The Elicitation, Representation, Application, and Automated Discovery of Time-Oriented Declarative Clinical Knowledge

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Abstract. Monitoring, interpretation, and analysis of large amounts of time-stamped clinical data are tasks that are at the core of tasks such as the management of chronic patients using clinical guidelines, the retrospective assessment of the quality of that application, or the related task of clinical research by learning new knowledge from the accumulating data. I briefly describe several conceptual and computational architectures developed over the past 20 years, mostly by my research teams at Stanford and Ben Gurion universities, for knowledge-based performance of these tasks, and highlight the complex and interesting relationships amongst them. Examples of such architectures include the IDAN goal-directed temporal-mediation and the Momentum data-driven monitoring architectures, both of which are based on the knowledge-based temporal-abstraction method; the KNAVE-II and VISITORS knowledge-based interactive-exploration frameworks for single and multiple longitudinal records; and the KarmaLego interval-based temporal data mining methodology. I point out the progression from individual-subject data-interpretation, monitoring, and therapy, to multiple-patient aggregate analysis and research, and finally to the discovery and learning of new knowledge. This progression can be viewed as a positive-feedback loop, in which new knowledge is brought back to bear upon both individual-patient management and on the learning of new and meaningful (temporal) associations.

Keywords: Knowledge Representation, Knowledge Acquisition, Temporal Reasoning, Temporal Abstraction, Temporal Data Mining, Information Visualization, Medical Decision-Support Systems, Guideline-based care.

1 Introduction: The Need for Representation and Application of Declarative Knowledge in the Medical Domain

The management of patients, and in particular, chronic patients, requires significant amounts of *declarative* ("*What is*") medical knowledge, such as the definition of key

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medical concepts (e.g., "moderately high blood pressure in the context of pregnancy"; "grade-II bone-marrow toxicity, in the context of a particular chemotherapy protocol"), in addition to *procedural* ("*How to*") clinical knowledge (e.g., the precise sequence of steps - such as measurements and interventions - to take, when high blood pressure is discovered in the third trimester of pregnancy; the correct procedure to handle bone-marrow toxicity after bone-marrow transplantation).

Furthermore, *Time* is an essential aspect of biomedical data. Many medical tasks, especially those involving chronic patients, require extraction of clinically meaningful concepts from multiple sources of raw, longitudinal, time-oriented data. A typical example might be “Modify the standard dose of the drug, if, during treatment, the patient experiences a second episode of moderate anemia that has persisted for at least two weeks.”

One can list at least four types of clinical tasks that require temporal reasoning:

1. **Monitoring and Diagnosis:** For example, continuously monitoring the patient's accumulating data, might require searching for the appearance of a triggering pattern such as “a gradual increase in diastolic blood-pressure levels” that might be part of a diagnosis of preeclampsia during pregnancy;
2. **Therapy**: Following a treatment plan, such as one based on an established clinical guideline, might require deciding when certain patterns that require action have appeared in the patient's data, thus complementing the guideline’s procedural (process-based) knowledge;
3. **Quality assessment:** Comparing the patterns formed by observed clinical data, such as administered treatments, with those that should have been generated by following the recommendations of a guideline**,** requires a determination to what extent do these patterns adhere to the intended guideline**;**
4. **Research:** The discovery of frequent patterns of dependencies over time between clinical concepts, can lead to the clustering of patients by different temporal pathways, and to the predictive classification of certain future outcomes (e.g., whether a diabetes patient will have certain renal complications) by exploiting past and present temporal patterns as features.

Together, these tasks imply several specific desiderata, which I discuss in the next subsection.

However, to introduce these desiderata, one must first consider how to bridge the gap between the rather abstract requirements of these tasks, and the actual low-level structure of clinical databases.

1.1 The Need for Intelligent Mediation: Bridging the Gap between Raw Data and Meaningful Concepts

Clinical databases store *raw*, *time-stamped* data (e.g., a series of Hemoglobin values at certain times and dates). However, care providers and decision-support applications, such as guideline-based care systems, reason about patients in terms of higher-level, *abstract*, clinically meaningful concepts, holding over significant time *periods* (e.g., three weeks of *moderate anemia* in the context of a pregnancy).

Thus, a system that *automatically* answers queries or detects patterns emerging, in a context-sensitive manner, from raw clinical data or from the concepts derivable from these data over time, is crucial for effectively supporting multiple clinical tasks, such as patient monitoring, guideline-based therapy, and medical research that generates new clinical knowledge.

To bridge that gap, we need a *mediator* between the human users or the decision-support applications, and the time-oriented clinical data, which can perform, in a manner transparent to the user (or the computational application), an *abstraction* of the time-oriented data from which the abstract concepts mentioned in the query are implicitly derived. We refer to these abstract concepts, which typically hold over time intervals, as *temporal abstractions*, and to such a module, which mediates queries regarding temporal abstractions from human users or decision-support applications, to the relevant data and knowledge sources, returning the high-level concepts in a manner transparent to the asker, as a *temporal-abstraction mediator*.

A *temporal-abstraction mediation architecture* enables access to heterogeneous time-oriented clinical data sources; supports querying for both patient raw data and their abstractions over time; and integrates multiple clinical data sources with several clinical knowledge sources. However, standard monitoring and data-analysis methods do not address the desiderata implied by the four tasks listed above:

1. The computational process must be able to exploit sophisticated existing domain-specific knowledge needed for abstraction of the time-oriented raw data, which I refer to as *temporal-abstraction knowledge*;
2. The computation is based on a well-founded underlying domain ontology (i.e., a model of concepts, their properties and inter-relations);
3. The abstraction must be sensitive to the context of the data;
4. The abstraction process must be specialized for temporal reasoning, and can exploit the existence of both time points and temporal intervals;
5. The abstraction process must be able to support distributed data, knowledge, and computational resources;
6. The abstraction mechanisms must be able to support monitoring, exploration, and mining of the data and their temporal abstractions.

Thus, a solution that addresses all of these needs must involve the creation of a comprehensive architecture that can support intelligent (knowledge-based) abstraction, monitoring, exploration, analysis and mining of time-oriented raw clinical data and of their abstractions.

Furthermore, a complete solution addressing all of the desiderata listed above must present a distributed architecture that caters for at least three core needs:

1. *Automated* means for *goal-directed* query & retrieval, and for *data-driven* monitoring & *detection*, of *known* clinically significant, meaningful patterns, in time-oriented data, by applying temporal-abstraction knowledge from multiple domain-specific knowledge sources, to multiple data sources;

2. Interactive, human-operated means for dynamic visual exploration of a time-oriented data repository, whether of one patient (in the case of management of a particular patient) or of multiple patients (in the case of exploring the data of a population), using on-the-fly integration with domain-specific knowledge, to query for *known* patterns and to identify *new* meaningful associations and patterns, and, when relevant, add them to the knowledge base;
3. Automated analysis, enumeration, and *discovery* of *new* meaningful, significant temporal-abstraction patterns (relationships amongst temporal-abstraction intervals), in the time-oriented data of multiple patients, including the capabilities for (a) clustering the data over time, and for (b) an analysis of the predictive value of various temporal patterns, exploited as features, for future meaningful outcomes.

2 Elicitation, Specification, and Application of Temporal-Abstraction Knowledge: The Knowledge-Based Temporal-Abstraction Method

As I have explained in the Introduction, specification of clinical procedural knowledge is a necessary, albeit insufficient step in providing a complete infrastructure for automated application of clinical knowledge, and in particular, of guideline-based knowledge. We also need to formally specify *declarative* knowledge, and bridge the gap between raw clinical data and the concepts interpreted from them. This is especially true for the highly prevalent time-oriented clinical data. Acquiring the temporal-abstraction knowledge that is necessary for abstracting raw time-stamped data into higher-level, interval-based concepts, managing and maintaining it is a consistent manner, and applying it in an automated fashion, requires a well founded, consistent ontology that includes all of the desired knowledge roles to be acquired.

As it turns out, a formal ontology sufficient for the representation of the knowledge necessary for the computational temporal abstraction exists: The *knowledge-based temporal-abstraction* [*KBTA*] *ontology,* which underlies the KBTA problem-solving computational *method* [1]. The KBTA method, originally implemented within the RÉSUMÉ system [2] and since then re-implemented multiple times, has been evaluated in several clinical domains, such as oncology, AIDS, assessment of children's growth and development, and diabetes [2-5]. The KBTA method has also been implicitly evaluated in multiple studies that have assessed the functionality and usability of several intelligent interactive visualization and exploration modules for time-oriented data of single and multiple longitudinal patient records, based on the KBTA paradigm, some of which I sum up in Section 4.

