathering of research efforts with a particular focus can be identified within a period of time. We list interesting research foci that are related to this review article in Figure 3. Note that these areas have been continuously studied for several decades, and researchers are searching for a comprehensive method.

The analysis of verb tense and aspect in natural language, such as past, present, or future, as well as the continuance or completion of the action or state, has been a principle concern of most researchers in linguistics since the 1960s [169–177]. According to Reichenbach [178], the tenses of verbs determine relations between three times: a speech time (S) which is the time point of the act of speech, an event time (E) which is the time point at which the described event took place, and a reference time (R) which is time from which the speaker is viewing the event on a time line. In the early 1970s, Bruce [175] built a computer question answering program, called Chronos, which accepts information in the form of tensed sentences and answers questions about the time of events. The analyzed NL features in the model include tense, time relations, and other references to time in language. He also proposed seven time-segment relations.

In the mid 1970s, Kahn and Gorry [179] developed a time specialist program which encodes time specifications of events, handling time-expressions including date, relative time and fuzzy time. The time specialist organizes events in three different ways: with a date line, by special reference events and by before/after chains. It checks temporal consistency of the facts and answers time-related questions. It was assessed in understanding disease scenarios used in medical diagnosis. The intelligent question-answering system developed by Findler and Chen [180] deals with durational and time-point information as well as causal relationships which satisfy different time restrictions. Causal, coexistensive, and relative time relations for a pair of events can be answered by the program.

Some studies in the1980s have shown that both linguistic and world knowledge should be used to make inferences about the temporal structure of discourse. Discourse relations, such as, "elaboration," "explanation" and "narrative," which can be derived from this knowledge, help in defining the narrative reference time and constraining the temporal relations between events [181]. The shifts of tense, verb aspects, and pragmatics can assist anaphora resolution [174] and discourse ordering [182]. Readers can refer to several studies [177, 181–184] for more information on the temporal structure of narrative.

Tense logic was introduce around 1960 by Prior [185]. His work aroused the subsequent efforts to formulate a temporal logic for natural language. Many logical approaches to temporal reasoning have been previously reviewed [186–188]. Shoham [52] showed that Allen's interval calculus [50] and McDermott's temporal logic [42] do not have completely clear meaning for sentences, and proposed a reified temporal logic having formal semantics.

Moens [189] argued that any temporal formalism for natural language should have an ontology for a semantics of linguistic categories like tense, aspect and temporal adverbials as well as for a theory of their use in defining temporal relations of events. Recently, based on Allen's interval temporal logic [29, 49, 50], Hobbs [190] led an effort on developing a DAML (DARPA Agent Markup Language) ontology of time that characterizes temporal concepts and properties, with the aim to cover the basic topological temporal relations on instants, intervals and events, measures of duration, and dates and times. It is expressed in first-order predicate calculus. Its relation to TimeML [191, 192] in natural language has been discussed in [193].

The best known attempts at representing temporal expressions in the last decade are probably the MUC Named Entity Time Task [194, 195], which recognized and classified time-referring expressions, the formalisms proposed by the TIDES group [196–198], which developed a standard for the annotation of temporal expressions, the TimeML group [191, 192], which developed a language for markup of events and their temporal anchoring in documents, and their applications in event ordering [193, 199].

In general, the analysis units in the field have evolved from the word (lexical) level, phrase and sentence (syntactic) levels, to the discourse (semantic and pragmatic) levels, and the computational methods that have been applied in the field have evolves from traditional logic-based approaches, to other reasoning mechanisms [200], and to ontology-based approaches.

4.2. Related Work in Processing Temporal Information with Clinical Narrative Data

4.2.1. Processing Time in Clinical Text—Though there is considerable research and discussion in processing time in computational linguistics, time has not yet gained adequate attention in medical natural language processing. However, it is well recognized that natural language processing is a difficult but important task in biomedical informatics. As some researchers have pointed out [152], structured clinical data in the EMR is often poorly recorded, and information may be missing about key outcomes and processes. In fact, important clinical outcomes, such as disease state and its evolution, are often stored only as unstructured data (such as in dictated medical notes). Discussions of NLP applications in biomedicine can be found elsewhere [201–203]. Tasks include encoding findings with medical terminologies, facilitating assessment and diagnosis, and integrating with other clinical applications for decision support purposes. To date, a number of MLP systems have been developed for extracting, structuring and encoding clinical information from text reports, making clinical data available for use by subsequent automatic agents [10, 160, 203]. In the following, we review a few MLP systems' methods for modeling temporal information. We present the current state-of-the-art in the field and then discuss the challenges at each level of linguistic analysis in section 4.3.

4.2.1.1 In the 1980s: In the early 1980s, a few studies were conducted on processing temporal information in medical text in NLP [40, 204–206]. Hirschman and Story [205] identified words and structures that carry time information in narrative and emphasized that the identification should embrace both explicit and implicit sources of temporal information. Explicit sources include verb tense, adverbial expressions of time, and connectives joining two sentences. Implicit sources include multiple references to the same event in a text, and narrative time progression. “The time program” [204, 207] was developed and embedded in the NLP system of the Linguistic String Project (LSP). The LSP was developed at New York University as one of the first comprehensive NLP systems for general English and was then adapted to medical text [208, 209]. The time program takes the output of the NLP system, recognizes and analyzes time information, and formalizes the variant time expressions in a representation which consists of five fields: relation, reference point, direction, quantity and time-unit. Furthermore, the time program obtains a representation of time for each narrated event. Figure 4 taken from [204] shows examples of the time representation for medical text. A directed graph representation was then described in [40]. The vertices of such a graph correspond to points in time, and the directed edges to the intervals of time between the points. The output of the time program can be used to answer time-related queries.

Obermeier [206] developed an NLP system, called GROK (Grammatical Representation of Objective Knowledge), for analyzing temporal information in medical text. It was illustrated using text that related to case histories of liver disease. An important notion in this study is “key events.” A key event is defined as a domain-specific concept which is used to order and group events around this key event. In other words, key events build up the temporal structure of a text. One output of GROK is a knowledge representation of a text, consisting of a series of events extracted from the text and chronologically ordered by the NLP system. An event consists of a domain-specific concept, a key event, a relation to key event, and a duration (see Figure 5). The NLP analysis serves as the input to a medical expert system.

