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Distributed, intelligent, interactive visualization and exploration of time-oriented clinical data and their abstractions

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Summary

Objectives: We present KNAVE-II, an intelligent interface to a distributed architecture specific to the tasks of query, knowledge-based interpretation, summarization, visualization, interactive exploration of large numbers of distributed time-oriented clinical data, and dynamic sensitivity analysis of these data. KNAVE-II main contributions to the fields of temporal reasoning and intelligent user interfaces are: (1) the capability for interactive computation and visualization of domain specific temporal abstractions, supported by ALMA — a computational engine that applies the domain knowledge base to the clinical time-oriented database. (2) Semantic (ontology-based) navigation and exploration of the data, knowledge, and temporal abstractions, supported by the IDAN mediator, a distributed architecture that enables runtime access to domain-specific knowledge bases that are maintained by expert physicians.
Methods and materials: KNAVE-II was designed according to 12 requirements that were defined through iterative cycles of design and user-centered evaluation. The complete architecture has been implemented and evaluated in a cross-over study design that compared the KNAVE-II module versus two existing methods: paper charts and an Excel electronic spreadsheet. A small group of clinicians answered the same queries, using the domain of oncology and a set of 1000 patients followed after bone-marrow transplantation.
Results: The results show that users are able to perform medium to hard difficulty level queries faster and more accurately by using KNAVE-II than paper charts and Excel. Moreover, KNAVE-II was ranked first in preference by all users, along all usability dimensions.

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Conclusions: Initial evaluation of KNAVE-II and its supporting knowledge based temporal-mediation architecture, by applying it to a large data base of patients monitored several years after bone marrow transplantation (BMT), has produced highly encouraging results.

1. Background: the need for abstraction, visualization, and exploration of time-oriented clinical data and concepts

Management of patients, especially chronic patients, requires collection, interpretation and exploration of large amounts of time oriented data. The task of creating interval-based concepts (abstractions) from time-stamped raw data is called *temporal abstraction* [1]. An example is abstraction of periods of bone-marrow toxicity (as defined in a particular context, e.g., following Bone-Marrow Transplantation and using a particular therapy protocol) from raw individual hematological data (Fig. 1).

Reasoning about propositions interpreted over time points and time intervals has a long history in philosophy, linguistics, computer science, and in particular, artificial intelligence. Examples include McDermott's point-based logic of time and actions [2], intended to support automated planning; Allen's interval-based logic of time [3], intended to support planning and natural-language understanding, and Shoham's temporal logic and analysis of temporal-semantic properties [4], which provided also a certain common ground to Allen's and McDermott's frameworks.

The ability to automatically create interval-based abstractions of time-stamped data, in particular in the medical domain, has multiple implications. Data summaries of time-oriented electronic data have an immediate value to a human user, such as to a physician scanning a long patient record for meaningful trends.

Several approaches were proposed to the temporal-abstraction task, typically focusing on clinical domains involving chronic patients, such as patients who have oncological or immunological diseases, insulin-dependent diabetes, or growth and development problems [5—10], or on more hectic clinical domains, in which data arrive rapidly, such as occurs in intensive neonatal or adult care units [11—13].

A consideration orthogonal to the rate of arrival of the information (although it is more common in "slow" domains), which is highly relevant to the issue of optimal visualization and exploration of time-oriented data and derived concepts, is how to treat the multiple temporal granularities (e.g., hours, days, months) inherent in any discussion of a longitudinal course. Several syntactic and semantic approaches were proposed and implemented [14,15].

Temporal abstractions also support recommendation and explanation of recommended actions by intelligent decision-support systems, as well as monitoring of clinical guidelines during application [16], and are a useful representation for intentions of clinical guidelines [17]. Meaningful time-oriented contexts enable generation of context-specific abstractions, maintenance of several interpretations of the same data within different contexts,

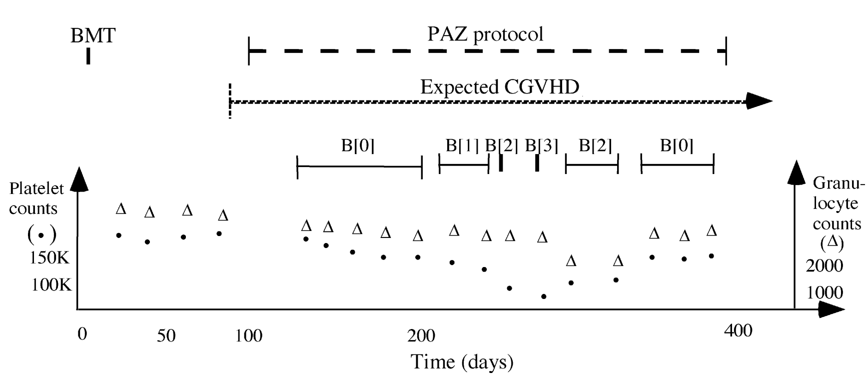


Figure 1 Temporal abstraction of a patient's data following a bone-marrow transplantation intervention. Raw data are plotted over time at the bottom. External events and the abstractions computed from the data are plotted as intervals above the data. (⊢ – –⊣) An external event (medical intervention); (●) platelet counts; (△) granulocyte counts; (⊢—►) a context interval; (⊢—⊣) an abstraction (derived concept) interval; BMT, bone-marrow transplantation (an event); PAZ, a therapy protocol for treating chronic graft vs. host disease (CGVHD), a complication of BMT; B(*n*), bone-marrow toxicity grade *n*, a (temporal) abstraction of platelet and granulocyte counts that holds over a particular interval.

and a certain amount of hindsight and foresight [18]. Domain-specific, meaningful, interval-based characterizations of time-oriented data are a prerequisite for effective visualization and exploration of these data [19—21].

A problem solver implementing a formal problem-solving method, the knowledge-based temporal abstraction (KBTA) method [1], called RÉSUMÉ, has been previously implemented and evaluated in several clinical domains [22]. The KBTA method requires explicit representation of four types of domain-specific knowledge: structural (e.g., part-of relations), functional (e.g., classification functions and definitions of complex patterns), logical (e.g., what concepts can be concatenated over time), and probabilistic (e.g., interpolation functions that bridge temporal gaps between similar concepts and fill in missing data), organized within a domain-specific temporal-abstraction ontology [1]. The knowledge required by the KBTA method underlying the RÉSUMÉ system is acquired from medical domain experts [23]. The knowledge base and computational mechanisms of the RÉSUMÉ system have been extended so as to enable representation of linear and repeating patterns using the CAPSUL temporal-pattern language and methodology [24]. The methodology was implemented and tested with respect to both acquisition and representation of patterns and detection of the patterns within a large longitudinal clinical database [25].

A stand-alone temporal-abstraction module is useless without the capability for effectively integrating it with the required clinical data and medical knowledge, and for effectively mediating temporal queries, when relevant, from various medical decision-support applications. An early temporal-mediation architecture, TZOLKIN [26] has been previously developed to integrate the databases, knowledge bases, and the computational temporal-abstraction module. Such architecture supports mediation of queries to time-oriented clinical databases. In our work, we have extended this early architecture to fully answer the requirements of care providers.

Supporting automated applications is not sufficient, however, to fully assist clinical care providers and researchers. An additional aspect of supporting clinicians performing tasks such as diagnosis, therapy, and research, is by supplying them with the technology for on-the-fly visualization, interpretation and exploration of the clinical data and of the higher level, knowledge-based, concepts that can be derived from these data.

Visualization and exploration of information in general, and of large amounts of time-oriented data in particular, is essential for effective decision making. Larkin and Simon [27] have demonstrated that the usefulness of visual representation is mainly due to (1) the reduction of logical computation through the use of direct perceptual inference, and (2) the reduction of necessary search for information through the use of efficient graphical representation.

Researchers in the areas of visualization of clinical time-oriented data [21,28], have developed useful visualization techniques for static presentation of raw time-oriented data and for browsing information. An excellent treatise on visualization is the series of books by Edward Tufte on methods to display information [29,30]. However, the methods presented in the above-mentioned papers and books are typically not interactive and relate to the raw data and not to abstractions of it. The Lifelines project [31,32] developed an intuitive visualization of historical events and data, demonstrated also in a medical domain, including an easy-to-use zoom-in and zoom-out interface. However, it does not build on any domain-specific abstraction knowledge and no underlying computational abstraction mechanisms. InfoZoom [33] uses a novel technique to display data sets as highly compressed tables which always fit completely onto the screen. The goal of their approach is not a completely automatic algorithm that searches for interesting results. Rather, they intend to enable the user to interactively explore and get a feeling of the data, detect interesting knowledge, and gain a deep understanding of the data set. Queries are performed by selecting parts of the displayed data. Derived attributes can be defined as in a spreadsheet program and are automatically updated when necessary. InfoZoom supports the medical expert in understanding the data and detecting the hidden knowledge. Our approach also enables interactive exploration of large amounts of clinical data; however, as will be demonstrated, it includes continuous access to an underlying architecture that performs the abstractions and to a domain-specific knowledge base; the knowledge base is used by he abstraction mechanisms as well as for navigating among various domain-specific concepts (e.g., from a pattern to its components) during the exploration process.