In Section 5, I focus on the use of temporal abstractions for temporal data mining.

A useful exposition of temporal abstraction (TA) in medical domains and of its broader underlying philosophical and computational context can be found in a dedicated chapter on temporal reasoning in medicine in *The Handbook of Time and*

Temporal Reasoning in Artificial Intelligence [6], while a broader view of temporal-abstraction and temporal databases in medicine can be found in a comprehensive recent research textbook focusing on temporal reasoning in medicine [7]. However, in this paper, I will introduce the KBTA methodology from the point of view of the *tasks* performed and the nature of the *knowledge* required to perform them.

2.1 The Temporal-Abstraction Ontology

The KBTA *method* decomposes the TA *task* into five TA subtasks: Temporal context restriction, Vertical temporal inference, Horizontal temporal inference, Temporal interpolation, and Temporal pattern matching, whose precise semantics have been described elsewhere [1,2], and which will be exemplified when explaining the semantics of the four TA *knowledge types*. The five TA subtasks are solved using five TA computational *mechanisms* [1,2] (Figure 1) operating in parallel.

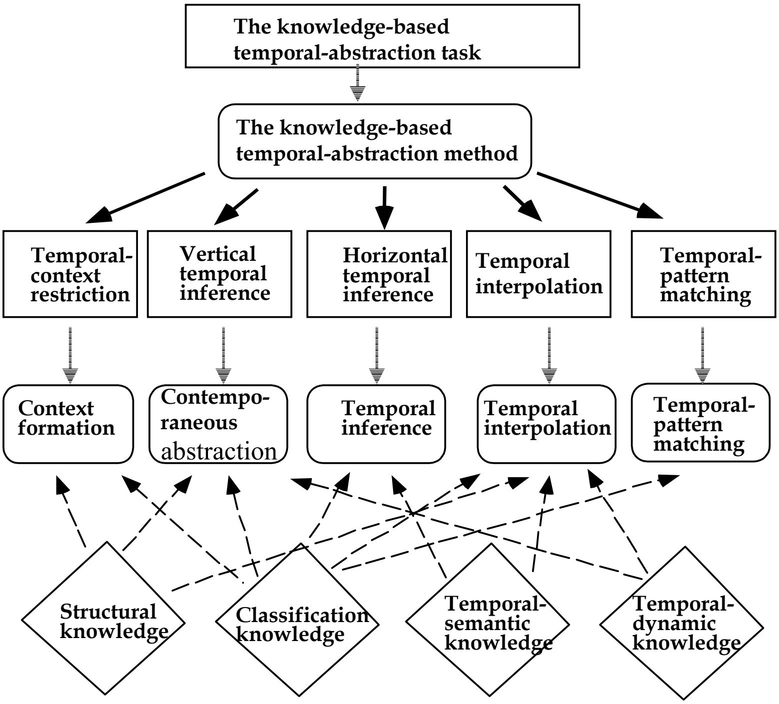

Fig. 1. The knowledge-based temporal-abstraction (KBTA) method. The TA *task* is decomposed by the KBTA *method* into five *subtasks*. Each subtask can be performed by one of five TA *mechanisms*. The TA mechanisms depend on four domain- and task-specific *knowledge types*. Rectangle = task; oval = method or mechanism; diamond = knowledge type; striped arrow = DECOMPOSED-INTO relation; full arrow = PERFORMED-BY relation; dashed arrow = USED-BY relation.

All of the TA mechanisms require the existence of four *TA knowledge types*: *Structural* knowledge, *Classification* knowledge, *Temporal-semantic* knowledge, and *Temporal-dynamic* knowledge [see Figure 1]; I discuss their semantics in Section 2.2.

Without delving into the formal details of the TA ontology, which are described in detail elsewhere [1, 6, 7], it is important to realize that it relies on only a small number of basic ontological entities, or *parameter propositions*, all of which can hold only on temporal *intervals* (possibly of zero duration, in the case of measurements):

1. *Events* (interventions) (e.g., insulin therapy; surgery; irradiation); they are related to each other through *part-of* and *is-a* relations.
2. *Parameters* (concepts) represent measured raw data and derived [abstract] concepts (e.g., hemoglobin values; anemia levels; liver toxicity grade); they are related to each other through *abstracted-into* and *is-a* relations;
3. *Patterns* (e.g., *crescendo angina*; *paradoxical hyperglycemia*) are composed of components, amongst which hold time and value constraints. Patterns are related to other abstractions, including other patterns, through *component-of* and *is-a* relations;
4. *Abstraction goals* (user views)(e.g., diabetes therapy) are used to explicitly set the context through specification of the abstraction process's objective. They are related through *is-a* relations;
5. *Interpretation contexts* (effect of regular insulin; being pregnant; being an infant) provide the necessary context for the abstraction process, since TA knowledge is only defined within some TA context. They are inter-related through *subcontext* and *is-a* relations (leading to nested, more specific *composite* contexts) and have an *induced-by* relation to all other entity types.

Interpretation contexts are a key aspect of the KBTA ontology and method. They create a frame of reference for all abstractions, which must hold within some context (e.g., pregnancy); on one hand, they efficiently *limit* the application of TA knowledge to only relevant contexts, while on the other hand, they lead to the application of the *most specific* knowledge (e.g., pregnancy *and* diabetes). They are highly flexible: *Any temporal relation* (e.g., During, After) can hold between the inducing interval-based entity and the induced interval-based interpretation context. Thus, an entity (e.g., a medication administration) can induce an interpretation context in the present, future (e.g., being under the effect of the medication) or even past (e.g., detection of a disease implies being in the context of its preceding phase in the preceding three weeks), thus leading to a limited amount of *foresight* and *hindsight*. Of course, induction of a new context can lead to the generation of new abstractions. In spite of this high expressivity and flexibility, it can be proven that the context-formation process is finite [8].

Contexts are also important for efficient knowledge engineering: The *same* interval-based entity (e.g., the same disease event) can induce *multiple* interval-based contexts (e.g., potential present and future complications), using a different set of temporal constraints for each of them, while the *same* interpretation context (e.g., *being under chemotherapy*) can be induced by *multiple* different types of entities (e.g., different types of chemotherapy medications), thus facilitating knowledge maintenance.

Finally, multiple interpretation contexts can hold in parallel, leading to multiple non-conflicting interpretations of the same data (e.g., within different diagnoses). There is no contradiction, since each interpretation holds within a different context [8].

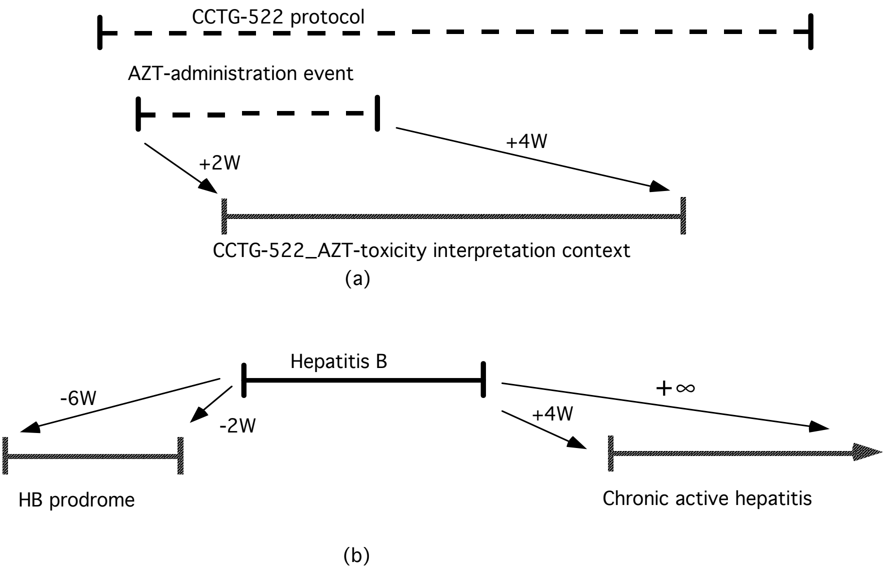

Fig. 2. Dynamic induction of context intervals. (a) An overlapping direct and prospective CCTG-522_AZT-toxicity interpretation context. The interpretation context starts 2 weeks after the start of the inducing event, and ends 4 weeks after the end of the inducing event. Note that the two interpretation contexts (not shown here), induced by the AZT-administration event and by the CCTG-522 protocol event, create a composite interpretation context whose meaning is "AZT-therapy–toxicity, as part of the CCTG-522 protocol." (b) Prospective (chronic active hepatitis complication) and retrospective (hepatitis B prodrome) interpretation contexts, induced by the external assertion or internal conclusion of a hepatitis B abstraction interval, a context-forming abstraction. Note the temporal constraints. Dashed line = event interval; _striped line = context interval; bounded line_ = abstraction interval.