4.2.1.2 In the 1990s: MedLEE [210, 211], a Medical Language Extraction and Encoding System, was developed by Friedman and has been used at New York Presbyterian Hospital since 1995. The system has been applied to many types of medical text, including discharge summaries, radiology reports, pathology reports, visit notes, and residents’ sign out notes. MedLEE can automatically encode clinical information in text reports into ICD, SNOMED and UMLS codes [212, 213]. The system relies on a grammar and a lexicon, as well as other knowledge-based components. It has a preprocessor that performs lexical lookup to recognize and categorize words and phrases, and a parser that uses the grammar to identify the structure of the sentence and generate the output structure, which consists of primary findings and modifiers.

MedLEE [210, 211] currently captures straightforward references to dates (“was admitted on June 30”), some statuses (“in the past”), and changes (“increase,” “decrease”). However, relative assertions (“developed a fever after surgery”) lose the relation (i.e. after) between the events (i.e. fever and surgery), and less common temporal assertions are not handled. Figure 6 shows a simplified XML output of MedLEE.

The Special Purpose Radiology Understanding System (SPRUS) [208] was developed at University of Utah. It is primarily semantically driven and has been used to processes radiology reports. It functions as a module within a clinical information system, the HELP system [214, 215]. Its later version, Symbolic Text Processor (SymText) [216], has been applied to encode admission diagnoses [217] and extract pneumonia-related concepts from chest x-ray reports[218]. MPLUS [219] is the latest successor of SymText. Both of the later systems apply a semantic model based on Bayesian Networks. These tools are not designed to capture explicit temporal information. However, they identify a change of state with possible values including unchanged, improved, recurrence, worsened, and so on. The absence or presence of a condition can be inferred by using the state value and other contextual information [220]. For example, a condition is absent in the patient if it is stated in the Family History Section, and a condition is inferred to be present if the condition “worsens” or even if there is “no change”.

4.2.1.3 In the 2000s: Hahn [221] argued that most current MLP systems suffer from neglecting text structure phenomena, such as referential relations between discourse units. He and his colleagues have developed MedSyndikate [221, 222], a NLP system for extracting medical information from findings reports. It transfers a text to formal conceptual representation structures and deals with anaphoric reference relations spanning sentences. It mainly focuses on pronominal and nominal anaphora, textual ellipsis and metonymy. The system analyzes the tense and the modality of a verb to assist the conceptual representation.

Recently, Hripcsak et al [57] have modeled the temporal information contained in clinical discharge summaries as a Simple Temporal Constraint Satisfaction Problem (STP) [34]. This study was conducted through a consensus process, which resulted in a set of encoding procedures and a list of issues related to encoding (including medical events, explicit and implicit temporal assertions, context, linking events, intermittent events, periodic events, temporal granularity, temporal vagueness, uncertainty, contradiction, and discontinuous disjunction). Based upon this work, Zhou et al [223] further proposed a systematic methodology and system architecture for representing, extracting and reasoning about temporal information in clinical narrative reports. The proposed system includes several major components. First is a Temporal Constraint Structure (TCS) [8] which is a formal structure that consists of a set of fields to encode various temporal expressions (see Figure 7), and the TCS tagger which implements the TCS. Second is an NLP system (MedLEE) for encoding and extracting medical events and formalized temporal data. Third is a post-processor for handling implicit and uncertain temporal information. Fourth is a system to automatically implement the STP modeling.

4.2.2. Other related work—This section, we introduce other related studies on processing textual temporal information that is stored in clinical databases or stated in clinical guidelines. Their modeling methods are reviewed. In addition, we introduce standards on modeling temporal components in the EMR, particularly a semantic modeling. Though in this paper we have limited the scope to English, researchers in biomedical informatics have addressed temporal processing in other languages [224, 225].

4.2.2.1 Modeling Textual Temporal Expressions in Clinical Databases: Many studies, as we list in section 3, must deal with textual temporal expressions stored in databases, such as “December 1998 for five weeks,” “from March to October” and “for several years.” In addition to building models (as described in section 2 and 3) and standards (which will be introduced in section 4.2.2.3) to formalize this information, important issues such as temporal granularity, temporal uncertainty and temporal heterogeneity must be handled. Though many of the relevant studies have been already mentioned in section 3, we here introduce a few studies that focus on natural language expressions. Dolin [129] described a study on the development of a conceptual data model for the temporal aspect of symptom data. Compared with atemporal models which usually treat time as any other modifier, this study applied object-oriented modeling approaches, which enable the temporal objects defined in the model to be inherited by other medical objects, such as problems. He proposed to use an attribute “granularity_qualifier” to represent the uncertainty of absolute date/time and duration. Combi and Pozzi [31] proposed a temporal model named HMAP and focused on modeling and querying information related to natural language sentences. In HMAP, intervals are represented by *start*, *end* and *duration*. They introduced a three-valued logic for managing uncertainty in temporal relationships. In [125], an approach was proposed for handling granularity for both anchored and unanchored temporal data. The study shows the representation of unanchored temporal data, procedures for converting the data to a given granularity, and operations between the data elements.

4.2.2.2 Processing Time in Clinical Guidelines: In the Asgaard project, Shahar et al [226] developed a framework for recognizing care providers’ intentions from their actions, and critiquing care providers’ actions using the guideline as well as the patients’ clinical data. They presented the Asbru language to represent and to annotate guidelines. The Asbru time annotation schema represents the uncertainty of starting time, ending time, and duration of a time interval. It also includes a reference and is written as ([the earliest starting shift, the latest starting shift], [the earliest finishing shift, the latest finishing shift], [the minimal duration, the maximal duration], reference). It uses specific symbols to represent cyclical time points and other time references, e.g. MORNINGS representing a set of mornings and *NOW* for current time. The RESUME temporal abstraction module [30] and Chronus temporal query module [32] were applied to this project. Other work in temporal modeling that was done as part of the Asgaard project and the Asbru guideline language can be found elsewhere [227, 228].

Terenziani [39, 79, 80] introduced the treatment of temporal constraints in clinical guideline in GLARE. Their temporal formalism represents minimum and maximum duration of each action, and minimum and/or maximum distance between any pair of endpoints of the actions involved. The STP framework [34] has been applied to check temporal consistency in guidelines acquisition and execution. They proposed to use a tree of STP frameworks to represent the constraints regarding repeated actions, where each action was represented as a node in a separated STP.