Several techniques specifically address the visualization of multidimensional data regarding clinical examinations [34]. In the MedView project [35], two information visualization tools were developed for visualizing clinical experience derived from large amounts of clinical data. The first tool (The Cube) implements dynamic three-dimensional parallel diagrams to enable the clinician to intelligibly analyze existing patient material and to allow for pattern recognition and statistical analysis. The system displays a 3D cube containing a number of parallel planes: each plane is devoted to one of the chosen attributes, and points on that plane display the individual values of the attribute for specific patients. The second tool, SimVis, was designed to help clinicians to classify and cluster clinical examination data. User interaction was supported by 3D visualization of clusters and similarity measures. The tools do not focus on temporal data or on abstractions of it.

Spotfire, a well known application for visual data mining and information visualization has been used in the pharmaceutical drug discovery task. Implementing dynamic queries, Spotfire supports easy import/export of data, rapid change of axes, color or size coding, and collaboration support [36—38]. Spotfire became a leader in dynamic data visualization with a very nice direct manipulation user interface; however, it lacks a time dimension (the default is that all data were gathered at the same time or are timeless), and has no knowledge base, or computational mechanisms that could use such a knowledge base to generate high-level abstractions. Another visualization project in the medical domain, the MeSHBrowse system, allows users to browse semantically associated links in the Medical Subjects Headings (MeSH) [39]. Although it displays a two-dimensional tree representation of associated categories to a selected concept, MeSHBrowse is not connected to the individual patient's data.

In recent years, researches have investigated various techniques for information visualization, including conceptual maps, radar maps, tree maps (conetree/camtree maps, hyperbolic tree), Kohonen maps, fish eye views and dynamic queries interfaces and more [40—44], as well as using well known statistical and graphical methodologies, such as 3D representations, scattergrams, pie charts, bar charts, and their derivative techniques. These display methods, however, typically do not focus on visualization of domain-specific temporal abstractions and on the issue of interactive manipulation and exploration of the data and multiple levels of its abstractions, using domain-specific knowledge. Typically, these capabilities have been omitted, because they require a formal, domain-independent representation of the domain-specific temporal-abstraction knowledge, considerable effort in modeling the visualized domain, and availability of computational mechanisms for creation of the abstractions.

The information visualization literature defines several techniques that enable interactive manipulation and exploration of data [42]. Brushing and linking enable dynamic connection of two or more views of the same data, such that a change to the representation in one view affects the representation in the other views as well [45]. Zooming is used to move "closer" to a particular item [46]. Zooming can help us to detect a specific data item within a set of closely-related items. Focus-plus-context makes a portion of the view — the focus of attention — larger, while simultaneously shrinking the surrounding objects [47]. Shneiderman [48] defines the central principle of the visual design guidelines as the visual-information-seeking-mantra that states: "Overview first, zoom and filter, then details on demand." In his data Type by Task Taxonomy (TTT) he adds three more actions: (1) relate by visualizing relationships between items, (2) keep a history of actions to support undo, replay and progressive refinement, and (3) allow extraction of sub-collections and of the query parameters.

We have implemented several of the above-mentioned functionality (mainly with respect to visualization of knowledge-based temporal abstractions) in a previous version of a system called Knowledge-based Navigation of Abstractions for Visualization and Explanation (KNAVE), as a stand-alone prototype module. Preliminary assessments of the KNAVE system, in the oncology domain, were highly encouraging, and demonstrated the feasibility of the whole architecture, and in particular of the knowledge-based exploration concept [19,20].

In order to provide a useful service for interactive exploration of time-oriented clinical data, additional requirements have been identified. The results of our preliminary studies have led to the definition of an enhanced version of the overall temporal-mediation architecture and, in particular, an enhanced interactive visualization and exploration tool: KNAVE-II.

Interactive visualization and exploration of clinical data and abstracted knowledge is supported by two mechanisms directly connected to the KNAVE-II interface, providing two main contributions to the field of intelligent user interfaces:

1. Adding the capability of interactive computation and access of domain specific temporal abstractions, a capability supported by the ALMA system [49], a computational engine that applies the domain KB through the clinical DB.
2. Enabling navigation and exploration of the clinical data and abstractions derivable from them, by moving through the links of a semantic network that is embodied in a series of domain-specific knowledge bases; the knowledge bases are maintained by expert physicians. The interactive mediation of the queries to the clinical databases, the relevant medical knowledge base, and the clinically meaningful abstractions that can be derived from the data using the

knowledge is supported by the IDAN mediator [50], a distributed architecture that enables online integration of clinical time-oriented data with relevant domain-specific knowledge, to produce the requested clinically meaningful temporal abstraction.

We implemented the user centered design approach to define a set of requirements that should be included in KNAVE-II. User Centered-Design (UCD) is a process that places the person at the center focusing on cognitive factors (such as perception, memory, learning, problem-solving, etc.) as they come into play during peoples' interactions with the interface [51]. UCD seeks to answer questions about users and their tasks and goals and use the findings to drive development and design. Adopting a user-centered design process leads to more usable systems and products dealing with both usefulness and usability [52]. The active involvement of users from the very early stages of concept development enables the incorporation of user-derived feedback into system design whereby a prototype is designed, tested and modified iteratively [53].

An independent group of three clinicians in internal medicine, pediatrics, and oncology from Stanford University's Medical Informatics Program and the Palo Alto Veterans Administration Health Care System, as well as three Ob/Gyn and other experts from the Soroka Medical Center, associated with Ben-Gurion University's School of Medicine, helped us to define the requirements. A multidisciplinary team composed of a user interface designer, a medical informatics expert, a software engineer and a knowledge engineer conducted with each expert at least three face to face interviews, five conference calls and sent and received several dozens of emails. All the diverse communications with the experts aimed at the design and evaluation of mockup and working prototypes. This user-centered design iterative process has led to the definition of twelve requirements for the provision of a comprehensive service for interactive exploration of time oriented clinical data, and its implementation as the KNAVE-II system (see Section 3).

2. Desiderata for interactive exploration of time-oriented clinical data

Our decade-long research into the subject of automated interpretation and exploration of time-oriented clinical data together with the user centered design approach have uncovered a set of desiderata that must be answered to truly assist clinical care providers, administrators and researchers who need to understand and explore a mass of time-oriented clinical data. The desiderata for provision of a service for interactive exploration of time oriented clinical data include the following requirements, which we will exemplify within the clinical scenario of management of oncology patients:

2.1. D-1: distributed and modular architecture

A modular, scalable architecture to enable the application of diverse (and preferable distributed) types of knowledge to the same clinical data, or the application of the same knowledge to different clinical data bases; the architecture should support access to both the data and the abstractions derivable from it.

The need for abstraction of meaningful domain-specific concepts and patterns in clinical tasks has been already noted [22]. In order to support decision support, clinicians should access diverse clinical data and apply different types of knowledge to that data. While applying the knowledge to the clinical data they make abstractions of that data to arrive to meaningful decisions. This task is very complex and time consuming. Thus, an architecture that enables access at the point of care (or quality assessment or research) to abstractions automatically extracted from the large mass of raw clinical data can save precious time and prevent errors.

Moreover, the distributed architecture is a key requirement, because domain-specific knowledge bases are often maintained by expert physicians who are geographically dispersed. Thus, a knowledge base regarding liver functions during the late recuperation phase following a bone-marrow transplantation, created at one site, can be automatically applied to data of patients who are being treated by a family practitioner at another site. A capability for displaying interactively the results of the integration of a certain set of clinical data with a certain set of medical knowledge instances will enable physicians who not necessarily as expert as the editor of the knowledge base to automatically apply expert knowledge to their own patients clinical data while being remotely located, thus providing a higher level of clinical decision support.

2.2. D-2: visualization of both raw data and its abstractions

Effective visualization and exploration should include both the raw clinical data and the abstract concepts derived from those data. These concepts should be derived in a context-sensitive fashion (e.g., by using the bone-marrow toxicity definition that is most specific to the particular combination of age, gender, therapy protocol, period before or after the bone-marrow transplantation intervention, or type of chemotherapy medication; and, for economic reasons, *only* that knowledge).

Interactive visualization of clinical data has been already supported in many previous works. It is already recognized that visualization and exploration of information of large amounts of time-oriented data is essential for effective decision making [27,31,32]. Although several applications provide the visualization of multidimensional clinical data [34,35,38], none of them supports any domain-specific abstraction knowledge or abstraction mechanisms. At most, InfoZoom [33] supports the medical expert in understanding the data and detecting the hidden knowledge. Our approach also enables interactive exploration of large amounts of clinical data, includes online computation of the relevant abstractions, and is supported by a continuous link to a knowledge base. It enables the clinician to visualize not only the raw clinical data of her patients (e.g., Hemoglobin values at particular time points), but also abstract, clinically meaningful concepts (e.g., "3 weeks of moderate anemia") that may save her time and support her clinical decision making.

2.3. D-3: temporal granularity

The visualization should support interactive exploration of time oriented data at different temporal granularities (e.g., hours, days, months).

Representation and visualization of various temporal granularities and their suitability for various clinical tasks have been widely studied [14,54].

This requirement seems to be very important for providing the physician with a capability for exploring specific known patterns at various time intervals (from few hours to several years) or even for discovering new patterns by looking at the raw data and its abstractions while viewing them within periods of time that are not necessarily previously defined. Thus, we need to enable the clinician or clinical researchers who are browsing a month's worth of data to zoom into the data or the derived concepts of each day in that month, or into any particular period (e.g., 6 particular days where the white blood-cell counts have rapidly decreased) within that month.