Figure 2 demonstrates several potential relations between an inducing interval-based entity (or set of entities) and the induced context interval.

In addition to context intervals, the output of the TA task includes abstractions of several *types*:

1. *State* abstractions (e.g., LOW, HIGH) classify the amplitude of one or more contemporaneous concept values;
2. *Gradient* abstractions (e.g., INC, DEC) characterize the direction of change of a raw or abstract concept;
3. *Rate* Abstractions (e.g., SLOW, FAST) characterize the rate of change of a raw or abstract concept;

4. *Trend* abstractions (a recent extension of the KBTA ontology) are a combination of Gradient and Rate abstractions and characterize the overall behavior of a time series;
5. *Pattern* abstractions (e.g., CRESCENDO) include components that are of several ontological types. Patterns can be of several subtypes: *Linear* [one-time] patterns; *periodic* [*repeating*] patterns; or *fuzzy* patterns (allowing for a partial match) [9-11].

2.2 Temporal-Abstraction Knowledge Types

For our current objectives, namely, to examine the nature of declarative knowledge, it is important to examine the four types of TA knowledge used by the five TA computational mechanisms; these can now be characterized as follows:

1. *Structural* knowledge (e.g., *part-of, abstracted-into, is-a* relations) is mainly *declarative/relational* knowledge that links the various entities into a semantic network. Creation of this network is usually the first phase in the acquisition of TA knowledge in any particular domain.
2. *Classification* knowledge (e.g., value-range functions; pattern definitions) is mainly *functional* knowledge, such as classification (a function) of one or more contemporaneous values (e.g., Hemoglobin-value; weight and height) in a particular context into the value of one abstract concept (e.g., level-of-anemia; Body-Mass-Index [BMI] abstraction = Weight/Height^2).
3. *Temporal-semantic* knowledge (e.g., the "*concatenable*" property) is mainly *logical* knowledge that enables inference from one or more temporal intervals, over which holds some predicate, into another interval. For example, two periods of moderate anemia, each lasting two weeks, can be concatenated into a single, longer, four weeks period of moderate anemia; however, two periods of pregnancy, each lasting nine months, *cannot* be concatenated into a single longer period of an 18-month pregnancy. The reason is that Moderate anemia (actually, within a particular context) is a *concatenable* predicate, which can be "glued" to a similar-value predicate that holds over an adjacent interval; pregnancy is not concatenable. Similarly, knowing that the patient was in a coma for a week, enables us to infer that she was in a coma on Tuesday of that week; however, knowing that during that time she had Labile Hypertension (an oscillating, non-monotonic blood pressure) does *not* suffice to infer whether she also had labile hypertension on Tuesday of that week. The reason is that Coma is a *downward-hereditary* predicate, which holds over any sub-interval of the interval over which it holds, while Labile Hypertension is not. (Temporal semantic knowledge is an operational, inferential extension of Shoham's temporal-semantic properties of temporal propositions [12].)
4. *Temporal-dynamic* knowledge (e.g., interpolation functions that bridge gaps among time points or time intervals) is mainly *probabilistic* knowledge about persistence of temporal predicates when their value is not directly measured or assessed. Thus, one might join two days of moderate anemia within the same week into a longer period of moderate anemia, bridging a

gap of several days, but not bridge a gap of several months. Temporal-dynamic knowledge depends heavily on the type of concept, its value for both of the points or intervals being joined, and the context [13].

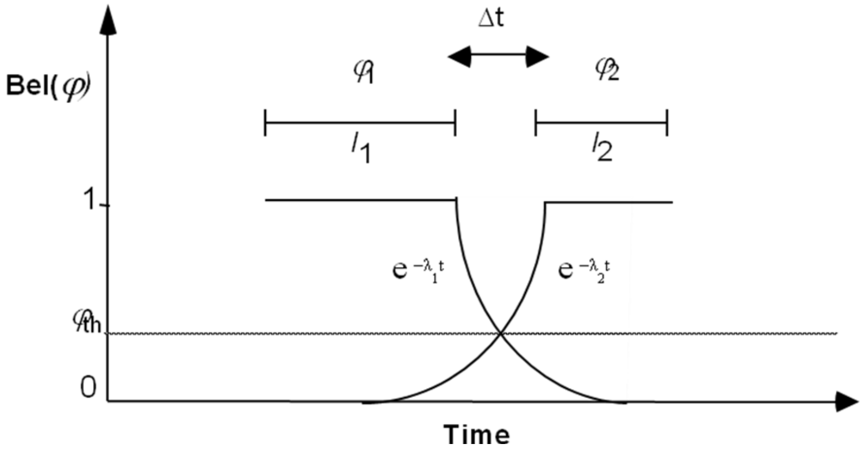

Fig. 3. Local and global persistence functions. The maximal time gap Δt that can be bridged between two predicates (parameter propositions) of the same type, which can then be joined, is returned by a global Δ function and decides whether the parameter propositions of the same type (e.g., a state-abstraction of the hemoglobin level) φ_1 and φ_2, interpreted over intervals I_1 and I_2, can be joined (and if so, what would be the value of the joined predicate, when the values are different). The time gap Δt can be interpreted as the maximal time gap during which the belief produced by either the local forward or backward decay (represented by a local-persistence (ρ) function) stays above a predefined confidence threshold φ_{th}. Bel(φ) = degree of belief in φ; φ_{th} = the task- and context-specific belief-threshold value.

Temporal-interpolation functions, which represent temporal-dynamic knowledge, actually can be further characterized [13], as demonstrated by Figure 3:

- *Local (ρ) persistence* functions represent the local persistence of the truth of a parameter proposition (a decay of the degree of belief forwards to the future, or backwards to the past), given a single parameter point or interval;
- *Global (Δ) maximal-gap persistence functions* return the maximal time gap Δt that still allows us to join two interval-based propositions into a single interval-based abstraction that is believed to be true, with a sufficient, task-specific, predefined degree of belief in the proposition, above some threshold belief, during the gap (a function of the parameter, its value, context, and the two interval durations). They can be viewed as an extension of local persistence functions, which often can be constructed from them: the proposition holds during the gap if it *still* holds (due to the first interval) or *already* holds (due to the second interval). Global functions are easier to acquire, since they can be linear functions of the interval durations.

- Global persistence functions can have four *qualitative types*: PP, NN, PN, and NP, depending on whether the Δ function, returning the maximal gap between the two intervals, is either (1) *Positive monotonic* (P), or (2) *Negative monotonic* (N), with respect to (a) the length of the first parameter interval L(I_1), or (b) the length of the second parameter interval L(I_2). For example, a PP characterization of Moderate_Anemia in the context of pregnancy means that given two such Moderate_Anemia intervals, the longer either interval is, the longer the maximal gap between them that can be bridged to join them.
- Claim 1: Positive-Positive (PP) monotonic Δ functions are *associative* (the order of joining intervals and points cannot change the resulting set of abstractions) [13]. This property is useful for rule-based inference systems, and guarantees that regardless of the order of arrival of data, the overall interpretation will be the same. Fortunately, the global interpolation functions of most clinical predicates belong to the PP category-the longer the duration of either interval-based predicate, the longer the gap allowed among them.

  However, several clinical predicates (e.g., pregnancy; severe cardiac arrhythmia) do not have this property, and are characterized by Negative-Negative (NN) monotonic global-interpolation functions: The longer the duration of the first or second abstraction, the shorter the maximal gap allowed between them for joining them, since there is a limit on the overall duration of the resulting abstraction (e.g., a very long arrhythmia might not be compatible with life, and a too long pregnancy is impossible). Unfortunately, it can be shown that the result of the abstraction process for such predicates depends on the order of their arrival. Thus:
- Claim 2: NN Δ functions are *not* associative [13].

It is still an open question whether PN and NP Δ functions can exist at all. It is reasonable that with appropriate semantic constraints, they should not exist.

One approach that eventually might settle the PN/NP global persistence functions existence question and also adds additional insights regarding the temporal interpolation task is the use of *Irregular-Time Bayesian Networks* (*ITBNs*) [14].