4.2.2.3 Building Time Standards for Data Exchange and Integration: Efforts have been made in modeling temporal components in the EMR in order to build a standard for data exchange amongst healthcare information systems or for data integration in large scale systems. For example, organizations CEN [229], HL7 [230] and openEHR [231] have defined basic temporal data types (e.g. *point in time* and *interval of point in time*), temporal structures (e.g. structures for modeling time series) and temporal variables in classes (e.g. variable *effectiveTime* in a class *Act*). Different from various medical information systems, which usually develop specialized methods to address unique requirements of clinical applications, these efforts focus on building uniform models, which aim to encode the temporal information explicitly and unambiguously to be understandable and interoperable among systems. However, semantic specifications for modeling clinical concepts are still lacking [232]. An early project called Time Standards for Healthcare Specific Problems (TSMI) [233] provided a semantic data model for descriptions of time related information. Figure 8 shows an example encoded by TSMI. It allows combinations of situations (e.g. *event* and *episode*), temporal links (e.g. *has-occurrence* and *has-duration*) and temporal expressions (e.g. *time point expression* and *duration expression*) which are defined in TSMI.

4.3. Challenges in Processing time in Clinical Narrative Data

Based on section 4.1 and 4.2, we can find that the progress that has been made in MLP in processing temporal information coincides with the evolution in general NLP. Therefore, experience gained from the general NLP field can be applied to MLP.

We list challenges in processing temporal information in medical text, as shown in the third column of Figure 2. These challenges are listed corresponding to the different layers of linguistic structures and analysis. However, the difficulties are not limited to these aspects. The list does not include other major problems in computational NLP in general, e.g. anaphora, ellipsis and conjunction, and major challenges in processing medical text, e.g. heterogeneous formats, occurrence of typographic and spelling errors, and intraoperability and interoperability of NLP systems, as listed in [9].

1) Diverse temporal expressions—In natural language, time can be represented in a natural way (e.g. “before tonight,” “right now,” and “during that period”), in a conventional way (e.g. “September 23, 2005” and “last Christmas”), or in a professional language with unique formats and styles (e.g. “q.i.d.” and “postop # 6” which means the sixth day after an operation). The same time can be written in many ways. For example, *01/03/02, 010302, 01032002 and Jan 3, 02*, all represent the same date. Zhou et al [8] revealed a wide diversity of temporal expressions in discharge summaries and classified them into a set of natural categories. However, a more comprehensive study is needed to cover medical text from different sources.

2) Medical grammar—Medical language, especially clinical notes, often ignores many restrictions that are required in the general English grammar [9]; for example, the fact that each sentence must have a subject. Clinical text is typically more compact: for example, “chief complaints: cough, fever” and “potassium 4.1, glucose of 115, albumin 2.7.” Medical events are largely expressed by nouns or noun phrases, whereas in general linguistics, events are often expressed by tensed and untensed verbs and nominalizations [54]. In addition, there are some misleading expressions specific to the medical domain. For example, the phrase “the patient presented with” does not necessarily mean that the event occurred in the past [223]. Therefore, the role of tense and aspect in temporal reasoning using medical text requires further investigation.

3) Ubiquitous ambiguities—Interpretation of an expression can be uncertain. For example, “010202” can be a number, a date, a symbol, or anything else. “Last year” can mean 2002 when uttered in year 2003, or 1995 when uttered in year 1996. “A patient had a fourteen to sixteen week size fibroid uterus” does not indicate a time but a size, because the time expression here refers to the size of the progression of pregnancy, which is used as a reference standard for the mass size. “In day two” can be in the second day of a hospital stay or in the second day of a treatment. Sophisticated semantic analysis and world knowledge are required to answer questions such as what senses are to be associated with a temporal expression and how the meaning of this temporal expression contributes to the meaning of a sentence or discourse that make up by this term.

4) Complex temporal relations in medical domains—Medical events are linked directly or indirectly in the text. In addition, there are many possible temporal relationships between two events; e.g. event 1 is either before or after event 2, but not during it [29]. Another example of temporally complex situations is a case in which a rash was treated with a medicine, which caused a new rash. The reasoning system must figure out that these two occurrences of rash are not the same, probably by drawing upon domain specific knowledge. One philosophical concern as described by Anscombe [234] is that there is a distinction between lexical and sentential meanings. For example, before and after are not converses, as “the patient was alive after he had the surgery” does not imply “the patient had the surgery before he was alive.” Extra assumptions should be made while uniformly treating temporal references. Anscombe also discussed the difference between instantaneous events and events that occupy a period of time. The paradoxical example given above causes no problem when it refers to two instantaneous (point-based) events, such as the death of the patient and the operation. If the events are not instantaneous, then before and after need to be interpreted with respect to the start and finish of the interval.

5) Implicit information—Many medical reports are compact and omit information that can be assumed by experts. “The patient had spiked to 101.4” means that the patient had a fever and his temperature was as high as 101.4 °F. Temporal information in natural language is not always stated explicitly, but requires interpretation or inferences using world knowledge and assumptions. For the sentence “he had heart failure previously,” a system must determine whether “previously” refers to a week ago or a year ago. In a manual reviews of discharge summaries, Hripcsak et al [57] reported that 64% of temporal assertions about events are implicit.

6) Pragmatics—Hahn and Romacker [235, 236] pointed out that most current medical text processing systems are actually sentence processors or even more restricted phrase processors which treat their sentences and phrases in isolation only. In fact, medical texts, like any other sort of text, exhibit textual structures, and ignorance of these structural relations will cause underdetermined or invalid content representations. Jurafsky and Martin

[11] argued that complete analysis of a text requires analysis of relationships between sentences and larger units of discourse such as paragraphs and sections.

The intended value of a time expression may require a prior time expression elsewhere in the sentence (local context dependence) or in the surrounding discourse (global context dependence). Anaphoric approaches are needed to resolve temporal adverbial information: e.g. “at that time”, “then” and “later.” For the statement “the patient had a fever on March 2,” the value of “March 2” may be linked a specific year based on the context.