2.4. D-4: absolute and relative time lines

The system should support both a *calendar-based* time line (e.g., answer queries regarding hemoglobin values during August 1994) and a *relative* time line, which refers only to clinically significant events (e.g., periods of decreasing liver function within 6 weeks from the start of chemotherapy).

This capability has been already been supported in previous studies. Kahn [9] showed in the TOPAZ architecture that physicians were interested in manipulating time lines in the context of a chemotherapy treatment and not in the absolute date that it occurred. Also Lifelines [31,32] enabled similar capability. An interactive visualization interface should enable to visualize how the application of a specific treatment protocol has affected the patient a few days or weeks after its provision at any level of granularity required by that specific clinical task.

2.5. D-5: intelligent exploration of raw data and abstractions

Effective exploration of both the raw data and their abstractions, using meaningful domain-specific semantic relations (e.g., derived-from, part-of). Thus, motion should be supported along the semantic network implicitly defined by the various types of domain knowledge required for computing the abstract concepts (e.g., bone-marrow toxicity levels) from the raw data of measurements and interventions (e.g., white blood-cell counts, hemoglobin values, and platelet counts; and the bone-marrow transplantation or various types of transfusions).

In the field of information visualization several techniques have been implemented to abstract higher level concepts from raw free-text data. Scatter/gather [55], scatter plots [56] and Kohonen maps [57] show clusters of words or documents organized by automatically extracted categories at several levels. They enable free exploration of the categories at different levels of abstraction till the level of the individual object (terms or documents). However, this requirement has not been implemented in the field of quantitative time related data supported by abstracted knowledge.

2.6. D-6: explanation

The system should enable an explanation of the abstractions by providing on demand the most relevant data and knowledge used to derive the abstraction currently considered (e.g., "Which particular data underlie the current bone-marrow toxicity abstraction? *How* was it derived and what classification-definitions and other types of knowledge were used?"). These explanations should be available recursively for all intermediate abstractions.

Since the late seventies, rule-based systems attempted to provide explanations in order to let the user understand and rely on the way the system arrived to a conclusion. Explanations — or even the potential of asking for them, whether that potential is exploited or not — increase the confidence of physicians using a medical decision support system [58]. Our requirement demands that the system should provide full details of the data that lead to an abstracted concept as well as the functional-classification, temporal-interpolation functions, or time and value constraints that define each abstraction.

2.7. D-7: statistics

The system should provide statistics (customized for each data type, whether numeric or symbolic) regarding both the raw data and the concepts abstracted from it. Providing various statistics has usually been one of the primary tasks supported by visualization interfaces (Card, 2003). They should be dynamic, recomputed each time any new data appears in the data base. However, this service has not been provided for abstracted knowledge that is based on quantitative time related data. The requirement demands that statistics should be provided for both types of data, raw and abstracted knowledge with the relevant matching statistical analysis and displays (i.e., not just for the hemoglobin values but also for the bone-marrow toxicity periods).

2.8. D-8: search and retrieval

The system should support easy and fast search and retrieval of clinically significant concepts. Search functionality has become one of the most popular features in any user interface. The search functionality should reduce the user's memory burden, provide feedback, let the user a sense of control over the search results, and easy reversal of actions [42]. The existence of multiple medical vocabularies and the lack of a standard terminology impose the need for a search and retrieval facility that enables to browse amongst the retrieved concepts and select those the user would like to visualize. Thus, the user should be able to quickly search for a concept such as *multi-organ toxicity*, either through a semantically organized concept hierarchy, through a fast text-string search, or through other means.

2.9. D-9: dynamic sensitivity analysis

The system should include capabilities for interactive exploration of the effects of simulated hypothetical modifications of raw data on the derived concepts, to increase the clinician's confidence in the robustness of the interpretation. Thus, one should be able to determine whether changing a particular suspicious platelet-count value on a certain day affects in any way an overall pattern of multi-organ toxicity during that month. *Sensitivity Analysis* (sometimes referred to as *What-if Analysis*) is a well known feature already integrated in electronic spreadsheets. It determines which values in a spreadsheet model have the greatest impact on the results. Input values are varied (over a range) and the amount of change on the results is recorded. The Microsoft Excel spreadsheet, for example, includes an application named TopRank to perform a multi-way what-if analysis on a decision tree. The user, however, needs to define the links among various concepts herself-they are not part of the domain's ontology — and the algorithms using those links; the concept of time is not a first class citizen within the computations; and the output concepts are not necessarily of the same type (and a part of the same timeline) as the input data, which would be highly desirable in order to continue and apply to these concepts all of the computational and display operators already familiar to the user.

2.10. D-10: clinical-task support

The system should be customizable for a specific clinical task (e.g., monitoring of diabetic or oncology patients), which might require repeatedly producing for each patient or a group of patients a cluster of closely related multiple abstractions (e.g., fasting, lunch and dinner blood-glucose abstractions together with insulin administrations and renal function abstractions; or various hematological abstractions together with various renal and liver functions). Clinical-task support is a requirement that refers to the ability of the clinician to customize the interface for specific clinical tasks. A research community who has been dealing with customization issues for a long time is the user interface community, which has often emphasized the notion of adaptive user interfaces [59]. Adaptive user interfaces are designed to tailor a system's interactive behavior considering both individual needs of human users and changing conditions within an application environment. Kappel et al. [60] propose to add customization as a new modeling dimension into their requirements framework. The scope of customization comprises all the modeling dimensions; however, it is especially crucial for the content, presentation and hypertext levels. Chen et al. [56] have also shown the potential usefulness of concept-based clustering, albeit in the case of searching the internet to find a page useful to the user. As will be seen when discussing the KNAVE-II system, we have defined two services for customization. One relates to the content to be visualized, enabling an expert physician to save in a special set of data elements and derived concepts commonly related to a specific clinical task (such as monitoring of diabetic patients) that can be applied to any patient that a physician wants to monitor on that respect. The other customization service relates to the graphical objects of the presentation by means of "plug-in" modules that are applied only in particular domains or contexts to provide a "look and feel" of a task-related interface. For example, in the case of the domain of monitoring the various clinical parameters of women who come to Ben Gurion University's Medical Center fertility clinic, the need has emerged for having a context-sensitive tool tip that will show a baby's smiling face and the multiple quantitative values regarding the embryo's development, different from the usual one used to visualize the woman's physiological data.

2.11. D-11: collaboration

The system should support collaboration between different clinicians and researchers who need to access the same patient data and concepts derivable from these data. The need for collaboration between medical staff or different clinical roles has already been established. Groz [61] defined a collaborative enterprise as a cognitive entity in which the processes of information acquisition, planning, decision-making, and learning have properties that in turn shape behaviors and determine outcomes, that applies to many patient management clinical tasks. In the medical domain, most studies focus on developing models and technologies to support clinical discussions, clinical decision making and common medical terminology [62]. However, the provision for collaboration based on the actual clinical data and concepts abstracted from them using a particular domain-specific knowledge base is still lacking. Such a capability might improve significantly the support for tasks such as clinical-trial management, in which clinicians and biostatisticians need to access the same data, but typically at different levels of abstraction. Similarly, it would be useful if the capability for sending to a domain expert or pointing to her a particular surprising pattern discovered within an oncology patient's record was supported as part of the same interface enabling exploration of the patient's record.

2.12. D-12: documentation

The system should support documentation of the exploration process for multiple future uses, such as the clinician's own review of patient data, collaboration, external auditing, and quality assessment at various administrative levels. This requirement can be supported at a simple level by talking a snapshot of the data (for example, using the standard print screen function). However, an advanced service should support documentation of the whole abstraction and exploration process, to better enable backward exploration from the current documented patient state and to assess the clinical decision-making process. Thus, the documentation should include not just a static graphical snapshot of a top-level hematological pattern, but also all the related values of the raw data, the knowledge relevant to these data, and the abstracted concepts that were explored and displayed at any selected time span.

The above-mentioned desiderata emerged from our extensive experience and from studies performed by multiple researchers. However, these desiderata have not been applied to the task of exploring qualitatively and quantitatively large masses of longitudinal clinical data, through the use of a context-sensitive domain-specific knowledge base and dedicated computational mechanisms, to support actual clinical tasks such as patient management.

3. The KNAVE-II architecture and operators

We have recently developed an advanced prototype module, KNAVE-II, a new intelligent interface designed to fulfill all the above-mentioned desiderata. In this section, we explain in detail how the KNAVE-II architecture supports all desiderata (D-1 to D-12).

3.1. D-1: distributed and modular architecture

In order to support the modularity and accessibility requirements (D-1) (in the sense used above, such as at the point of care), a new knowledge-based distributed temporal-abstraction mediation architecture, *IDAN* [50], was designed and implemented. IDAN uses a modern version of the RÉSUMÉ problem solver, *ALMA* [49]. The modular architecture includes automated acquisition of domain-specific temporal-abstraction knowledge, a computational temporal-abstraction mechanism using that knowledge, a data-access service that accesses time-oriented databases, and controlled-vocabulary servers. The modular architecture includes multiple knowledge bases and time-oriented databases (Fig. 2).