Discrete-time Markov models do not handle time irregularity well: Kalman Filters, Hidden Markov Models, and Dynamic Bayesian Networks require the specification of a constant time difference between each two consecutive observations. This leads to inefficient computation or to information loss, and limits the inference to only whole multiples of the modeled time granularity (e.g., minutes). On the other hand, Markov models that represent time *continuously*, handle well time irregularity, but suffer from other limitations; they assume either a discrete state space (as Continuous-Time Bayesian Networks do), or a continuous state space (as stochastic differential equations). ITBNs generalize Dynamic Bayesian Networks, such that each time slice may span over a time *interval* rather than a single time *point*, and the time difference between consecutive slices may *vary* according to the available data and inference needs, leading to increased computational efficiency and increased expressivity [14]. The resulting *distribution* of missing values during gap intervals is an interpolation.

The *temporal-abstraction task* can now be defined more formally as follows, in the terms of the TA ontology: Given at least one abstraction-goal interval, a set of event intervals, a set of parameter intervals, and the domain's TA knowledge, produce an *interpretation* - that is, a set of context intervals and a set of (new) abstractions - such that the interpretation can answer any temporal query about all of the abstractions *derivable from the transitive closure of the input data and the domain's TA knowledge*. The TA task is thus a knowledge-based data-integration task.

2.3 Elicitation and Specification of Temporal-Abstraction Knowledge

Once the precise knowledge roles implied by the TA ontology are formally defined with respect to structure, relationships, and semantics, they can be acquired from medical domain experts, often through a collaboration with medical knowledge engineers. This task was initially performed using the Protégé framework [15].

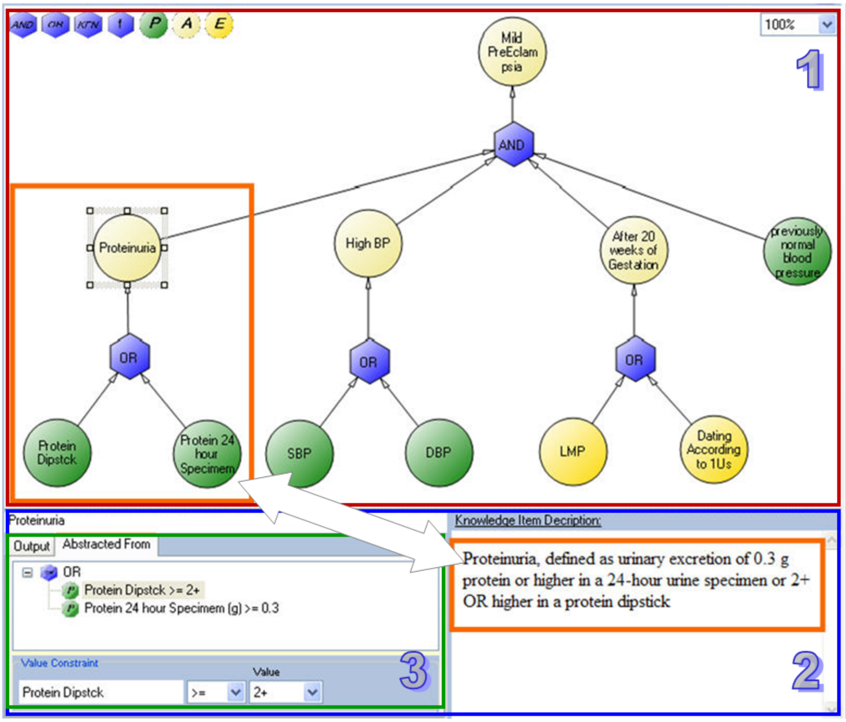

Fig. 4. Part of the *Knowledge Map* interface of the GESHER module for specification of declarative temporal-abstraction knowledge. Abstract concepts are defined in terms of raw concepts or lower-level abstract concepts; their properties (such as local persistence before or after being measured [see Section 2.2]) can be explicitly defined. Terms such as *Diastolic Blood Pressure* (*DBP*) are raw concepts that must be mapped to the electronic medical record.

More recently, TA knowledge has been acquired from medical domain experts using more specific tools. Figure 4 displays the *Knowledge Map* interface of the GESHER module [16] for specification of declarative knowledge, and in particular, of temporal-abstraction knowledge. Underlying the interface is the KBTA ontology. Abstract concepts are defined in terms of raw or intermediate concepts, and their properties (e.g., persistence before or after being measured) can be explicitly defined.

A rigorous evaluation has demonstrated that not only knowledge engineers, but also clinical editors (e.g., medical residents) trained in the use of the GESHER module, can specify declarative clinical knowledge with high correctness and completeness; the best results were achieved by using pairs consisting of a domain expert and a knowledge engineer [16]. These results extend the results of Shalom et al. [17, 18], who had proven that clinical editors (domain experts trained to use knowledge-specification tools) can specify guideline-based procedural knowledge.

3 Mediation of Declarative Clinical Knowledge: The IDAN Knowledge-Based Temporal-Abstraction Architecture

Mediation of abstract queries from medical decision-support applications to clinical databases that contain raw data requires an intelligent mediation service, especially when declarative TA knowledge is needed to answer the query. The first temporal mediator was Tzolkin [19]; its full-blown version is manifested by the IDAN mediator.

3.1 The IDAN Temporal-Abstraction Mediation Service

IDAN [20] is a distributed, goal-directed (query-driven) *temporal-abstraction mediator* that exploits the KBTA method and its ontology, although its highly generic architecture does not depend on that ontology. The IDAN mediator provides a clinical user or a decision support application with an inference engine to query in a transparent fashion time-oriented clinical patient data, basic temporal abstractions, or complex temporal patterns. Note that specialized temporal-reasoning inference is required to answer complex queries about temporal abstractions or patterns.

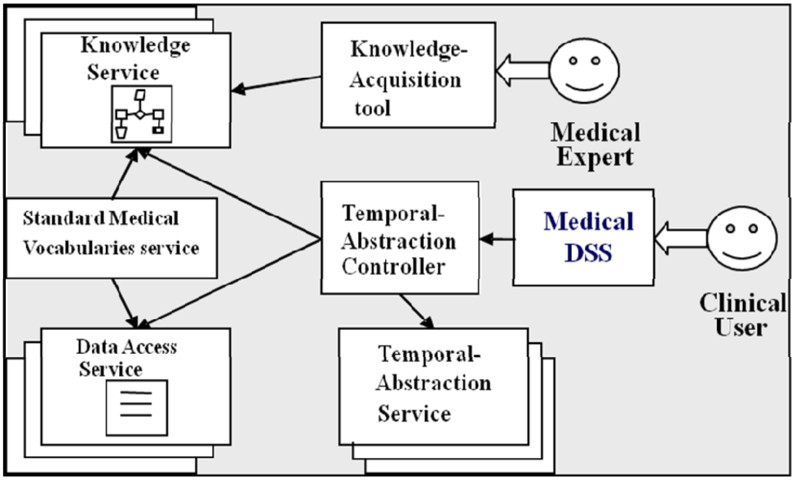

Fig. 5. The architecture of the IDAN knowledge-based temporal-abstraction mediator. A clinical user interacts with a medical decision support system (DSS), such as for guideline application or for intelligent exploration of patient data. The DSS [abstract] query is answered by applying relevant temporal-abstraction knowledge to appropriate time-oriented clinical data.

Figure 5 displays the architecture of the IDAN temporal-abstraction mediator. The mediator's controller effectively mediates a complex, knowledge-based query, involving several domain-specific clinical abstractions, by retrieving the relevant medical knowledge and clinical time-stamped data; the temporal-abstraction service then applies the appropriate context-sensitive knowledge to the relevant clinical data.

One question that immediately occurs is, How do we link, or rather *map*, a generic temporal-abstraction knowledge base, possibly providing the basis for a set of procedural guidelines in a particular clinical domain, to the specific local EMR, so as to be able to apply the GL knowledge in a manner customized to each patient's data?

The answer is to use *standardized medical vocabularies* when specifying the leaves of the guideline's knowledge map (see Figure 7).

One such system linking a declarative knowledge base to a set of clinical data bases is the *Medical Adaptor* (**MEIDA**) system of German et al. [21]. The MEIDA system has been evaluated by linking several different declarative knowledge bases to several different clinical databases, using a set of standardized vocabularies to represent the raw knowledge concepts, and mapping them to the relevant clinical database. It is interesting that, beyond using mapping heuristics such as performing a string-based search for the concept name within the local database, or using the type of vocabulary by which the concept has been defined in the knowledge base, the evaluation demonstrated the surprising efficacy of exploiting a new *measurement units* ontology to disambiguate several alternatives [21]. Note that the *schema* of the local database (such as, how is a patient ID determined, and where is it stored) must also be considered. Indeed, a similar study by Peleg et al. [22], who developed a *Knowledge-Data Ontological Mapper* (*KDOM*) that maps declarative concepts to the local database schema at a higher level, using an HL-7 model, has demonstrated how clinical-guideline knowledge can be mapped to a specific clinical database.