7) Granularity of the information—Temporal information may be specified at different granularities. It is unclear what unit of measure should be adopted to represent different granularities. For example, “three months ago” may refer to a specific month or a specific day. It is also unclear how the system should switch from one temporal domain to a coarser or finer one. Projection from finer to coarser granularity or the reverse involves complex semantic issues. That is, one must assign a proper meaning to the association of facts at different temporal layers [4, 120, 122, 123, 237].

8) Temporal fuzziness and uncertainty—Temporal information in medical text is often imprecise or uncertain because exact or complete data and knowledge are not available. For example, “several days ago” is fuzzy as to what is the exact value for “several”; the statement “the patient had a previous episode last month that lasted 2 or 3 days” does not specify a precise date or a precise duration; and “the pain started by mid-July” presents a set of possible dates. Researchers in medical informatics have used a time range to represent uncertainty information. However, most of the ranges are defined based on the human experience. Some studies [126, 238–241] proposed to handle imprecise and uncertain information in temporal reasoning in the framework of fuzzy sets and possibility theory.

9) Semi-interval problem—One difficulty is the semi-interval problem as discussed earlier in this paper in section 2.4; i.e., we may only know the temporal beginning or ending of an event but not both. For example, only the starting time of appendectomy was recorded in the electronic medical record, but not the ending time; or it was mentioned that a central venous catheter (CVC) was placed before the operation, but there is no real information about if CVC was removed before or after the operation. Clinical domain knowledge may play an important role for solving this problem. For example, the time of an appendectomy procedure can be measured in minutes to hours and should definitely before discharge. Related studies in AI can be found in [48].

10) Inconsistency—Temporal information for an event can be inconsistent when data are unreliable or obtained from several sources. For example, in a clinical report, if it is stated that an event started before admission and that the exact same event started after admission, then there is a contradiction. Inconsistency may be more common when integrating data from different sources. Discovering the source of the inconsistency is a difficult task in temporal reasoning [13]. Deciding which temporal constraints to eliminate to solve the inconsistency may require more information beyond constraints themselves; for example, certainty information might be helpful for deciding which statement is true.

5. Key Areas for Future Research

Limitations and challenges in previous studies can point the way to future work in the field. Temporal reasoning with structured data is more advanced, and future directions for structured data have been summarized elsewhere [1, 2]. Reasoning about time in natural language is one of the most challenging areas. Others have pointed out the need for more research in temporal granularity, fuzzy time, temporal contradiction, intermittent events, periodic events, and uncertainty [8, 57, 204, 205, 223]. In addition, we present several broad research directions.

1) Enhancing functions of current MLP systems in processing temporal information

In order to augment the performance of these systems, improved temporal representations and temporal reasoning with NLP data must be achieved. Processing time should be involved in each phase of natural language processing. That is, temporal information must be handled in each level of linguistic units, from morphology and lexicography to syntax and semantics, and finally to pragmatics. Different sources of knowledge and computational techniques should be applied to this field. Although many useful methods, techniques and other resources can be taken directly from general NLP, research in MLP is still required to address medicine-specific scenarios.

The first thing to start with might be to study how temporal information is conveyed in medical narrative. Different types of medical documents should be collected and then a formal structure should be developed to formalize diverse temporal references for further automated processing. Verb tense (past, present and future), aspect (progressive, perfective) and modality (will, would, may, might) have been analyzed for determining the state of medical conditions; however, their role in temporal reasoning has not yet been widely studied. Beside tense, analyzing the temporal structure of a sentence should concern the functions of temporal subordinating conjunctions (e.g. while, whenever, before and as soon as) and temporal adverbials (e.g., then, soon and recent). Resolving temporal granularity and uncertainty has been constantly a challenge not only for medical informatics but also for general NLP. One of the most difficult tasks that MLP researchers face today is probably at the pragmatics analysis level, since most current MLP systems mainly stay at the sentence level. Temporal reasoning is an important mechanism for connecting the events in a discourse. Understanding the temporal property of a text and discovering complex temporal relations will assist in complete analysis of the text.

Besides linguistic analysis of the text, computational models for temporal reasoning as introduced in section 3 must be considered as well. Balancing the tradeoff between expressive power and computational tractability to look for a suitable formalism for discovering more implicit temporal information in the text may be one of the most important concerns in this step.

2) Incorporating medical knowledge into temporal reasoning systems

Some linguists [242] argue that medical text, such as medical summaries, "have a stereotypic structure. They can be viewed as a sequence of episodes, which correspond to phrases, sentences, or groups of sentences dealing with a single topic." Thus, medical domain knowledge is important to understand the structure and context of a medical text to improve temporal reasoning. One interesting research area would be to incorporate different medical knowledge (e.g. medical terminologies and specialized medical domain knowledge) into temporal reasoning systems. For example, the hierarchical structure of a terminology can help identify whether two different statements refer to the same event (e.g. references to ampicillin and to a course of antibiotics). In addition, well defined semantic relations (such as causal relationship) can help order events. Medical knowledge in specialized fields is also important, for example, in defining reference events in a liver transplant domain.

3) Resolving coreference

A challenging topic in NLP is coreference resolution [243, 244]. Coreference is the phenomenon where two expressions in an utterance both refer to the same thing. An example might be a report containing two references to the same ankle surgery. Coreference resolution is critical for temporal reasoning, but conversely, discovered temporal information can be used to assist in deciding if two statements refer to the same thing. For example, if the temporal assertions about these two "ankle surgery" events are close enough to each other, they might refer to the same operation.

4) Evaluation of the systems

Evaluating MLP systems in practice is critical to progress. However, it is difficult to evaluate an MLP system due to the difficulty of obtaining a gold standard and of sharing the data across institutions [245, 246]. Raters may have different opinions on annotating temporal expressions or ordering events in a text, which lead to a lower inter-rater and intra-rater agreement. In addition, obtaining a gold standard is very costly, since it involves much manual processing.

Evaluating a temporal system at every linguistic level might be tedious but necessary. Questions that should be answered include: How accurately does the system identify temporal references? Are the grammar rules helpful for analyzing the temporal structure of a phrase or sentence? Does the proposed semantic analysis help in disambiguating the different senses of a temporal expression? How well does a system infer the temporal structure of a discourse? Is a temporal formalism suitable for reasoning about time in such a medical text?