Each use of a KNAVE-II operator issues implicitly a command to the application interface of the IDAN

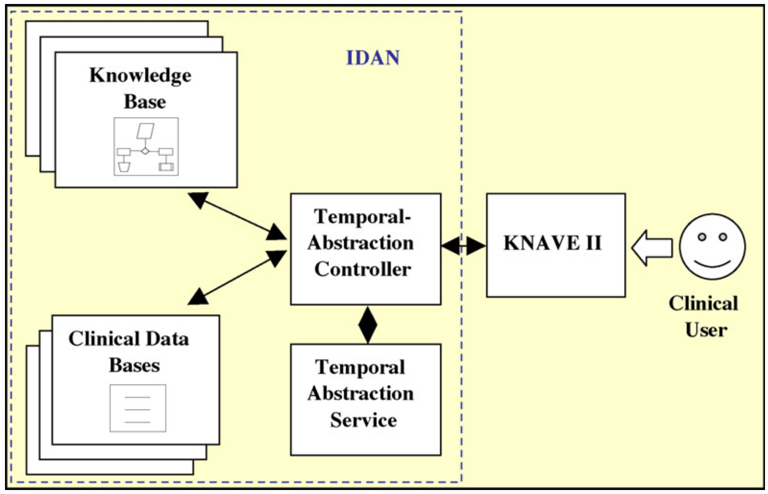


Figure 2 The distributed architecture of the IDAN knowledge-based temporal-abstraction mediator and its relationship to the KNAVE-II system. End users interact with KNAVE-II to submit time-oriented queries. The temporal-abstraction mediator answers these queries using data from the appropriate local data-source, and temporal-abstraction knowledge from the appropriate domain-specific knowledge base. The integration of the data and knowledge is performed by the temporal-abstraction service, a Web service containing the ALMA temporal-abstraction computational module. KNAVE-II then enables users to visually and dynamically explore the resultant abstractions, using a specialized graphical display and direct access to the domain-specific knowledge. Arrows indicates a ''uses'' relation.

temporal-abstraction controller (see Fig. 2), usually as an XML message. For example, clicking on an abstract concept in the ontology browser issues a goal-directed query to compute that concept, which leads to querying the knowledge base for the definition of that concept and for the raw data needed to compute it, and then to querying the clinical database for the necessary data. The data and knowledge are then sent to the temporal-abstraction (Web) service, containing the ALMA module, which integrates the data and knowledge and returns the answers set to the controller, which in turn returns it to the querying application, in this case KNAVE-II.

To make the knowledge reusable and facilitate its application to multiple clinical databases, we are using, to represent the clinical raw-data concepts found at the leaves of the knowledge-base's abstract concepts, only terms (and measurement units) taken from a set of controlled medical terminologies. We have created a standard medical vocabularies service (see Fig. 2) that serves as a search engine for a set of distributed, web-based standard medical vocabulary servers that we had implemented. The main vocabularies used by the IDAN architecture include the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) [63] and the Systematized Nomenclature of Medicine, Clinical Terminology (SNOMED-CT), a comprehensive diagnostic terminology [64], in the case of clinical diagnoses; Current Procedural Terminology (CPT) in the case of diagnostic and therapeutic procedures [65]; the Logical Observation Identifiers Names and Codes (LOINC) standard, in the case of laboratory tests and physical signs and symptoms [66]; and the American National Drug File (NDF) ontology in the case of medications.

The use of standard vocabularies is a key concept in our framework; it enables us to share temporal-abstraction knowledge sources that are not specific to a particular set of data-source terms, but can be applied to any clinical database that stores similar domain-specific data types. The vocabulary server is used by local data-source owners to associate local data-source concepts with standard medical concepts, and also by medical experts to associate clinical terms in the temporal-abstraction knowledge base, with standardized medical terms.

A full scalable distributed architecture requires the capability of remote connectivity to diverse databases, knowledge bases, vocabularies and algorithms to enable the application of types of knowledge to the same data and different databases to the same knowledge. KNAVE-II is a client to the web-based distributed architecture described above, and is implemented as a downloadable client application from our internet website. After installation at the user's site, the system recognizes the current KNAVE-II version and updates it automatically through its internet connection.

A configuration service enables users of a KNAVE-II client to select, at the beginning of an exploration session, the desired database, the desired temporal-abstraction service (a Web service encapsulating the ALMA temporal-abstraction computational module), and an appropriate knowledge base (of the application, needed by the selected temporal abstraction service). The selection of a temporal-abstraction service constrains the choice of relevant knowledge-base sources.

3.2. D-2: visualization of both raw data and its abstractions

To solve the visualization desiderata, we use an intelligent user interface. *Intelligent user interfaces* are knowledge-based interfaces that mediate between person and machine to increase the ease and effectiveness of user interactions [67,68]. KNAVE-II is a knowledge-based interactive visualization and exploration intelligent user interface. The interface is used to explore a single patient record or a set of such records. Fig. 3 shows the main interface of a KNAVE-II visualization and exploration client, as used for exploration of an oncology patient monitored after bone-marrow transplantation. KNAVE-II enables interactive, dynamic exploration by the user of raw data and their abstractions in the domain of oncology. Fig. 3 demonstrates our current design for the integration of the knowledge browser (which reflects the contents of the domain's temporal-abstraction knowledge base, that is, its temporal-abstraction ontology) and data-browsing panels (which show the contents of the database or of the results of a temporal abstraction process applied on such contents). Each panel represents a different concept (raw data, such as white blood-cell counts; abstractions, such as white blood-cell levels and bone-marrow toxicity grades; or even higher-level, more complex patterns, such as multi-organ toxicity or decreasing platelet half-life). One could imagine several other ways of displaying the resulting abstractions, such as displaying both raw data and concepts derived from it within the same panel. However, one of our main design choices was to separate concepts into different panels, so as to enable performing operations such as computation of statistics, zooming in and out, various exploration, explanation, and dynamic sensitivity analysis, on each concept and each abstraction of that concept separately (this design choice can be overridden only through the use of a domain specific plug-in module, mentioned when discussing Desideratum D-10). However, panels can be moved around freely, and even overlaid on top of each other. Zooming into and out of temporal granularities or particular time periods is applied to all panels simultaneously, thus preserving temporal alignment among all data and derived concepts, unless a panel is zoomed into and magnified, or unless a panel is asynchronized from the other panels, by using the time-synchronization function (pin-shaped) icon, which toggles between synchronized panning of all panels or individual motion of any panel in which the pin is removed (see Fig. 3).

3.3. D-3: temporal granularity

KNAVE-II implements five operators (zoom-in functions) for manipulating temporal granularity: (a) a *user defined granularity zoom* enables specification of any desired temporal granularity (e.g., year, month); (b) a *calendric-range zoom* uses a standard calendar function to enable the user to specify the start and end time points to zoom-in into a specific absolute time range; (c) a *single-panel zoom* opens and magnifies a particular panel displaying raw data or a derived concept in a separate sub-window; (d) a *time-granule-sensitive zoom* enables users to select a specific predefined period of time of a predefined granularity, within the timeline of a particular panel (e.g., "August 1995") by clicking on that granule (e.g., click on "August" within the "1995" time line) and (e) a *content-based zoom* to mark-up specific contents in the panel (e.g., a group of bone-marrow toxicity abstractions of grades 2 and higher) and then zoom into the temporal range implicitly determined by the selected time range, whether that range defines any predefined complete temporal-granularity unit or not. Fig. 4 demonstrates the random-granularity, calendric-range, and time-granule-sensitive zooms, and Fig. 5 presents an example of the content-based zoom.

3.4. D-4: absolute and relative time lines

Changing dynamically the point of view from an absolute (calendar-based) time line into a relative time line is another KNAVE-II innovative capability. The relative time line is set by identifying clinically significant events in the domain's temporal-abstraction ontology (e.g., bone-marrow transplantation time, *start of chemotherapy, birth of the child*) which serve as a date of reference (time zero) to all the other displays. Once the relative time-line has been selected the time display will change to $\pm$ time units starting from that event, based on the time granularity selected (hours, days, months, years). The user can interactively select the event to be used as the zero-time reference, through access to the predefined list of potential reference points (Fig. 6).

3.5. D-5: intelligent exploration of raw data and abstractions

Exploration of raw data and abstract concepts includes navigation along semantic links in the

