Representation, Application, and Discovery of Temporal-Abstraction Knowledge

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Declarative Knowledge in the Medical Domain: The Need for Intelligent Interpretation of Multiple Time-Oriented Clinical Data

- Many tasks, such as those involving chronic patients, require extraction of meaningful concepts from multiple sources of raw, longitudinal, time-oriented data
  - Example: “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”

- Examples of clinical tasks that require temporal reasoning:
  - **Therapy**
    - Following a treatment plan based on a clinical guideline
    - Complements the guideline’s procedural (process-based) knowledge
  - **Monitoring and Diagnosis**
    - Searching for “a gradual increase of fasting blood-glucose level”
  - **Quality assessment**
    - Comparing observed treatments with those recommended by a guideline
  - **Research**
    - Discovery of hidden dependencies over time between clinical parameters
The Need for Temporal Data Mining

• The analysis of the clinical data of multiple patients, accumulating over time from multiple sources, can lead to many insights
  – We can discover temporal patterns that are relatively frequent (beyond a given threshold), thus creating clusters of temporal behaviors (pathways) of patient sub-groups
  – Some of these patterns, together with non-temporal data such as demographics, can assist in the classification of the patients (according to diagnosis, cost, etc) or in the prediction of clinically significant future outcomes (e.g., renal damage in a diabetes patient)

• Effective analysis includes not just time-stamped raw data, but also periods of context-sensitive abstractions, or high-level interpretations, of the data
  – “Two months moderate anemia in a 60+ years old woman”, instead of several HGB values
  – “A year of progressive hepatic dysfunction”, instead of several series of enzyme values

• Such an interpretation requires an explicit representation of the context-sensitive clinical knowledge, in a manner that can be used by automated computational tools
The Need for Intelligent Mediation: The Gap Between Raw Data and Meaningful Concepts

- Databases store raw, time-stamped data
- Experts and decision-support applications reason in terms of abstract, (e.g., clinically) meaningful concepts, typically over significant time periods
- A system that automatically answers queries or detects patterns regarding either raw data or concepts derivable from them over time, is crucial for effectively supporting multiple tasks, from monitoring, through interactive data mining, to automated discovery of meaningful temporal patterns
The Challenge

- **Typical** monitoring and data-analysis methods:
  - Do not use sophisticated domain-specific knowledge
  - Are not based on an underlying domain **ontology** (i.e., a model of concepts, their properties and inter-relations)
  - Are not sensitive to the **context** of the data
  - Are not specialized to **temporal** reasoning, and in particular, do not exploit temporal **intervals**
  - Are not geared for **distributed** data, knowledge, and computational resources
  - Do not support **monitoring & exploration & mining**
The Solution: Intelligent Monitoring & Exploration

- A distributed architecture that caters for three needs:
  - *Automated* means for monitoring and recognition of meaningful patterns, in time-oriented data, by applying temporal-pattern knowledge from multiple domain-specific knowledge sources to data from multiple data sources.
  - *Interactive, human-operated* means for dynamic visual exploration of a time-oriented data repository, using on-the-fly integration with domain-specific knowledge, to identify new meaningful patterns and add them to the knowledge base.
  - *Automated* analysis, enumeration, and detection of meaningful, significant temporal-abstraction patterns (relationships amongst temporal-abstraction intervals).
The IDAN Temporal-Mediation Architecture

- Enables access to heterogeneous time-oriented clinical data sources
- Supports querying for both patient-specific raw data, and their abstractions
- Integrates one or more data sources with one or more medical knowledge sources
- Supports applications such as interactive visual-exploration and automated guideline application
The IDAN Temporal-Abstraction Mediator
[Boaz and Shahar, AIM 2005]
A Temporal-Mediation Application Example: The MobiGuide Project

[Peleg, Quaglini, Shahar, European. J. e-Practice, 2013]

- Coordinated by Mor Peleg, Haifa University, Israel
- Funded by the EU; an FP7 Integrated Project
- 13 partners from 5 countries
- Monitoring of chronic patients through bodily sensors and a smart phone
  - Cardiac arrhythmia patients in Italy
  - Diabetes and high blood pressure in high-risk pregnancy in Spain
- Provision of alerts to the patients through the mobile phone, and guideline-based decision support to their care providers through the Web
- Abstraction of the monitored raw time-oriented and of the historical patient data, to support interpretation, alerting, decision support, quality assessment, and mining, is performed by the IDAN temporal-abstraction mediator
Generation of Abstractions: The Knowledge-Based Temporal-Abstraction Method
(Shahar, AIJ, 1997)

• Knowledge-based temporal abstraction (KBTA): A computational framework for interpretation of time-oriented data

• Decomposes the TA task into five TA sub-tasks, each solved using one of five TA computational mechanisms, all mechanisms operating in parallel