On the application level, the aims of evaluation may vary according to the problems that need to be solved. In general, research will answer the following questions: What type of temporal information is needed to solve this problem? Does the system accurately extract the required temporal information from the text? How accurately and efficiently does the system answer temporal questions?

5) Integrating narrative data with structured data

As soon as systems can successfully represent and reason with temporal information contained in narrative data, one promising future direction is to integrate narrative information with structured database information. Such integration could help carry out higher level reasoning tasks (e.g. temporal abstraction), or implement applications such as information retrieval or information visualization. While temporal abstraction for structured data is usually built from temporal primitives, original narrative data contains different levels of abstraction (see Figure 9). Integrating these two data types would require complicated conversion, mapping and merging.

6. Conclusion

Temporal representation and reasoning have been studied in depth in recent decades. In computer science, especially in artificial intelligence and database management, time has been studied extensively, resulting in many publications and meetings. In addition, researchers in medical informatics have made great contributions to this field, with the goal of supporting medical decision making and improving the quality of health care. Despite advances, many areas still deserve attention. Processing text data, in general, is a hard problem in computing. Given the recent progress and success of medical language processing and of its uses in medical informatics applications, processing temporal information in medical textual data promises to be a very fruitful area of research.

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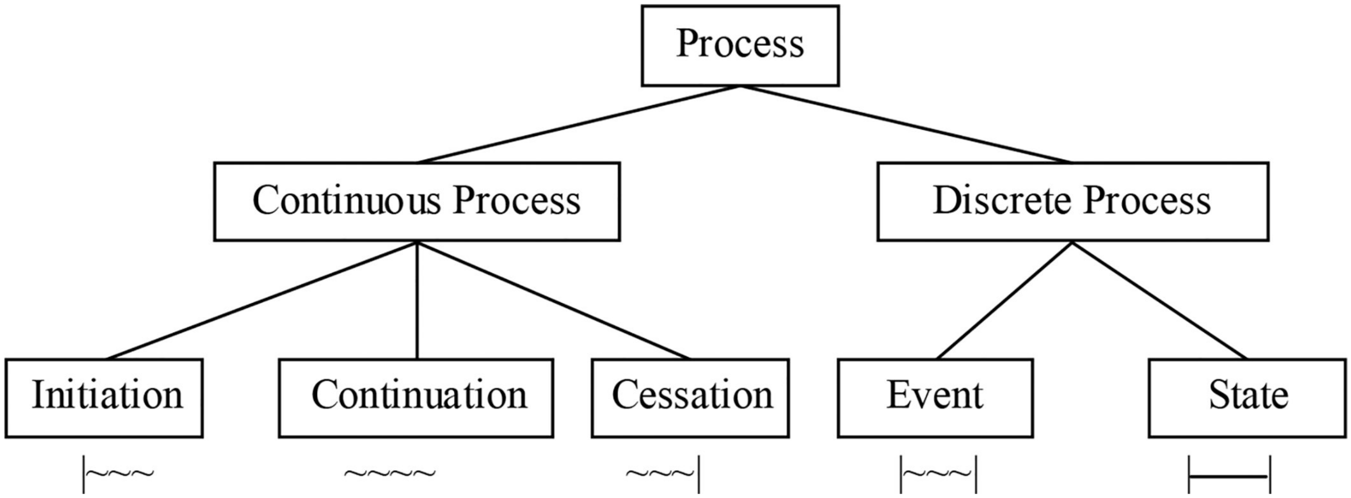


Figure 1.
Types of Processes (adapted from [53])