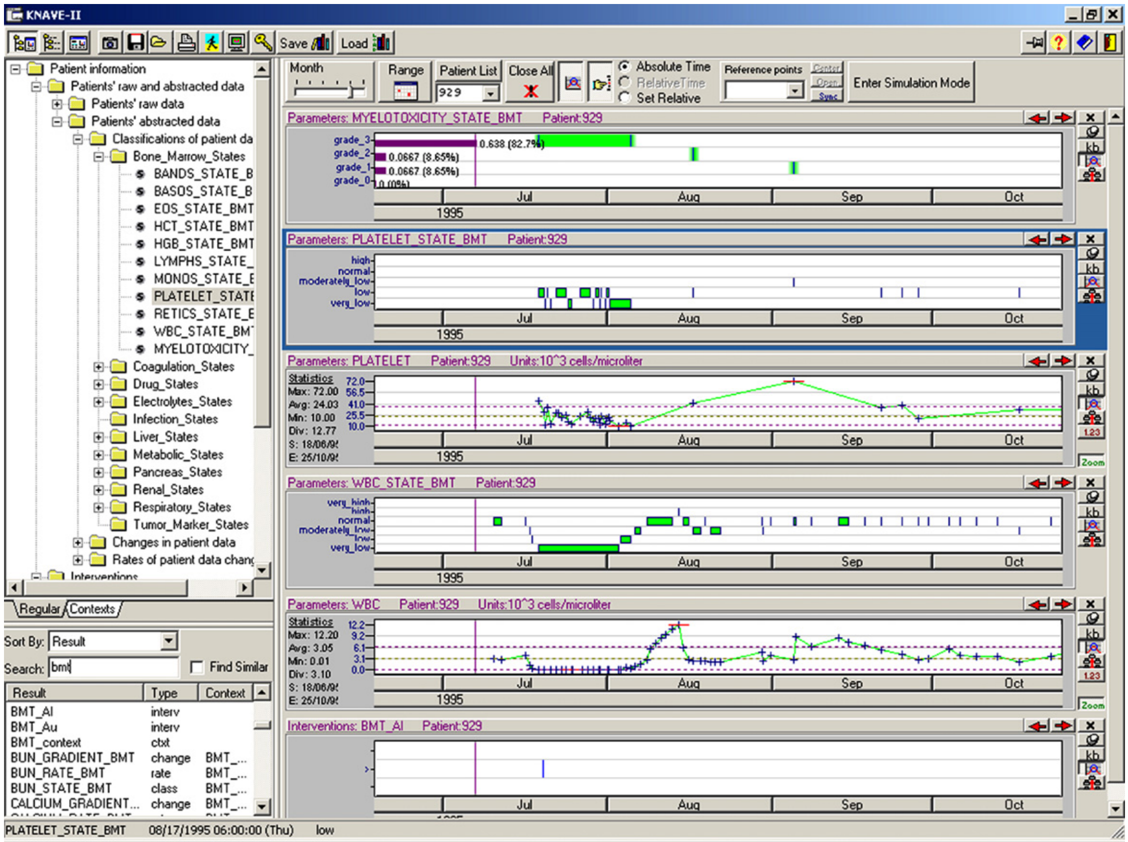


Figure 3 A view of an individual oncology patient's data in the KNAVE-II system. On the left hand side, a browser to the clinical domain's ontology, coming from the ontology knowledge base, is shown. The user selects a raw data type (third, fifth and sixth panels from the top) or an abstract concept (first, second and fourth panels) by clicking on a node in the browser's ontology tree, for example, the WBC State appears in the 4th panel from the top. The user can also search for a concept using a standard string-search function, as shown in the left hand bottom panel; the concept is then retrieved an, if the user double clicks on it, computed on the fly and displayed as a panel on the right hand side. Exploration operators, represented as icons in each *panel*, enable the user to perform actions such as: (a) re-align the display of the panels, using the time-synchronization function (pin-shaped) icon, which toggles between synchronized panning of all panels or individual motion of any panel in which the pin is removed; (b) query the knowledge used to derive the concept through the "*kb*" icon; (c) add statistics regarding raw and derived concepts, by clicking on the *statistics* (graph) icon below the *kb* icon (see the statistics displayed on first, third and fifth panels from the top, respectively); (d) semantically explore the concept and the semantic network of relations around it, by clicking on the semantic-explorer (cross) icon below the statistic icon; (e) skip to the nearest period in the past or future in which data can be found, using the left and right arrows, respectively. A set of top-level (menu) *global widgets* above the top panel controls all panels: (f) the *random granularity zoom* enables slide-bar zooming to any desired temporal granularity; (g) the *calendric-range zoom* enables zooming into a time range, by specifying the start and end time points, using a standard calendar; (h) the *patient-selection* box enables the user to select the current patient-record to explore; (i) the *global-statistics* button adds or removes statistical information to or from all panels; (j) the *absolute/relative time line* functions enable the user to set a specific event (such as a particular type of medical intervention) as the date of reference (time zero) for all the other displays, by selection from a list of predefined *reference points*; (k) The *search and retrieval service* enables lexicographic search, by typing a string in the input window on the bottom left-hand part of the interface. The search retrieves all the related concepts from the domain's temporal-abstraction ontology. Clicking on the *Find Similar* checkbox triggers retrieval of similar-sounding concepts without requiring the user to have prior knowledge about the exact form a concept appears in the ontology knowledge base. The retrieved concepts can be ordered according to their type and related context (e.g., post-BMT), and then *opened* in either the semantic explorer, to explore their semantic relations or properties, or (after computing the concept for the current patient) as a separate panel on the right hand side of the screen, for visualization and further exploration.

domain's temporal-abstraction ontology, such as abstracted-from relations, using the semantic explorer (Fig. 7). For any domain, the semantics of the query, visualization, and exploration processes are the same, since these processes use the terms of the domain-independent knowledge-based temporal-abstraction ontology [1]. All concepts in the temporal-abstraction ontology have an

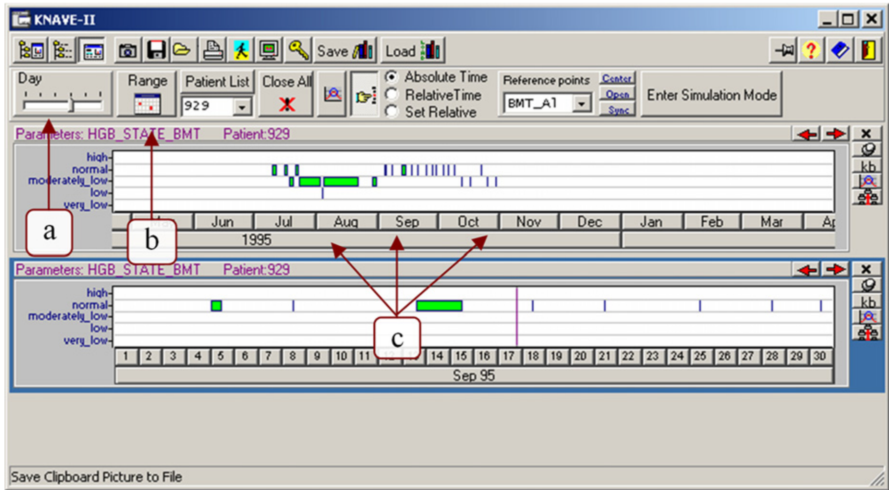


Figure 4 Three of the operators for changing temporal granularities: (a) *the random granularity zoom* uses a predefined scale of temporal granularities; (b) the *calendric-range zoom* opens a calendar and enables specification of start and end time points to zoom into; (c) the *time-granule-sensitive zoom* enables users to zoom into a specific predefined period of time, by clicking on any specific temporal granularity button within the timeline of a particular panel, e.g., zooming into September 1995 by clicking on the "*Sep*" button in the monthly granules above the "1995" bar. Zooming back into the whole of 1995 is then accomplished by clicking on the "Sep 95" bar. The "1995" bar will then reappear, above which would be the monthly granules, as shown in the upper panel.

is-a relation, which enables the user to explore the class the concept belongs to and its other siblings within that class, or the sub-concepts the concept in focus subsumes, by going up or down, respectively, in the type hierarchy of the semantic explorer's local knowledge browser (the full version of which is also displayed on the left side panel of the main screen, see Fig. 3). In Fig. 7, we can see that PLATELET_STATE_BMT *is-a* BONE-MARROW_STATE, and by further climbing in the knowledge browser hierarchy we could have found that it is-a STATE. However, for any domain, the main semantic-exploration operators use the domain-specific contents of the relations of the temporal-abstraction ontology, which depend on the type of entity explored (these relations are referred to in Fig. 8 as "special relations"). The result is a uniform-behavior, but context-sensitive (with respect to the knowledge) visualization and exploration interface in all time-oriented domains. We have defined four types of special semantic relationships of a concept in the knowledge-based temporal ontology: a "meta-children" relation, such as abstracted-from in the case of parameters, or parts in the case of events; a "meta-parents" relation, such as abstracted-into in the case of parameters, or part-of in the case of events; a "meta-siblings" relation, such as the other arguments in the function defining the parameter, or other components on the pattern into which the current entity is abstracted, or other parts of the event which the current event in focus is a part of; and a "context relation", such

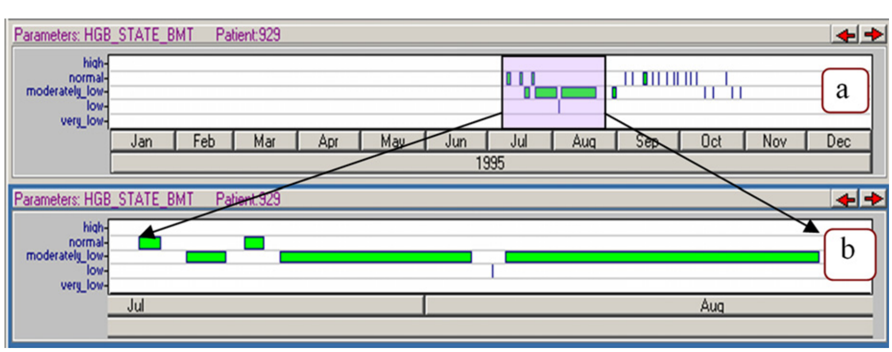


Figure 5 The content-based zoom enables users to mark specific contents in the panel, whether within a complete temporal-granularity unit or not (see shadowed area), and then zoom into the temporal range implicitly determined by these contents. The user indicates the temporal region of interest by marking-up the range of interest (see shadowed area in (a)), which then is expanded to fill the whole panel (b).