• Includes an explicit temporal-abstraction (TA) ontology (events, parameters, patterns, contexts) and four TA knowledge types (structural, functional, logical, probabilistic)

• Underlies tools for semi-automated acquisition of temporal-abstraction knowledge from domain experts
The Temporal-Abstraction Ontology
(Shahar, AIJ, 1997)

- Events (interventions) (e.g., insulin therapy; surgery; irradiation)
  - part-of, is-a relations

- Parameters (measured raw data and derived [abstract] concepts)
  (e.g., hemoglobin values; anemia levels; liver toxicity grade)
  - abstracted-into, is-a relations

- Patterns (e.g., crescendo angina; paradoxical hyperglycemia)
  - component-of, is-a relations

- Abstraction goals (user views)(e.g., diabetes therapy)
  - is-a relations

- Interpretation contexts (effect of regular insulin; pregnancy; infant)
  - subcontext, is-a relations

- Interpretation contexts are induced by all other entities
Temporal-Abstraction Output Types

- **State abstractions** (LOW, HIGH)
- **Gradient abstractions** (INC, DEC)
- **Rate Abstractions** (SLOW, FAST)
- **Pattern Abstractions** (CRESCEndo)
  - Linear [one-time] patterns
  - Periodic [repeating] patterns
  - Fuzzy patterns (partial match)
Temporal-Abstraction Knowledge Types

• **Structural** (e.g., `part-of`, `is-a` relations)
  - mainly declarative/relational

• **Classification** (e.g., value ranges; patterns)
  - mainly functional

• **Temporal-semantic** (e.g., “concatenable” property)
  - mainly logical

• **Temporal-dynamic** (e.g., interpolation functions)
  - mainly probabilistic
Data Visualization for an Individual Patient

Abstraction

Interpolation

value

value

value
The KNAVE-II Single-Subject Browsing and Exploration Interactive Interface
[Shahar et al., AIM 2006]
Evaluation of KNAVE-II
(Palo Alto Veterans Administration Health Care System)

- Eight clinicians with varying medical/computer use backgrounds
  - A second study: six additional clinicians & more difficult queries
- Each user was given a brief demonstration of the 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
- A cross-over study design compared the KNAVE-II module versus two existing methods (in the 2nd study, users chose which):
  - Paper charts
  - An electronic spreadsheet (ESS)
- Measures:
  - **Quantitative**: time to answer and accuracy of responses
  - **Qualitative**: the Standard Usability Score (SUS) and comparative ranking
The KNAVE-II Evaluation Results
(Martins, Shahar, et al., AIM 2008)

- **Direct Ranking comparison:** KNAVE-II ranked first in preference by all users.
- **Detailed Usability Scores:** SUS mean scores: KNAVE-II 69, ESS 48, Paper 46 (P=0.006) (> 50 is user friendly); in the second evaluation: KNAVE-II 64, ESS 45.
- **Time to answer:**
  - 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: 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.
- **Correctness:**
  - Using KNAVE-II significantly enhanced correctness: The correctness scores for KNAVE-II (92% [110/120]) versus ESS (57% [69/120]) in the second study, which used more difficult queries, are significantly higher for all queries (p<0.0001)
Exploration of Subject Populations: The VISITORS System
[Klimov and Shahar, MIM 2009; AIM 2010; JIIS 2010]

• **VISualization** and exploration of **Time-Oriented** raw data and abstracted concepts for multiple **RecordS**
  – Knowledge-based time-oriented interpretations of the raw data
  – Graphical construction of subject-selection query expressions
  – Visual display and interactive exploration
  – Multiple-record aggregation and association

• Evaluated for functionality and usability by clinicians and knowledge engineers, with encouraging results
Selection of Subjects by Subject and Time Interval Queries

[Klimov and Shahar, JIIS 2010]

- The *ontology-based temporal-aggregation* (OBTAIN) expression language
- Three types of queries:
  - *Select subjects* (*Who had this pattern?*)
  - *Select Time Intervals* (*During which periods did this pattern occur?*)
  - *Get Data* (*What were the data for these subjects?*)
- Selection constraints include:
  - *Demographical constraints* (non-temporal): ID, age, smoking, sex, …
  - *Time and value knowledge-based constraints*: measured parameters, interventions, temporal-abstraction concepts
    - Pair-wise constraints between concepts
    - both *absolute* and *relative* (following a reference event) time lines
  - *Statistical constraints*: filter the patients’ data on the basis of a specific statistical function
Exploration of an Individual Chronic-Care Patient’s Record (1)

Knowledge browser

Temporal abstraction - Platelet state

Raw data - Platelet tests
Exploration of an Individual Chronic-Care Patient’s Record (2)