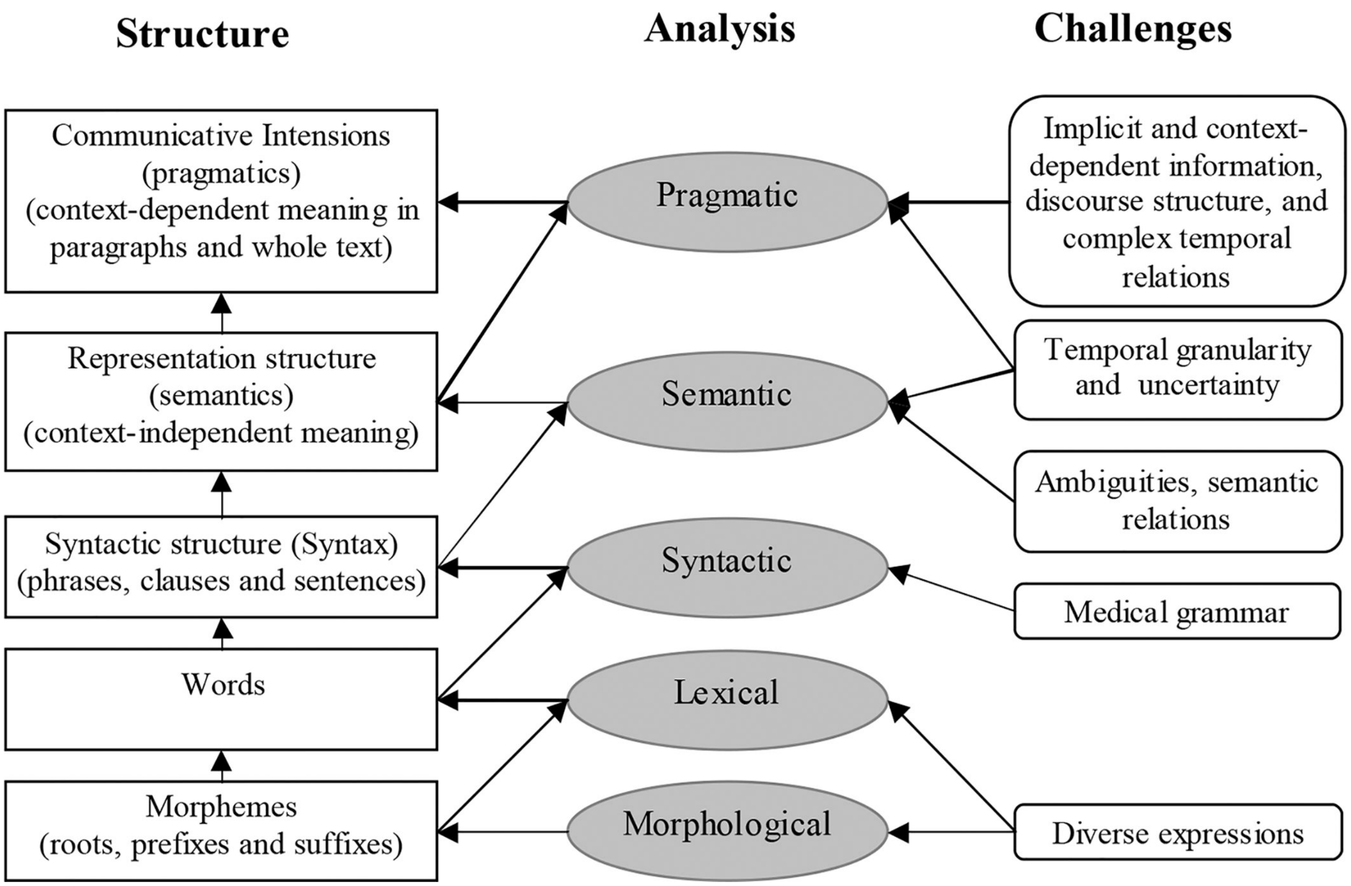
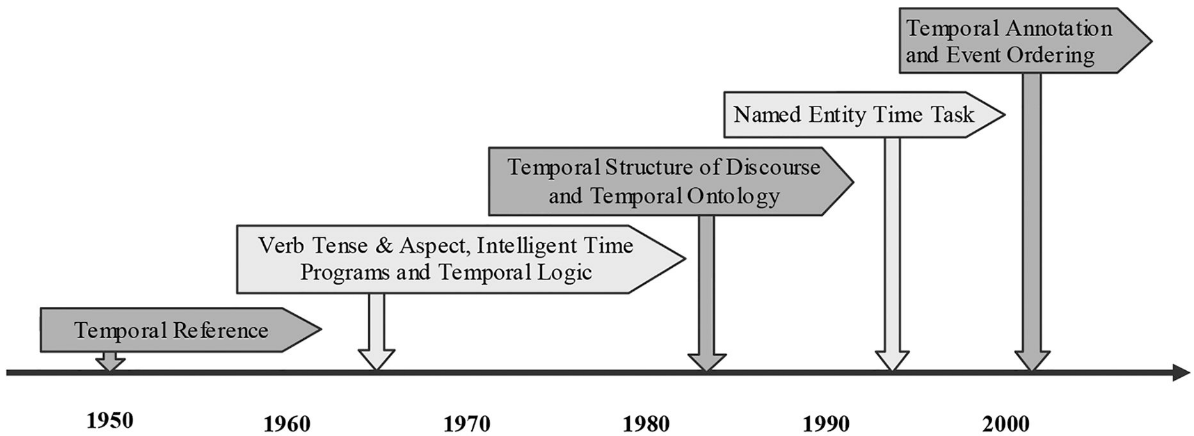


Figure 2.

Levels of linguistic structure and analysis (see details in section 4.1), and related challenges in processing time in medical text (see details in section 4.3)



Reichenbach, 1947[178]

Verb Tense and Aspect
Bull, 1960 [169]
McCawley, 1971 [170]
Vendler, 1967 [176]
Dowty, 1972 [171]

Time-intelligent Question-answering Systems
Bruce, 1972 [175]
Findler and Chen, 1973 [180]
Kahn and Gorry, 1977 [179]

Temporal Logic
Prior, 1967 [185]
Allen , 1984 [50]
Shoham, 1987 [52]

Temporal Structure of Discourse
Dowty, 1986 [182]
Mann and Thompson, 1987 [183]
Nakhimovsky, 1988 [177]
Webber, 1988 [174]
Lascarides, 1991 [181]

Temporal Ontology
Moens and Steedman, 1988 [189]
Hobbs, 2002 [190]

Named Entity Task
MUC6, 1995 [194]
MUC7, 1998 [195]

Temporal Annotation
Setzer, 2001 [198]
Ferro et al, 2001 [197]
Pustejovsky et al, 2002 [191]

Event Ordering
Hobbs and Pustejovsky, 2003 [193]
Mani and Schiffman, 2004 [199]

Figure 3.
A simple timeline and selected work of processing temporal information in natural language

Text 1: Higher fever was first noted one day before admission. Fever has persisted.
Text 2: Patient was discharged when signs of pneumonia were gone.

Text	Event #	Connec-tive	Text	Relation	Reference Point	Adjustment		
						Dir.	Quant.	Unit
1	E1		Higher fever was fist noted	At	Admission	-	1	day
	E2		Fever has persisted	From To	E1 Time of narration			
2	E1		Patient was discharged	At	Last narrated topic	0/+		
	E2	When	Signs of pneumonia were gone	At	E1			

Figure 4.
Time representation for medical text in "the time program" (adapted from [204])

Event1
- Symptom: nausea/vomit/abdominal/swelling, jaundice
- Key event: admission
- Duration: admission

Event2
- Symptom: diabetes mellitus
- Key event: admission
- Relation to key event: 6 years before
- Duration: six years

Figure 5.
Time representation for medical text in GROK system (adapted from [206])

Text:

The patient was diagnosed with squamous cell lung carcinoma in November, 1987. He has a history of alcohol abuse.

MedLEE XML output:


```
<problem v = "carcinoma of lung" idref = "p16">
        <bodyloc v = "squamous cell" idref = "p12">< </bodyloc>
        <certainty v = "high certainty" idref = "p8"></certainty>
        <date v = "19871100" idref = "p22">
                <reltime v = "in" idref = "p20"></reltime>
        </date>
        <sid idref = "s1"></sid>\
</problem>

<problem v = "alcohol" idref = "p39">
        <behavior v = "user" idref = "p41"></behavior>
        <certainty v = "high certainty" idref = "p31"></certainty>
        <sid idref = "s2"></sid>
        <status v = "history" idref = "p35"></status>
</problem>
```


Figure 6:

A simplified XML output of MedLEE. In this case temporal information is tagged using semantic types “date”, “reltime” and “status.” The output also contains other contextual information.