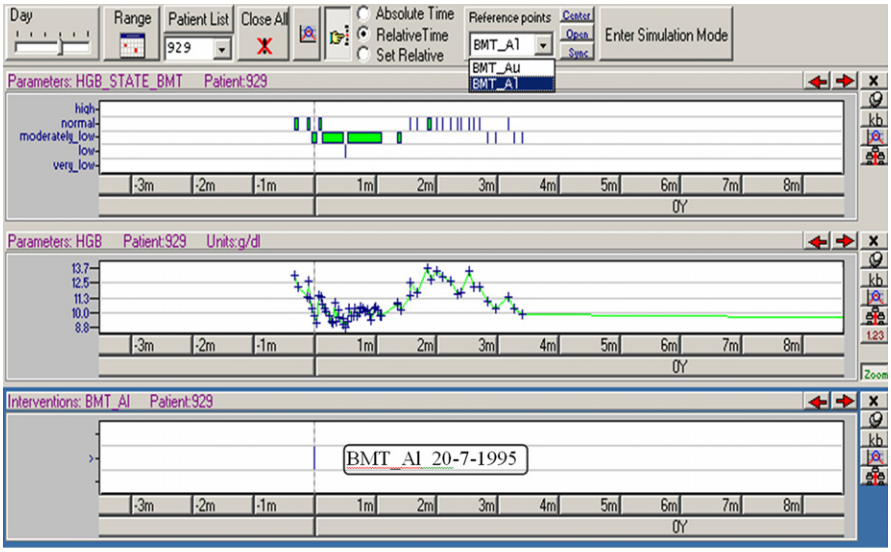


Figure 6 Absolute/relative time lines in KNAVE-II. Once the *relative time-line* was set by selecting the Allogenic Bone-Marrow transplant (BMT-Al) as the reference point the time display will change to $\pm$ *units* starting from that event. The selection of the time reference event can be done by direct manipulation or by selecting a predefined reference event from the knowledge-base, in which case KNAVE-II will show the nearest event enabling direct browsing between events (in the case that there were more than one such points in the patient's record). Here, both the Hemoglobin (HGB) raw data and its abstraction into the State of Hemoglobin (HGB-State-BMT) is displayed in granularity of months relative to the BMT-Al event. Clicking on the ''Open'' button opens a panel, in which the reference event is displayed (see bottom panel). As in the case of all raw data and concepts, moving the mouse over the event opens a tool tip baloon with information about the contents of the displayed entity.

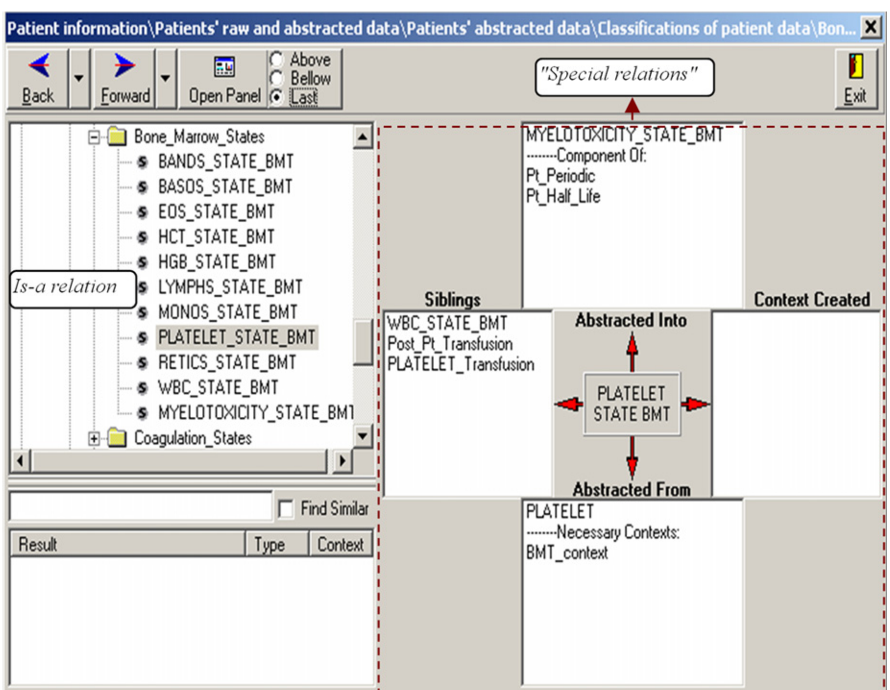


Figure 7 Exploration of data and knowledge in KNAVE-II. The *semantic explorer* is evoked by clicking on the exploration button of the panel (see Fig. 3). The user uses the semantic relationships of a concept, which depend on its type (e.g., *abstracted-from*, *abstracted-into*, *siblings*, *created context*, and is-a, in the case of a raw or abstract data type) to navigate to other concepts semantically related to the original concept. The ''special relations'' are emphasized here by a dashed-lines boxed area.

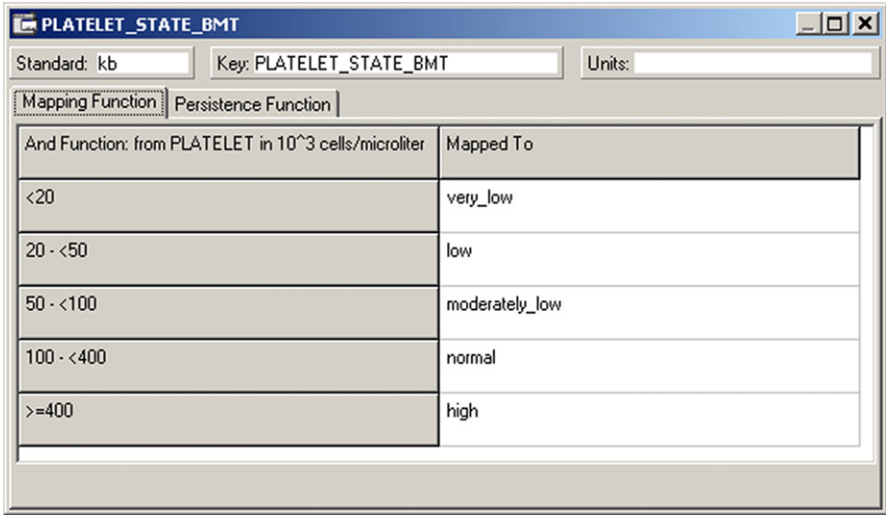


Figure 8 Knowledge-based explanation, evoked by clicking on the knowledge-base (*kb*) button in a panel (see Fig. 3). The user thus examines the temporal-abstraction knowledge that was used to derive a specific displayed concept. Note that the user can click on the "*Persistence Function*" tab to explore the interpolation function used to join separate data points or intervals into a longer interval. In the case of a raw-data type, the explanation would consist on only the standard vocabulary used (e.g., LOINC), the key in that vocabulary, and the measurement units.

as the generated-context relation for most entities, or the generated-from relation in the case of contexts themselves. These special relations depend on the type of concept in the current focus and enable the user to navigate to other concepts semantically related to the focused concept. Table 1 summarizes and briefly describes the types of special semantic relationships.

3.6. D-6: explanation

We added the capability for browsing the contents of the domain-specific knowledge base relevant to the derivation of each panel in a context-sensitive manner. During exploration, the user is able to obtain context-sensitive explanations to questions such as "From which data is this concept abstracted?", by using the semantic explorer, and moving from a derived concept into its components; and to questions such as "What classification function defines this abstraction?" by clicking on the knowledge-base icon in each panel and then focusing on the type of knowledge of interest to the user, such as the table that maps raw data into the browsed concept (Fig. 8). In the case of a raw-data type, such as a Hemoglobin value, the "knowledge base" explanation would consist of only the standard term used to map that concept into the specific vocabulary (e.g., LOINC), the value of the key in that vocabulary (e.g., LOINC code), and the measurement units (e.g. grams per 100 cc).

3.7. D-7: statistics

To support clinical research, it is imperative to provide several types of descriptive statistics as part of the interactive visualization and exploration. Statistics in KNAVE-II can be computed and

Table 1 Types of special semantic relationships used for intelligent exploration of concepts

Type	Relation			
	"Meta-children" relation	"Meta-parents" relation	"Meta-siblings" relation	Context relation
Parameter	Abstracted-from	Abstracted-into	Other parameters abstracted into the "parent" parameter	Generated contexts
Event	Parts	Parts-of	Other parts belonging to the "parent" event	Generated contexts
Pattern	Components	Components-of	Other components defining the "parent" pattern	Generated contexts
Context	Sub-context	Super-context	Other sub-contexts of the super-context	Generated from

displayed for either raw data or abstracted parameters. The computation of statistics is sensitive to the particular time window displayed in each panel, and thus changes dynamically when the contents of the panel are changed. Default statistics for raw data types include descriptive statistics such as mean, maximum, minimum, $\pm$standard deviation, etc. (see third panel from the top in Fig. 3). In the case of abstract data types, the default statistics displayed are a detailed distribution (in absolute time periods and relative proportion to all displayed values) of the total *duration* of the intervals over which each value of the abstraction (e.g., GRADE-II bone-marrow toxicity) held within the particular time window dynamically selected or, the temporal granularity (e.g., month of September) zoomed into (see first panel from the top in Fig. 3). (In addition, the absolute and relative start and end time and duration of each interval are displayed within the tool tip when passing over the interval.)