Thus, it is provably feasible to map a declarative knowledge base to a local EMR.

3.2 Incremental Temporal Abstraction: The Momentum System

The IDAN temporal-abstraction mediator is an excellent solution for a *goal-driven* or *query-driven*, application of TA declarative knowledge: The query is answered by accessing only the relevant knowledge and data required to answer it. However, other types of applications require continuous, *data-driven*, monitoring of patient data, and might also need to store the continuously computed abstractions for purposes of future query and analysis. These two computational objectives are achieved by the *incremental knowledge-based temporal-abstraction* (*iKBTA*) method [23], an extension of the KBTA method.

The iKBTA method has been implemented and evaluated within the **Momentum** system [24]. The Momentum system extends the active database concept into an active time-oriented database, which continuously performs temporal abstraction of arriving raw data using the domain's TA knowledge. It also provides persistence of the derived concepts and of their justifications, by storing the computed abstractions and their justifications in a specialized database. Finally, it can re-compute previously concluded abstractions efficiently (i.e., incrementally, on a need-to-modify-only basis) when old data are modified, or when data with a past *valid-time* stamp arrive with a present *transaction time*, thus potentially invalidating some previous interpretations (i.e., abstractions). For example, given a newly known normal value for Hemoglobin on last Tuesday that has only been asserted today, it might no longer be true to think that the patient had moderate anemia through the whole previous week based on the Monday and Thursday values.

The Momentum system merges two important tasks, *temporal abstraction* and *temporal maintenance* (i.e., the capability for storage, update, and query time-oriented data and their abstractions) [25], within a persistent temporal database framework.

3.3 Applications of the KBTA Method

The KBTA method, underlying a goal-driven temporal-abstraction mediator such as IDAN, or a data-driven continuous abstraction module such as Momentum, has been applied in multiple medical and nonmedical domains.

Applications of KBTA in medical domains include its use for procedural, guideline-based care in multiple clinical domains, such as AIDS therapy [2]; oncology [2,3]; congestive heart failure [26]; preeclampsia [26]; assessment of children's growth [4]; therapy of insulin-dependent diabetes [3, 5]; and others.

The KBTA method was also found as highly useful in multiple non-medical domains, such as for evaluation of traffic-controllers actions [27]; summarization of meteorological data; integration of intelligence data over time; and monitoring electronic security threats in computers and communication networks [28, 29].

However, in the next two sections, I will focus on two quite different types of applications of declarative (TA) knowledge: Visualization and exploration of longitudinal clinical data, and knowledge discovery from temporal databases.

4 Knowledge-Based Visualization and Exploration

It is much easier to make significant clinical decisions based on longitudinal clinical data, when these data can be visualized in multiple meaningful ways [30]. One meaningful way for displaying and interactively exploring clinical longitudinal data is by enabling the user to visualize and explore the *interpretations* that can be derived from the data, by applying to them on the fly the relevant, context-sensitive TA knowledge, resulting in *model-based visualization* of time-oriented data [31].

4.1 The KNAVE-II and VISITORS Intelligent Exploration Systems

The IDAN temporal-abstraction mediator and the KBTA methodology underlying it have therefore been used as the basis for the **KNAVE-II** intelligent visualization system [32], designed to monitor, visualize and explore individual longitudinal patient records, such that *all exploration is performed through the TA ontology* (Figure 6).

The KNAVE-II system has been evaluated rigorously at the Palo Alto Veterans Administration Health Care System [33]. A cross-over design study compared the performance of clinicians using the KNAVE-II module to the same clinicians when using either of two existing methods (in a second study, the users chose which method): Paper charts, and an electronic medical record represented within an electronic spreadsheet (ESS) with which the clinicians were familiar. The initial study included eight clinicians with varying medical/computer use backgrounds; a second study added six additional clinicians and more difficult queries. Each user was given a brief demonstration of the KNAVE-II interface.

The evaluation used an online database of more than 1000 bone-marrow transplantation patients followed for 2 to 4 years. Each user was asked to answer 10 queries common in oncology protocols, about individual patients, at increasing difficulty levels (complex queries often included several different parts, each of which was considered as a separate query). The measures included quantitative measurements of the time to answer and the accuracy of responses (on a predefined gold-standard scale). The study also assessed qualitative measures such as the Standard Usability Score (SUS) and comparative ranking of the three tools.

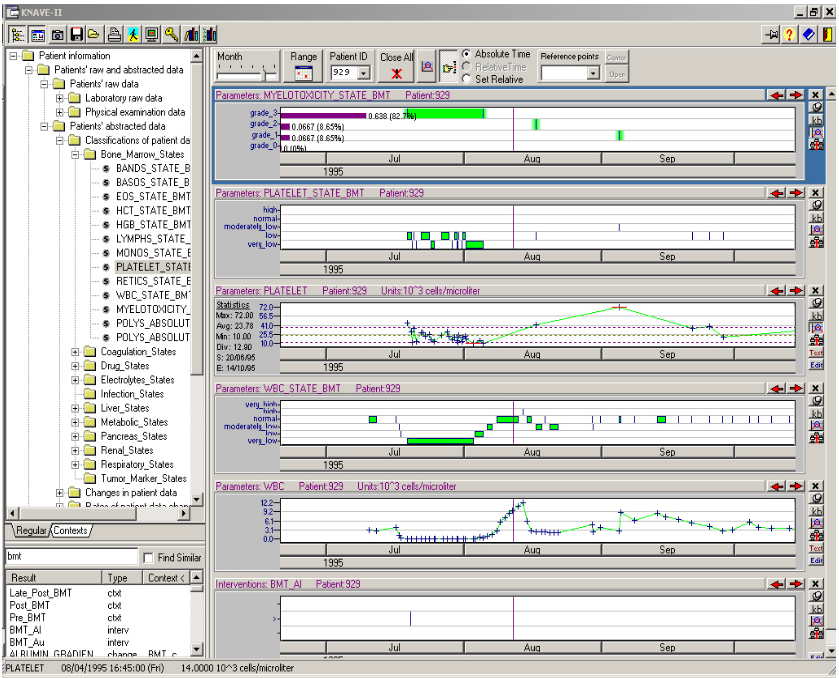

Fig. 6. The interface of the KNAVE-II system for individual patient-record exploration. The knowledge-based browser, displaying the domain's temporal-abstraction ontology, is on the left. Clicking on a concept uses a temporal mediator to compute it from the raw data and display it in a panel on the right. (Abstractions are displayed as intervals, as in the top two panels). The user can zoom temporally into and out of the data, pan the timeline, convert the absolute calendar timeline into one relative to some event, ask for statistics, such as mean, mode, or frequency of certain values, and perform an analysis of the sensitivity of abstractions to changes in data.

The KNAVE-II system was ranked first in preference by all users. the mean SUS scores were 69 for KNAVE-II, 48 for the ESS, and 46 for the Paper charts (P=0.006); in the second evaluation the SUS score was 64 for KNAVE-II and 45 for the ESS.

With respect to the *time to answer the protocol's queries*, in the first evaluation users were significantly faster using KNAVE-II, up to a mean of 93 seconds difference versus paper, and 27 seconds versus the ESS, for the hardest query (p = 0.0006). In the second evaluation, which basically pitted KNAVE-II versus the ESS, the comparison with the ESS showed a similar trend for moderately difficult queries (P=0.007) and for hard queries (p=0.002); the two hardest queries were answered a mean of 277 seconds faster when using KNAVE-II rather than the ESS.

With respect to the *correctness of the answers*, using KNAVE-II significantly enhanced correctness in assessing the patient's state according to the bone-marrow transplantation protocol's definitions. The correctness scores for KNAVE-II (92% [110/120]) versus ESS (57% [69/120]) in the second study, which used more difficult queries, were significantly higher for all queries (p<0.0001).

The **VISITORS** system [34] also exploits the IDAN mediator and the TA ontology, but is specific to the visualization and exploration of *multiple* time-oriented records (Figure 7), and supports research and new clinical knowledge discovery (Figure 8).