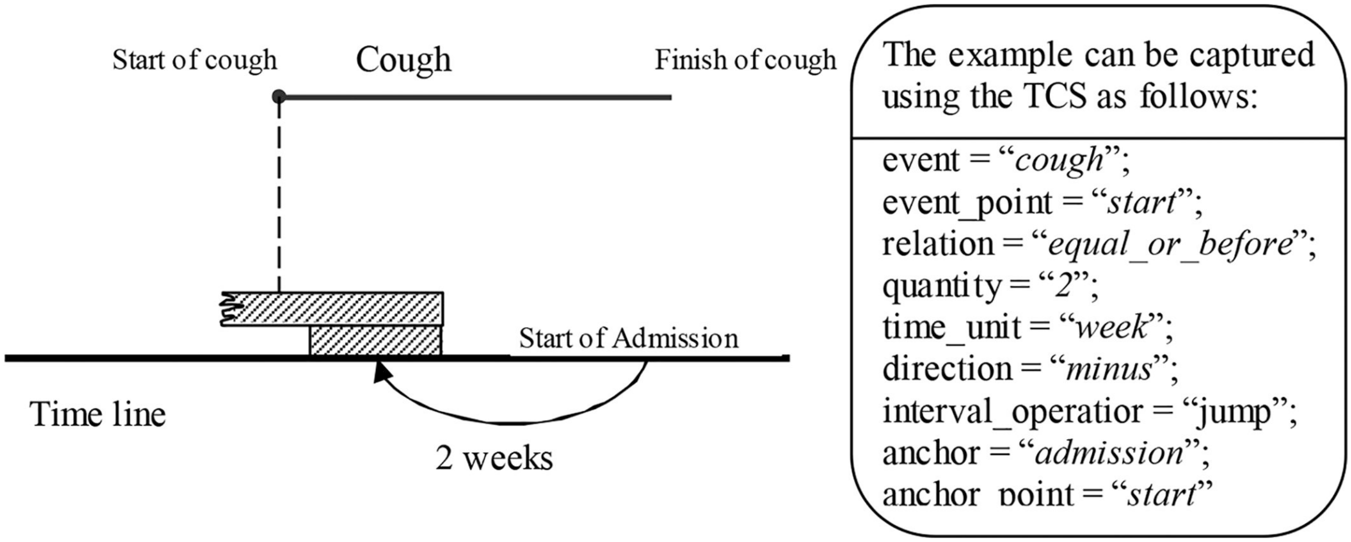


Figure 7.

(Adapted from [8]) Example temporal expression "his cough started at least two weeks before admission" modeled on a time line, depicting the event "cough" anchored by "admission." The bars represent the vagueness of the temporal information, which widen the limits of the constraints.

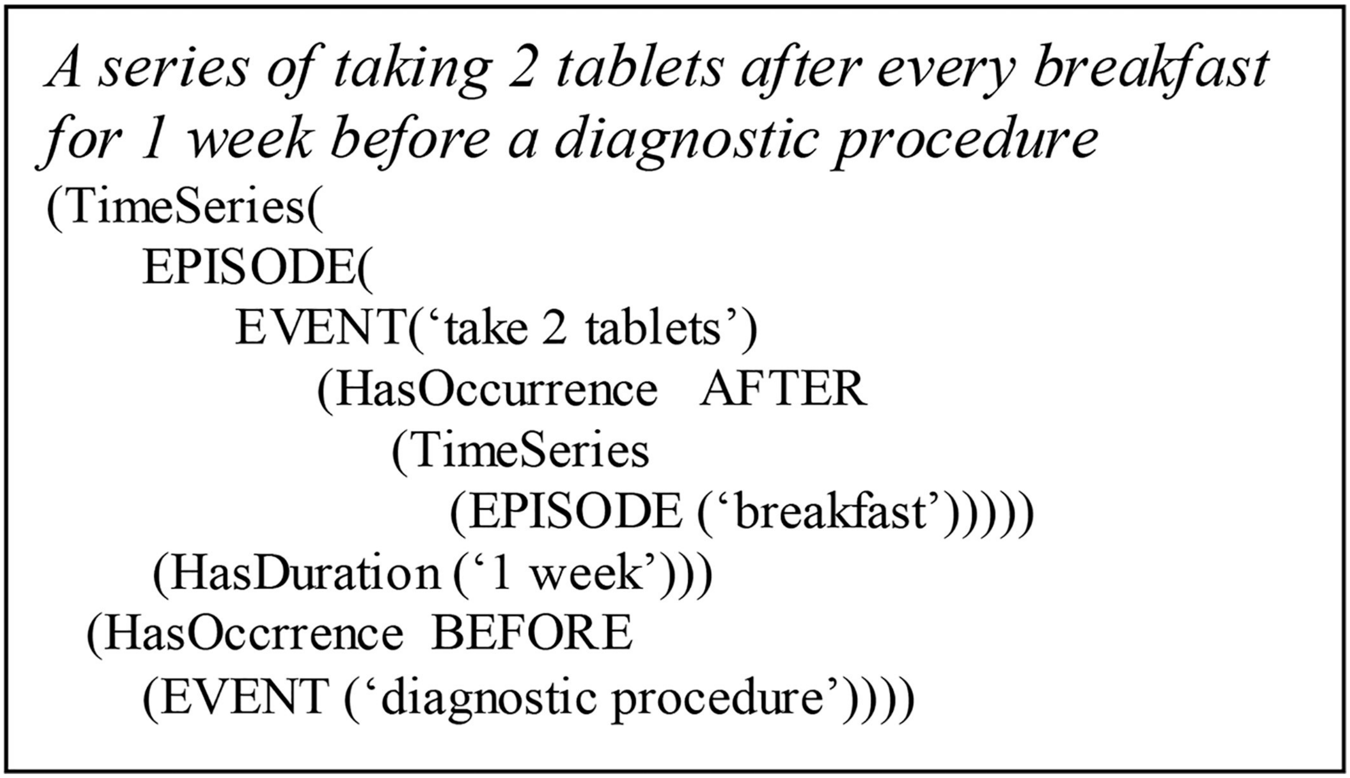


Figure 8.
A statement encoded using TSMI standard (adapted from [233])