3.8. D-8: search and retrieval

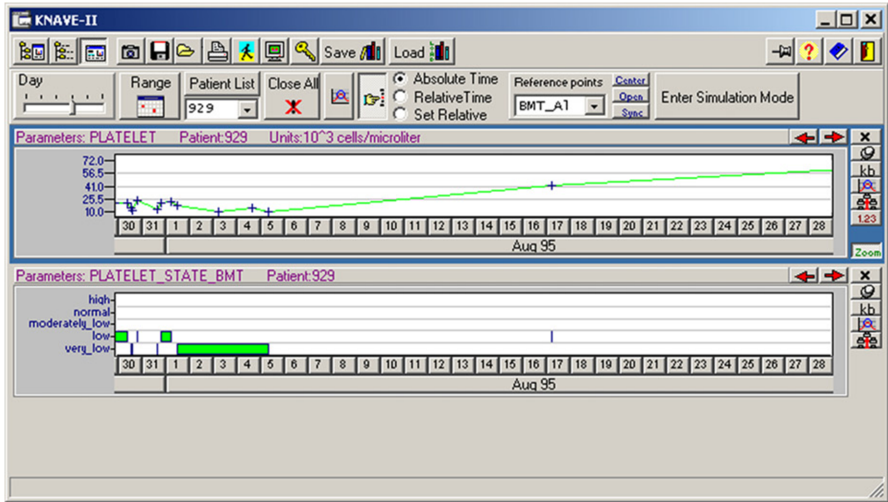
KNAVE-II supports easy and fast search and retrieval of ontology-based clinically-significant concepts. Besides the possibility for actively looking within the knowledge browser (see left hand frame in Fig. 3), which directly exploits the access to the domain's ontology, or using the semantic explorer to navigate within that ontology, by starting from a related term (see Fig. 7), it is possible to use a text-based search to find any arbitrary concept. The search and retrieval service (at the left bottom side of the main interface, see Fig. 3), enables a text-string lexicographic search. The search retrieves all the related concepts from the domain's temporal-abstraction ontology. The Find Similar function triggers retrieval of similar-sounding concepts without requiring the user to have prior knowledge about the exact form a concept appears in the ontology knowledge base. The retrieved concepts can be ordered according to their type and the related context (such as BMT), and then opened in either the semantic explorer to explore their properties and related concepts, or displayed (after computing the concept for the current patient whose data is examined), within a separate panel for visualization and further exploration.

3.9. D-9: dynamic sensitivity analysis

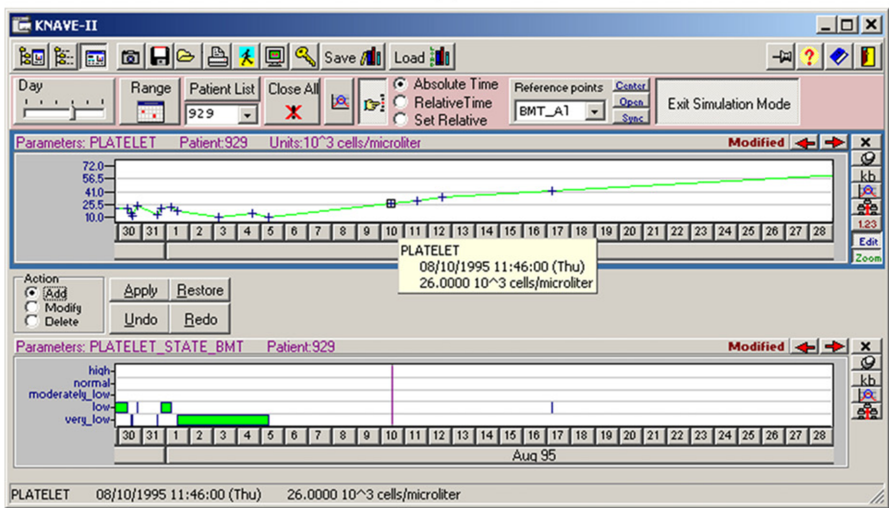
The exploration functionality offered in KNAVE-II supports, among other features, dynamic simulation of hypothetical modifications to raw data. By using the tight link to the underlying computational capabilities of the IDAN temporal-abstraction mediator, which can propagate the effects of any data modifications to the resultant abstractions, the user is able to simulate the effect of modifying the data, thus adding a dynamic sensitivity analysis (''What-if dynamic simulation'') capability by modifying, deleting, or adding values within a specific panel. Exploiting the direct access to the domain's temporal-abstraction ontology and to the temporal abstraction server enables the simulation-based explanations (see Fig. 9a—c). The display reflects the computational implications of these modifications in all the raw data and abstracted concepts related to the modified data. When the dynamic sensitivity analysis is enabled the system accesses, through the IDAN mediator, a simulation state in which the modified values are kept in the cache and do not affect the real patients' data in the data base, thus enabling easy reversibility of the computations and their effects in the cache, and a return to the state before any simulated modification was done. An indication for modification of the concept is displayed (see Fig. 9b) and navigation through views with varying degrees of modification of the underlying data can be performed using operators that control the underlying computational propagation process, such as add, delete, and modify, as well as *apply*, *restore*, *undo* and *redo* (Fig. 9b). It is also possible to open another copy of the patient's record and compare the hypothetically modified concepts with the actual ones.

3.10. D-10: clinical-task support

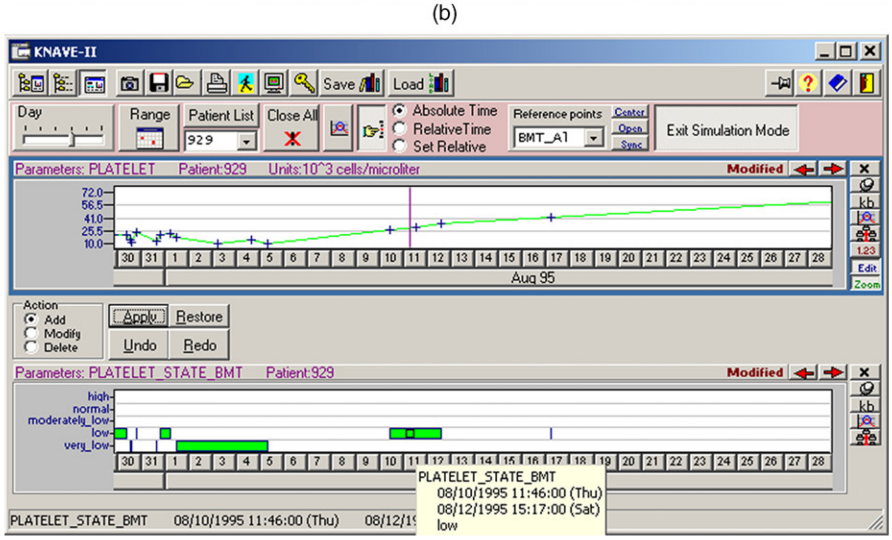
D-10: clinical-task support is achieved by enabling the physicians and medical researchers to easily browse several raw-data and abstract-concept panels that are all related to a specific clinical task (e.g., monitoring of diabetic patients). KNAVE-II enables customization of the displays for each specific clinical task, by enabling the user to save, at any point during the exploration, all the current panels as a new *profile* (e.g., a diabetes profile, or a hematological profile, a useful abstraction in the case of the oncology domain). The selection of a specific profile applies it to the current selected patient record. In addition we have added functionality for customizing the interface itself for particular clinical domains or tasks, by adding a domain-specific plug-in module associated with each knowledge base. For example, the tool-tip can display additional data types, but still within the same overall framework and while still supporting all of the usual exploration operators, For example, it was often found useful to display multiple attributes of a concept and not just one value, as in the case of displaying medications, so as to show as one value



(a)



(b)



(c)

Figure 9 (a) The *Dynamic sensitivity analysis* capability of KNAVE-II, supported by the underlying IDAN architecture, enables the user to add hypothetical raw data, modify the existing data by changing their values and time-stamps or delete selected data. By clicking on the *Enter Simulation Mode* button the menu frame turns into pink to indicate to the user that *simulation mode* was selected (b). (b) Performing a dynamic sensitivity analysis within the simulation mode. The user added three platelet data points between 10 and 12 of August 95. When the user modifies data in the simulation the dose, the mode, the administration frequency, etc.; or in the case of various attributes of embryos followed in the fertility clinic.

3.11. D-11: collaboration

Clinicians and researchers usually like to consult or share the result of the exploration of data and abstractions with colleagues. KNAVE-II enables collaboration by saving the selected data and abstractions of a particular exploration to a special exploration file format. The exploration files encapsulate the relevant data, concepts, knowledge classes, and display format appearing within a complete set of panels (e.g., all the hematological data and abstractions viewed, the relative timeline that was used to explore them, and the knowledge used to create the concepts). An exploration file can be saved to a shared directory or sent by email to a collaborating colleague. The collaborator can open the file and explore the same data and knowledge, starting from the same point in which the image of the exploration was saved. She also can add other raw-data and abstract-concept panels that seem to be relevant to the case in discussion, and continue the visualization and exploration session (and even send it back to the original clinician or researcher). An exploration file can be visualized and explored off-line by another KNAVE-II module, even without access to the mediator, the KB and the DB.