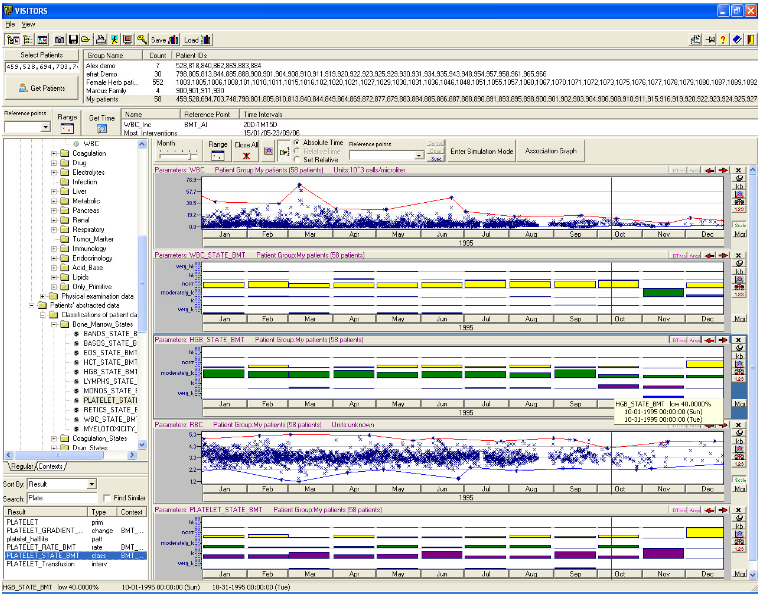

Fig. 7. The main interface of the VISITORS system for multiple-record exploration. The ontology-based browser appears on the left. The user selects a set of patients using a graphical specification tool, and then clicks on a concept, causing it to be computed for all selected patients. The user can zoom into and out of the raw or abstract concepts, examine raw-data values (top panel), chart the distribution of various temporal abstractions over arbitrary time periods (2nd and 3rd panels), use a timeline relative to some predefined event such as the bone-marrow transplantation, and investigate probabilistic associations among different concepts.

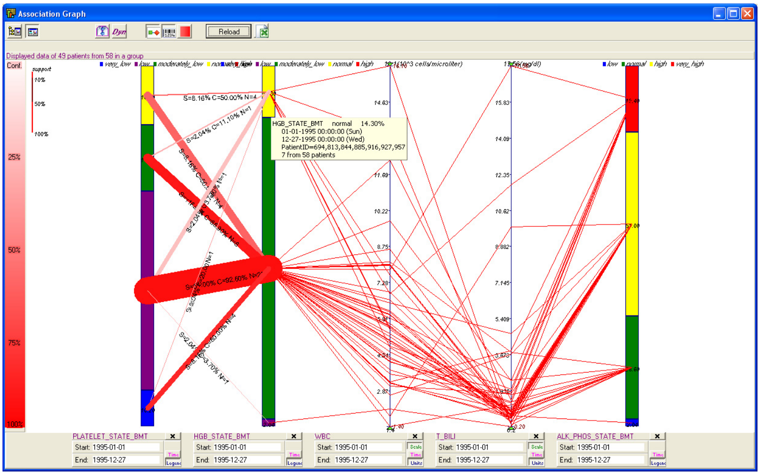

Fig. 8. Using temporal association charts in the VISITORS system. The user selects two or more concepts, whose distribution during the selected time periods is displayed, and examines the associations among them. Abstractions for the same subject group are connected; support and confidence of an association are indicated by width of link and depth of color, respectively. Here, 54% of the patients had a Low Platelet value *and* a Moderately_low Hemoglobin value; having the first value implied a high probability (92.6%) of having the second value.

The VISITORS system answers three main types of queries: *Select subjects* (*Who* had a given pattern?), *Select Time Intervals* (*When* did a given pattern occur?), and *Get Data* (*What* were the data for these subjects?*)*. Note that the second query includes also interesting cases difficult to compute without a knowledge-based temporal mediator, such as: Find time intervals (in a month-granularity resolution) during which the *HGB value state was considered lower than "normal"* in the post-bone-marrow transplantation period, for *more than 50%* of the subjects.

To select patients, the VISITORS system uses the *ontology-based temporal-aggregation* (OBTAIN) expression language [35] and a graphical tool to select patients using both demographic and knowledge-based, clinical concepts derivable from the raw data. The OBTAIN expression language was evaluated by the capability of users to correctly and quickly formulate effective patient-selection queries in it, with encouraging results [35].

The functionality and usability of the VISITORS main interactive exploration module were evaluated using a database of more than 1000 oncology patients and involved a group of 10 users—five clinicians and five medical informaticians [34]. Both types of users were able in a short time (mean of 2.5±0.2 min per question) to answer a set of clinical questions, with high accuracy (mean of 98.7±2.4 on a predefined scale, from 0 to 100). There were no significant differences between the response times and between accuracy levels of the exploration of the data using absolute (calendar-based) versus relative (referring to some clinical key event) time lines. A system usability scale questionnaire demonstrated the VISITORS system to be usable (mean score for the overall group: 69.3), but the clinicians' usability assessment was significantly lower than that of the medical informaticians.

Finally, the capability of both clinicians and the informaticians to answer clinically meaningful questions regarding a patient population using the VISITORS system was evaluated by having them use the VISITORS system's *Temporal Association Chart*s (*TAC*s) tool, which display probabilistic associations over time among selected concepts, and indicates both the absolute support to each association and the confidence in it (i.e., the probability of having a concept with a certain value appear after a particular value of the other concept was detected) (Figure 8) [36].

Both types of users were able to answer the questions in reasonably short periods of time (a mean of 2.5±0.27 minutes) and with high accuracy (95.3±4.5 on a 0-100 scale), without a significant difference between the two groups. All five questions requiring the use of TACs were answered with similar response times and accuracy levels. Similar accuracy scores were achieved for questions requiring the use of TACs and for questions requiring the use only of general exploration operators. However, response times when using TACs were slightly (but significantly) longer [36].

The rigorous evaluations of the KNAVE-II and VISITORS applications demonstrate the significant benefits of a sharable, formal medical declarative knowledge base. The time to assess the state of one or more patients decreases in a striking manner, while the accuracy of the assessment significantly increases.

4.2 Monitoring and Detection of Infections: The MeDetect System

Another type of visualization using declarative TA knowledge is demonstrated through the Medetect system, a decision-support system developed for monitoring infections in the infection-prevention unit at the Soroka Medical Center in Beer Sheva.

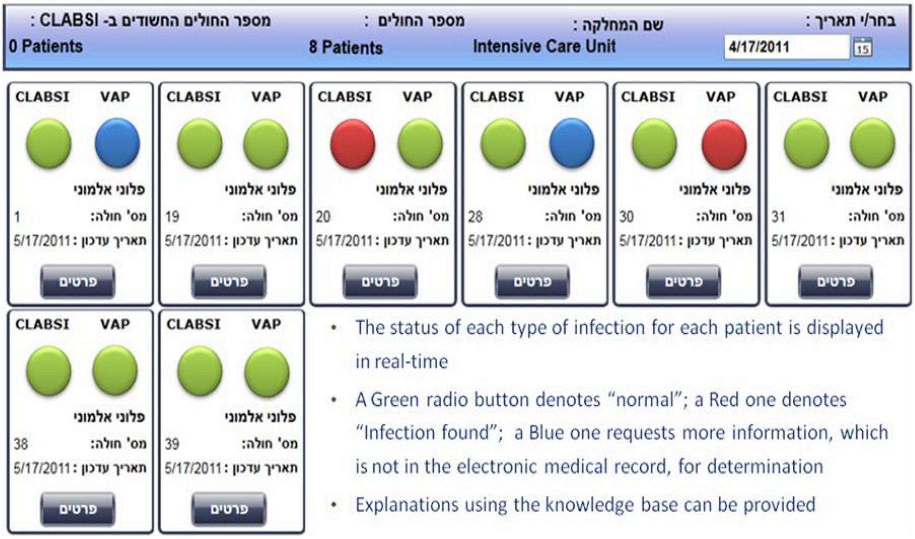

Fig. 9. The main interface of the Medetect system for continuous abstraction of the status of a group of intensive care unit patients (each represented by a small frame), with respect to a set of predefined infection temporal patterns (VAP and CLABSI, in this case). Green or Red buttons denote normal or pathological states, respectively; a blue button denotes suspicion and requests information that cannot be accessed through the electronic record (e.g., an X-Ray result).

In the Medetect system, designed to monitor patients in the intensive care unit (ICU), several complex patterns defined by the Center for Disease Control (CDC) were defined using the GESHER module. In particular, *ventilator-associated pneumonia* (VAP) and *central-line associated blood-stream infection* (CLABSI). The patterns are computed by the IDAN temporal-abstraction mediator and displayed using a specialized interface. Figure 9 shows the main interface of the Medetect system.