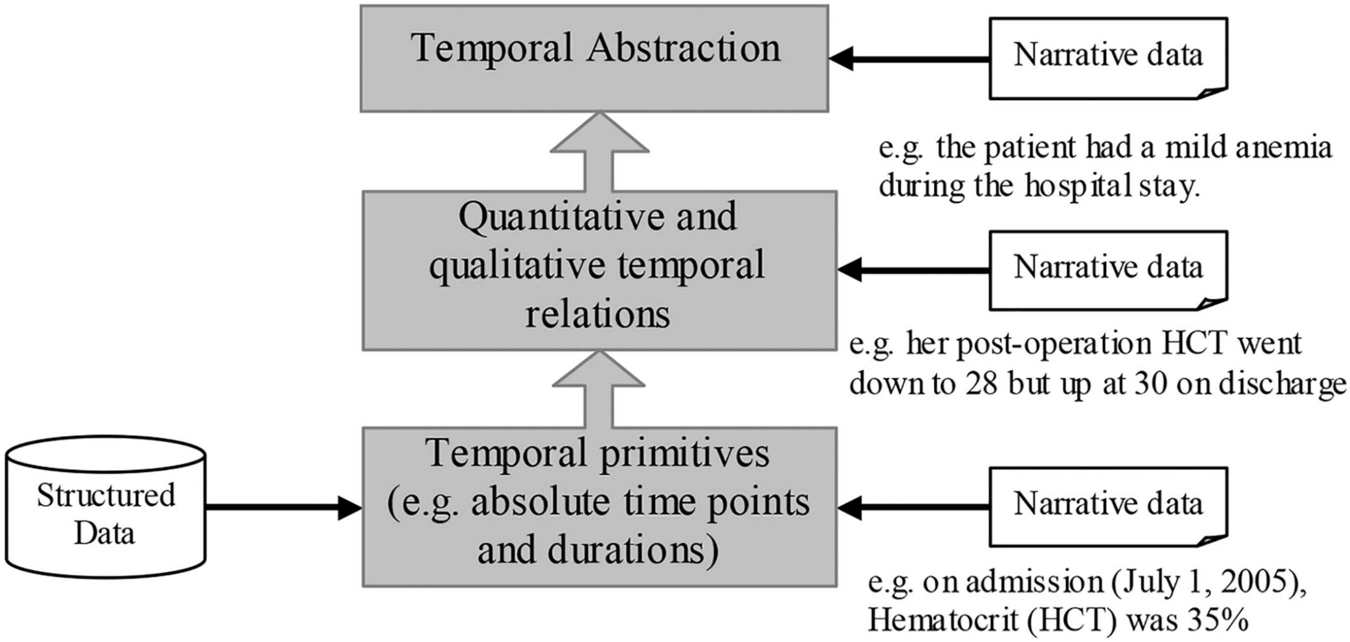


Figure 9.
Input to temporal abstraction tasks from structured data and narrative data

Table 1.

Theoretical and methodological studies in processing temporal information in medicine

Theories and methodologies	Related work
Category 1: applying theories and models in temporal reasoning in AI	
Probabilistic approaches [66]	Associated with the tasks of interpreting or forecasting with time- stamped clinical data whose values are affected by different sources of uncertainty. Many studies in time [60, 67–71] have applied Bayesian probabilistic networks.
Event calculus [22]	Applied to assess the evolution of a patient's status [72]. It also has been adopted as the temporal ontology in a temporal abstraction approach for clinical time-oriented databases [73].
Markov decision process [74]	Applied to solve decision problems in which the optimal choice has to be revised periodically in accordance to the evolution of the patient's conditions [75].
Allen's interval [29]	Applied to the tasks of temporal abstraction and query process to determine qualitative temporal relationships between medical events [24, 30, 32, 33, 76].
Temporal constraint network [34]	Used to facilitate patient-monitoring and problem-detection [36], manage medical resources [38], and treat temporal constraints in clinical guidelines [37, 39, 77–80]. It has also been applied to model temporal information in clinical discharge summaries [57].
Case-based reasoning [81]	Used to determine similarities in patient treatments mainly with respect to their pattern of time and dosage [82]. Schmidt [83] proposed a method for prognosis of temporal courses, which combines temporal abstractions with case-based reasoning.
Category 2: developing frameworks that meet needs from clinical applications	
Temporal Database Management	Involves tasks of storing, processing and retrieving time-oriented information [84, 85]. Various modeling approaches have been studied. Wiederhold proposed a Time Oriented Databank (TOD) [86] which created a cubic view of time-stamped clinical data. Kahn et al [24, 33] described a query language called TQuery. Das [87–89] proposed a method for temporal integration called temporal mediation which addresses the problem of temporal model heterogeneity. Other approaches involve relational models [90, 91], entity-relationship models [92, 93] or object-oriented models [94–96].
Temporal Abstraction	Relates to the task of creating interval-based concepts (abstractions) from time-stamped raw data [30]. Many studies have been conducted [5, 30, 58, 73, 82, 83, 97–107], specifically focusing on clinical domains such as chronic diseases, growth and development problems, and intensive neonatal or adult care unit settings, where clinical data are either cumulative or arrive rapidly. Shahar [5, 30, 98] developed the RESUME system, which utilizes specific explicit domain ontologies and contains several mechanisms that deal with five temporal-abstraction subtasks.
Temporal Data Visualization	Involves tasks of collecting, navigating and visualizing time-oriented information. Some early work used raw clinical data. For example, Cousins [108] developed a system called *a time line* with a set of operators and a user interface that allows time lines to be manipulated. Later on, systems appeared with a more flexible zoom in and zoom out interface [109, 110]. Shahar et al [102, 111–115] developed methods and systems for visualization of domain specific temporal abstractions. Other methods [116–118] in this field include 2D and 3D visualization, and various statistical and graphical methodologies.
Category 3: resolving issues such as temporal granularity and uncertainty	
Temporal Granularity	Involves tasks of representing and storing time points and time spans with different and mixed granularities, converting a temporal primitive from one granular level to another, and handling granularity mismatches between two sets of data [2, 4, 31, 57, 60, 61, 87, 88, 119–125].
Temporal Uncertainty	Relates to tasks of handling vague and uncertain temporal information which is due to imprecise or unreliable data and knowledge [1, 31, 57, 126–129], e.g. fuzzy sets theory was used to model imprecise temporal information within a diagnostic framework [128].