3.12. D-12: documentation

Standard clinical, research and administrative procedures require documentation of the patient's clinical data to the patient's file, thus showing the exploration that supported a clinical decision. KNAVE-II enables taking a snapshot of the exploration process, saving it as a documentation file that cannot be further manipulated. In addition, we added the capability of saving the current exploration as an *exploration file*, as explained above, which supports documentation of the exploration process while preserving the option of further exploration in the future to better understand the reason that a particular interpretation was derived. This dynamic snapshot is enabled by saving the current state of the application that includes the selected displayed panels but also all the related values of the raw data and the abstracted concepts active at any selected time span.

4. Evaluation

A preliminary evaluation of the overall distributed architecture, and in particular of the current exploration interface, had been carried out by our collaborators in the Palo Alto, CA, USA, Veterans Administration Health Care Center, and is described in detail elsewhere [69].

The temporal-abstraction service was running on one of the Ben-Gurion University (BGU), Israel, Beer Sheva, servers. For the purpose of the evaluation, the knowledge service and data service were running on other BGU servers.

The evaluation used an online retrospective database of more than 1000 unidentifiable laboratory-test records of bone-marrow transplantation patients who were followed for 2—4 years at the Rush medical center, Chicago.

The knowledge source used for the evaluation was an oncology knowledge base specific to the bone-marrow transplantation domain, previously elicited from one of our colleagues at Stanford University [23].

The subjects included eight clinicians with varying medical background and experience in the use of computers. Each user was given a brief (10—15 min) demonstration of the KNAVE-II interface. Each user was asked to answer 10 queries common in oncology, about individual patients, at increasing difficulty levels; queries were inspired by typical oncology protocols. For example, from a protocol sentence such as "if after the bone-marrow transplantation there was a period of bone-marrow toxicity of grade two or more within the past 2 months, attenuate the dose of the drug by 20%" the following query can be produced, a query that appeared in our study within the set of queries of hard, but not the hardest level of difficulty: "Give the starting and ending dates of the last period of grade 3 myelotoxicity following the bone-marrow transplantation" [69].

A cross-over study design compared the KNAVE-II module versus two existing methods: paper charts and an Excel electronic spreadsheet. Each user answered equivalent questions using all three methods in randomized order.

mode a *Modified* status appears in the upper right hand side of the pannels involved. The *Apply* button triggers the computation of abstractions derived from the modified raw data, while the *Undo* button cancels the modifications and their effects. (c) Assessing the effects of the dynamic sensitivity analysis. By clicking on the *Apply* button the user triggers the computation of the platelet_state_BMT abstract concept, which is dynamically abstracted from the modified raw data (as an interval on the same dates). By clicking on the *Exit Simulation Mode* button, KNAVE-II deletes all simulated data and their effects in the cache, and returns to the state before any simulated modification was done (a).

The measures used for the evaluation included quantitative measures such as the time to answer and accuracy of responses, and qualitative measures such as the Standard Usability Score (SUS) [70] and comparative ranking of all tools by usability.

The results were quite encouraging. In the direct-ranking comparison, KNAVE-II was ranked first in preference by all users, along all dimensions (such as ease of use), except, of course, for familiarity in using the tool (an aspect introduced for validation).

The SUS mean scores (the overall SUS range is 0—100) were 69 for KNAVE-II, 48 for Excel, 46 for Paper ($P = 0.006$) (over 50 is usually considered as a friendly interface).

With respect to quantitative measures of the time to answer: users were significantly faster using KNAVE-II as the level of difficulty increased, up to a mean of 93 s per query faster versus paper and 49 s faster versus Excel, for the hardest query (time to answer queries ranged from 5 to 300 s; $P = 0.0006$).

Regarding the correctness of the answers, using KNAVE-II significantly enhanced correctness versus using paper, especially as level of difficulty increased ($P = 0.01$); the comparison with Excel showed a similar trend.

5. Discussion

We have introduced KNAVE-II, a fully implemented intelligent visualization interface, which is able to use the advanced features of a distributed architecture for intelligent visualization and exploration of time-oriented data. The computational architecture underlying KNAVE-II supports the generation and exploration of context-sensitive interpretations (abstractions) of the time-stamped data in terms of domain-specific concepts and temporal patterns.

Thus, two of the major innovations in the KNAVE-II architecture are:

(1) Direct access to and continuous use of a set of *temporal-abstraction computational mechanisms* (based on the KBTA method), which supports real-time generation (and, thus, visualization) of domain-specific meaningful concepts and patterns, by applying domain specific knowledge to the data. Unlike previous systems, which focused mainly on visualization of raw data and various statistical functions of it, we focus mainly on visual display of *interpretations* (temporal-abstractions) of the time-oriented data. We consider that capability to be more useful for clinical decision support, although we do support the application, in uniform fashion, of all exploration operators for both raw and abstract concepts.

(2) The capability for direct access to one or more of the *domain-specific knowledge-bases* used for the abstraction, which enables the user of the KNAVE-II system to interactively explore the abstractions and the raw data alike, by navigation along the semantic links implicitly defined by the knowledge roles of the semantic network that is derived from the domain's temporal-abstraction ontology.

Moreover, the KNAVE-II general architecture is task-specific (in contrast to domain specific) and highly scalable and modular, and can be applied to time-oriented databases in any clinical domain (or even in a non-clinical domain; the underlying computational temporal-abstraction methodology had been also applied to the task of traffic control, for example [71]). Using KNAVE-II requires a designer to link the IDAN controller to the relevant data base(s) and to the domain specific knowledge base, thus enabling the application of domain-specific temporal abstraction knowledge to each relevant database.

We have started by listing multiple desiderata for supporting the needs of care providers, quality-assessment professionals, and clinical researchers who need to browse large amounts of time-oriented clinical data and reduce the cognitive burden involved in that task. Our key insight is the addition of an interactive intelligent interface supported by an architecture that automatically integrates knowledge and data. One of the core needs of a framework for intelligent data analysis is the capacity to explore dynamically both raw data and the interpretations derivable from these data (using domain-specific knowledge); and perform this task in a scalable fashion.

Initial applications of KNAVE-II and its supporting knowledge-based distributed temporal-mediation architecture, to a large data base of patients monitored several years after bone marrow transplantation (BMT), have provided highly encouraging results. KNAVE-II was ranked first in preference by all users, when compared with a computerized Excel electronic spreadsheet and with printed versions of Excel, without having been familiar with this tool prior to the experiment. Usability evaluation indicated a significantly better support for the exploration and visualization of time oriented clinical data. The usability scores were significantly higher for KNAVE-II, compared to Excel and to paper charts. Users also performed better using KNAVE-II than with the other two tools. Users of KNAVE-II were significantly faster, compared their use of standard tools, as the level of difficulty increased; note that a mean difference of 93 s per query versus paper and 49 s versus Excel, for the hardest query, translates into many hours that might potentially be saved per physician or per clinical researcher each week, for example. Using KNAVE-II significantly enhanced correctness versus using paper, especially as the level of difficulty increased; the comparison with Excel showed a similar trend, which we expect to be highly significant as we continue to compare the tools across increasingly difficult queries. The enhanced accuracy provided by the IDAN/KNAVE architecture translates into better support for runtime quality assurance and retrospective quality assessment.

6. Future work

Our current plans for future work involve enhancement of the architecture in several ways:

1. Developing the computational and graphical capabilities for visualization and exploration of aggregations of patients selected according to dynamic criteria. For instance, exploration of the distribution of the duration and severity levels of bone-marrow toxicity episodes, for all patients who received a certain chemotherapy protocol. This functionality will extend the support that currently we provide for D-2 and D-5 for visualizing and exploring raw data and abstracted knowledge from one patient to entire populations.
2. Enhancing the generic capability for addition of customized plug-in modules that extend the capabilities of KNAVE-II. For example, we mentioned the need for display of multi-attribute parameters required for specific clinical tasks (D-10). Examples include listing the various attributes involved in the administration of medications (dose, mode, frequency, etc.), and the potential need for overriding the current default of displaying each concept within a separate panel, which might sometimes be modified, as when displaying systolic and diastolic blood pressures together. Such modifications are typically domain or task-specific, and can be achieved through a plug-in module that capitalizes on the significant powerful operators that are already a part of KNAVE-II. We would like to create a library of such plug-ins and facilitate new creation or modification by local knowledge engineers.
3. Supporting on-the-fly specification (at exploration time) of new temporal patterns, possibly saving them as part of the user's profile in addition to the exploration of the data using predefined concepts and patterns from the domain's temporal-abstraction ontology combining the support currently provided for requirements exploration of raw data and abstracted concepts (D-5) and dynamic sensitivity analysis (D-9).
4. Adding the capability for simulation of the effects of dynamic modifications of the domain-specific *knowledge*, not only of the data, as part of the dynamic sensitivity analysis (D-9).
5. Experimenting with a natural language interface, and even a speech recognition interface, both capitalizing on the underlying rich ontology and semantic network embodied in each domain's temporal-abstraction ontology. We expect this capability to facilitate the interaction with the multiple functionalities of the KNAVE-II user interface (D-1 to D-12) by enabling the manipulation of all the GUI actions by simply issuing voice commands.

We are in the process of performing additional evaluations of the overall architecture, using a more diverse set of users and a more complex set of queries; we also intend to evaluate the cognitive and task-specific effects of the more advanced features of the KNAVE-II system, which are mainly meaningful for complex tasks such as clinical research, quality assessment, or repetitive management of large numbers of patients. These include features such as dynamic sensitivity analysis and the creation and application of clinical task-related profiles.

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