An evaluation of the Medetect system was performed in a retrospective manner on the data representing 8 months in the Soroka medical center and included 295 anonymous patients. Of these, 17 were eventually diagnosed with VAP and 14 were eventually diagnosed with CLABSI. With respect to specificity, the alerts raised by the Medetect system did not include any false positives. With respect to sensitivity, 11 of the 14 CLABSI cases (78.5%) were detected by the system, and all 17 (100%) of the VAP cases. The main reason to the reduced sensitivity for CLABSI was lack of data necessary for the diagnosis in the electronic database.

5 Temporal Data Mining Using Temporal Abstractions

The increasing use and availability of longitudinal electronic data presents a significant opportunity to discover new knowledge from multivariate, time-oriented clinical data, by using various data mining methods. In particular, discovery of frequent temporal patterns has significant potential benefits. It might lead to the *clustering* of patients who have a similar temporal pattern of interaction among their diseases, medications, and certain symptoms. Such patterns are useful for detecting and understanding typical disease pathways with respect to clinical manifestations and resulting costs. In other cases, discovery of frequent temporal patterns can lead to the *prediction* of certain future outcomes, given certain current temporal patterns.

However, multivariate time-oriented data are often present at various levels of abstraction and at multiple temporal granularities, thus requiring a transformation into a more abstract, yet uniform dimension suitable for mining. A preprocessing step of temporal abstraction (of both the time and value dimensions) can transform multiple types of *time-point*-based *raw* data into a meaningful, *time-interval*-based abstract (symbolic) data representation, in which significant, interval-based temporal patterns can be efficiently discovered as frequent patterns of *temporal relations* amongst the intervals. Interval-based temporal data mining has been shown to be quite useful in multiple biomedical domains [38].

5.1 The KarmaLego Temporal Data Mining Framework

Moskovitch and Shahar [39, 40] introduced a modular, fast time-interval mining method, KarmaLego, which, starting from an input set of interval-based concepts abstracted from the original raw time-stamped data, efficiently enumerates all temporal patterns that exist within the data at a frequency above a given threshold, exploiting in the process the *transitivity* inherent in temporal relations.

A *Temporal Interval Related Pattern* (*TIRP*) is an unambiguous, complete description of the conjunction of all of Allen's [41] 13 temporal relations possible among a set of *symbolic* (abstract) time *intervals*, listed in lexicographic order [40]: A set of symbolic intervals and a set of the temporal relations among them (Figure 10).

The Karmalego framework introduced also the use of flexible, more robust, *fuzzy constraints* to define in an internally coherent fashion all temporal relations by an *epsilon value*, such that symbolic intervals need not, for example, meet each other at exactly the same minute, and thus introduced a mutually exclusive, more robust definition of all of Allen's basic temporal relations. Furthermore, the KarmaLego framework also introduced an option for *pre-clustering* the symbolic temporal intervals by their *duration*, thus increasing uniformity among the discovered TIRPs, although potentially reducing support for each of a larger number of types of symbolic intervals.

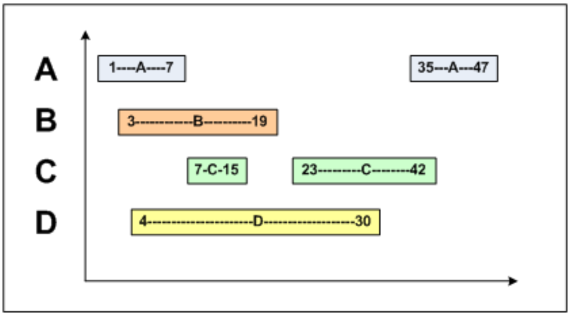

Fig. 10. A *Temporal Interval Related Pattern* (*TIRP*), denoting the unambiguous temporal relationships that exist amongst all of its interval-based components, such as the Overlaps/overlapped (o,o), Meets/met by (m,m), Before/After (b,a), and Contains, contained (c, c) temporal relations: {A1 o B, A1 o D, A1 m C1, A1 b C2, A1 b A2, B o D, B c C1, B b C2, B b A2, C1 b C2, C1 b A2, C2 o A2, D c C1, D o C2}, listed in a predefined lexicographic order.

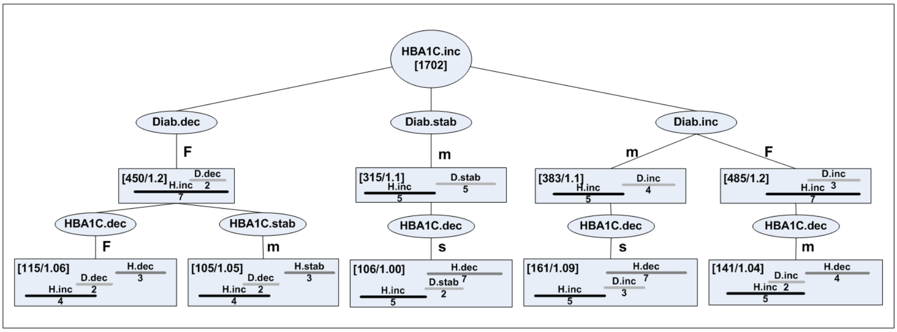

Fig. 11. Exploration of *Temporal Interval Related Patterns* (*TIRPs*) in the diabetes domain. Each path in the tree denotes a particular temporal pattern. Oval nodes denote specific symbolic (abstract) intervals, such as a decreasing, increasing, or stable gradient of diabetes medications dose (D.dec, D.inc, D.stab) and similarly for HbA1C (H.dec, H.inc. H.stab). Links represent temporal relations (F=Finishes, M=Meets, S=Starts). For each path ending at a rectangular node, the pattern is displayed visually: The number of patients, *N* in which the TIRP was detected at least once (*Vertical Support*), and the *Horizontal Support*, *H* (mean frequency of the TIRP within the records of the patients in which it was found), are displayed as [*N/H*].

The KarmaLego framework was used to explore a set of records of diabetes patients [40]. The set contained 2038 diabetic patients' data accumulating over five years (2002-2007). It included monthly measurements such as HbA1c, Glucose, and Cholesterol values, and medications purchased, including diabetic (insulin-based) medications, statins, and beta-blockers, normalized by the *Defined Daily Dose* (DDD). The laboratory-test values were abstracted using the KBTA method, based on domain expert specifications. The medication doses were abstracted, using the *Equal-Width Discretization* method [39], into three states. The results are displayed in Figure 11. For each path; the number of patients *N* in which the TIRP was detected at least once (the *Vertical Support*), and the *Horizontal Support H* (mean frequency of the TIRP within the records of the patients in which it was found), are displayed. Interestingly, the frequency of many of the discovered patterns differed by the patients' gender.

5.2 Using Temporal Interval Related Patterns as Features for Classification

The TIRPs discovered by KarmaLego can be used as features for a classification task; this idea was demonstrated in several medical and nonmedical domains. In one example, an intensive care unit (ICU) dataset of patients who underwent cardiac surgery at the Academic Medical Center in Amsterdam during April 2002-May 2004 was investigated [39]. The static (nontemporal) data included details such as age, gender, and surgery type; the temporal data (heart rate, blood pressure, F_iO_2, etc) were measured each minute during the first 12 hours. The classification task was defined as determining whether the patient was mechanically ventilated more than 24 hours during her postoperative ICU stay. The dataset included 664 patients; 196 patients were mechanically ventilated for more than 24hrs (29.5%). Multiple aspects were investigated, such as the value of the Epsilon temporal-relations fuzziness factor value, the discretization method, and the feature-selection method. The overall accuracy was 79.6% for most combinations involving five discrete states, using a very simple equal-width discretization method that divides equally the numerical range of each concept.

6 Related Work

Knowledge-based medical decision-support systems in the 1970s and early 1980s settled for simplistic symbolic-token abstractions common in diagnostic systems, such as in MYCIN [42] or Internist-I [43], in which the user was essentially required to perform the abstraction herself, into symbolic tokens that could then be used by the reasoning system as a part of the input, such as "three weeks of moderate anemia".

The importance of automated temporal abstraction in the medical domain, for knowledge-based summarization of longitudinal records and for decision support, was recognized, however, long ago [7], starting with Fagan's rule-based ventilator management (VM) system [44, 45] in the intensive-care domain. Fagan's VM program included the concept of a context, by mapping raw data, such as blood pressure, into a context-sensitive range of values (e.g., *acceptable*), enabling the ultimate application of context-free rules and context-free aggregation of abstractions that assumed a common range of the abstract terms.

Note that VM's resultant context-free intermediate set of abstractions, which assume a similar set of terms such as "acceptable" or "Low, Normal, High," contrasts with the context-sensitive nature of KBTA properties, which are always context-dependent; even the set of values into which each concept can be abstracted might be quite different, depending on each concept (e.g., blood glucose value, versus Hemoglobin) and on each context (e.g., pregnant woman, versus a diabetes type II patient).

The focus on automated reasoning from raw time-oriented clinical data was continued by systems such as Down's summarization program [46] and de Zegher-Geets' IDEFIX system [47, 48], both of which used Bayesian models to infer higher-level intermediate and top-level abstractions (e.g., Nephrotic Syndrome) from the data, time-oriented queries, and a rather simple two-layer (Down) and three-layer [de Zegher-Geets) abstraction hierarchy. In contrast, the Temporal Control Structure (TCS) system by Russ [49] was mostly a specialized truth-maintenance system that maintained the relationship among raw data and inferences from them, in which the abstraction rules were essentially ad-hoc programs written in LISP by the user. Note that none of these systems provided an expressive temporal-abstraction ontology or consistent computational semantics.

Kahn's TOPAZ system [50-53] was a major step forward. It included an integrated, multiple-temporal–model interpretation scheme: (1) a numeric model that modeled quantitatively underlying processes as differential equations, and modified an atemporal, population-based model into a temporal, patient-specific model; (2) a symbolic, interval-based model that aggregated clinically interesting events into an interval-based hierarchy, using context-specific rules; and (3) a symbolic state-based model that generated text paragraphs in the domain's language from the interval-based abstractions, using augmented transition networks (ATNs).

To implement his architecture, Kahn developed the TNET management system and the TQuery temporal-query language. TNET was then extended by Kahn into ETNET, a knowledge-representation, temporal-reasoning and temporal-management system that used context-specific rules.

Nevertheless, TOPAZ essentially produced one highly domain-specific model (one concept [granulocytes], a single anatomic site [bone marrow], a unique disease [Hodgkin’s lymphoma], and a particular chemotherapy protocol [MOPP]); due to the lack of an expressive underlying ontology, it is not clear how reusable it could be across other clinical domains. Certainly, new knowledge is not easy to parameterize.

Another major step in the area of reasoning about time-oriented clinical data was provided by Haimovitz' and Kohane's TrenDx system [54-57], built on top of Kohane's constraint-network temporal utility package (TUP) system [58, 59].

TrenDx encoded patterns as *trend templates* (TTs) that describe typical clinical patterns as a set of vertical and horizontal constraints. TTs have a set of value constraints of the form $min \leq f(D) \leq MAX$; min, MAX, are minima and maxima of the function f defined over the measureable concepts D in the temporal range of the interval. Unlike the data-driven RESUME system implementation of the KBTA method, the TrenDx system implemented a goal-directed approach to pattern matching, starting with a given constraint-based temporal pattern. TrenDx was tested on cases in the pediatric growth-chart and intensive-care domains.

One interesting and quite unique feature of TrenDx was that TTs could be matched to *partial* patterns by maintaining an *agenda* of candidate patterns that might fit the data (in theory, even one point). Note that in KBTA, as well as in other pattern-matching approaches, only complete patterns that fit all constraints can be detected.

The TrenDx system is an excellent example for a whole category of query-driven pattern-matching systems that is well worth examining. Systems such as TrenDx focus on different goals from the previously mentioned abstraction systems, namely, they try to match given top-level temporal patterns to the input raw data, rather than attempt any general abstraction or summarization. Furthermore, unlike KBTA-based systems such as RÉSUMÉ or the IDAN temporal mediator, TrenDx used arbitrary functions without any knowledge base or abstraction hierarchy, such as already existing in the IDEFIX system. Note that TTs need to be re-constructed for new tasks: Old, intermediate parts of the abstraction hierarchy are not reusable, since they are not explicitly defined. Acquisition of a new TT involves definition of all levels of abstraction. No knowledge roles (e.g., *significant deviation*, a property of Gradient abstractions in the KBTA ontology), which might perhaps be implicit within some of the constraint functions, can be reused, nor is there any intent to facilitate their elicitation and acquisition from clinical users; nor is there any use of inheritance among pattern types and instances, since there is no explicit hierarchy. Thus, there can be no capability for answering queries regarding intermediate-level abstractions from which the top-level pattern is derived, and also no capability for using precomputed intermediate abstractions in the input, since the pattern matching process must start from the raw input data.

However, similar to the temporal-summarization systems and to the KBTA-based systems, TrenDx assumes incomplete information about the clinical domain, which prevents construction of complete numerical models. In that respect, both the various implementations of the KBTA method and the TUP-based TrenDx system have in common the attempt to generate from the raw data associative patterns, when knowledge is incomplete and data is sparse.

The importance of the research in the area of *Information Visualization* and in particular in the area of *Visual analytics* is continuously increasing [30]. Visualization of longitudinal clinical data has been explored, for example, in the LifeLines system [60, 61] and even the KNAVE-II concept of alignment of a timeline relative to key events eventually appeared in the literature [62].

However, the KNAVE-II and VISITORS systems are rather unique in their focus on (1) use of an underlying general temporal-abstraction ontology (the KBTA ontology) coupled with a domain-specific knowledge base, and (2) their reliance on a temporal-abstraction mediator, which includes within it a temporal-abstraction computational module. The knowledge base and the computational modules enable these systems to compute context-sensitive abstractions on the fly, provide knowledge-based explanations to these abstractions, navigate the visualized abstractions by exploiting the underlying ontology, and perform interactive, dynamic sensitivity analysis of the displayed abstractions, by computing patterns from revised raw data.

Temporal data mining has recently become a flourishing and important area in knowledge discovery. Unlike approaches that are mostly based on Before-After temporal relations, however, such as is assumed by the *Sequential Pattern Mining Algorithm* (*SPAM*) [63], or that rely on an aggregation of temporal relations such as *Before*, *Meets*, and *Overlaps* into a *Precedes* relation [38], The KarmaLego algorithm exploits *all* of Allen's 13 temporal relations [41]. Furthermore, it enumerates the complete, *unambiguous* temporal relationships among *all* of the pattern's interval-based components. However, as in the other interval- mining algorithms, KarmaLego exploits the apriori principle, namely, that a super-set of an infrequent pattern is infrequent. In fact, the KarmaLego algorithm is an extension and a more efficient implementation of the concept of a temporal enumeration tree suggested by Papapetrou et al. [64], which have used only 5 temporal relations, as well as the epsilon temporal-relation-fuzzification value for a subset of these relations.

7 Summary, Discussion, and Conclusions

It is clear from the overview presented in this paper that declarative knowledge in general, and declarative temporal knowledge in particular, plays a large role in multiple tasks relevant to the use of computational methods in medicine, from monitoring and therapy of individual patients, through the visual exploration of the longitudinal data of individual patients and of populations of patient, for the purpose of decision support, policy making, clinical research, and the discovery of new knowledge. This review of a particular line of research focusing on the representation and application of *declarative* clinical knowledge, can be considered as complementing a similar review of research focusing on the representation and application of *procedural* clinical knowledge [65]. Indeed, to design effective clinical decision-support systems in the 21st Century, both aspects must be considered.

Other applications for declarative clinical knowledge abound. For example, the comparison of patterns found in the patient's record to the patterns that should have been generated through a correct use of a particular guideline can provide us with accurate assessments of the degree to which the physician adheres to the guideline [66]. Note that *fuzzy temporal patterns* were used in that case, due to the requirements for generation of a quantitative partial match, and not just a binary indication.

One recent application of declarative medical knowledge is the automated summary of longitudinal electronic patient records as a set of temporal abstractions, which can then be pruned and organized as natural-language narrative in one or more languages, thus providing a succinct free-text summary of the patient's course at a desired temporal or abstraction granularity. Initial highly promising work has been carried out in Aberdeen University [67], focusing mostly on the automated generation of natural language summaries for relatively short periods, such as 45 minutes of neonatal intensive care; we are currently trying to generalize and extend that work [68].

Finally, as meaningful patterns are discovered and validated through the use of tools such as VISITORS and KarmaLego, these patterns can be added, either automatically or through semi-automated tools such as the GESHER module, to the domain's knowledge base. The enhanced knowledge base can then be used even more effectively to discover higher level patterns in the same or new data, thus creating an iterative process that continuously expands our declarative medical knowledge.

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