Temporal abstraction – WBC state

Raw data – WBC tests
Temporal pattern – Myelotoxicity state
Exploration of an Individual Chronic-Care Patient’s Record: Using a Relative Timeline (1)

Raw data – WBC tests
Exploration of an Individual Chronic-Care Patient’s Record: Using a Relative Timeline (2)

Raw data – WBC tests
Exploration of an Individual Chronic-Care Patient’s Record: Using a Relative Timeline (3)

Temporal abstraction – WBC state
Exploration of an Individual Chronic-Care Patient’s Record: Using a Relative Timeline (4)
Exploration of an Individual Chronic-Care Patient’s Record: Using a Relative Timeline (5)
Exploration of an Individual Chronic-Care Patient’s Record: Using a Relative Timeline (6)
Visualization of Multiple Patient Records

- Value
- Time

- High: 20%
- Normal: 20%
- Low: 60%

March 2011, April 2011, May 2011
Exploration of Multiple Chronic-Care Patient Records

Subject groups

Multiple-subjects raw data - WBC counts

Temporal abstraction - Distribution of WBC State values

Statistics: min, max, mean, STDV, variance, percentile
Exploration Of Multiple Chronic-Care Patient Records: Using a Relative Timeline To Compare the Effect of Two Procedures

V-Shaped WBC State recovery pattern for BMT-AI patients

V-Shape WBC State recovery pattern for BMT-Au patients
Temporal Association Charts (1)

Distribution of the WBC-State values within the 1st month following BMT

Association Relation between values of two concepts during the 1st month following BMT (link width=support; color saturation =confidence)
Week 1-2: Most of the patients have had a “very-low” WBC count

Week 2-4: Most of the patients have had a “normal” WBC count
Granularity-Based Temporal Association Charts

52 patients have had this association

Only 2 patients have had this association
Temporal Association Charts: Exploration of an Association

- **Support is decreasing**
- **Confidence is stable**
Temporal Association Charts: Self Associations

WBC State recovering: Associations among data of the same concept over time
Temporal Association Charts: 
Viewing Multiple Associations with a Single Target

WBC State relationships: 
Associations between WBC states and four other concepts during the first month following BMT
Example: Comparing The Effect of HbA1C State Values On the Probability of Future (5th Yr) Micro Albuminuria in Males and Females

Males:
High HbA1C levels significantly increase risk in Y5 (from 14% to 31%), given high-range of the “normal” albuminuria level in Y1 (“Normo-High”)

Females:
High HbA1C levels do not seem to increase risk in Y5, given a high-range of the “normal” albuminuria level in Y1 (“Normo-High”)
Time Intervals Mining

• A recent growing research field, attempting to discover multivariate temporal patterns from abstracted or raw time interval-based events

• The discovered patterns are potentially useful for
  – Clustering subjects into several temporal pathways
  – Classification of the subjects by their temporal course
  – Prediction of meaningful outcomes
Input: Time-Oriented Raw Data
Adding Temporal Abstractions
### Time Intervals Related Patterns Discovery – an illustration (I)

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Time Intervals Related Patterns Discovery – an illustration (II)
A **Time-Interval Relation Pattern** (TIRP) is a conjunction of temporal relations among symbolic time intervals

\{A_1 \circ D, A_1 \circ D, A_1 \circ C_1, A_1 \circ A_2, B \circ D, B \circ C_1, B \circ C_2, B \circ A, C_1 \circ C_2, C_1 \circ A, C_2 \circ A\}

The size of a TIRP is the number \(k\) of time intervals, thus, it includes up to \(k(k-1)/2 = (k^2-k)/2\) temporal relations.
KarmaLego – Fast TIRP Mining
[Moskovitch & Shahar, IDAMAP 2009, AMIA 2009, KAIS, in Press]

\[ R_i = \{ \text{Before, After, During, Overlaps…} \} \]
A KarmaLego Example: Looking at a Diabetes Dataset

[Moskovitch & Shahar, AMIA 2009]

- Contains 2038 diabetic patients’ data accumulating over five years (2002-2007), monitored by a large HMO
- Includes monthly measurements such as of 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, into three states
Exploration of Diabetes TIRPs: An Example
[Moskovitch & Shahar, AMIA 2009]

Shown: Levels of [vertical] support; [No. cases/Horizontal support]
Visualization of TIRPs: The KarmaLegoV Tool

- Enables browsing of a KarmaLego TIRP enumeration tree; includes several options:
  - Presenting the next level, i.e., the next time-interval related to the current TIRP, and its temporal relation
  - Sorting by *vertical support* (% of subjects who have the pattern), *mean horizontal support* (number of instances of TIRP per subject), and *interestingness measures*
  - Visualizing the current [mean] TIRP and its instances
  - Visualizing the distributions of external static (non-temporal) properties, such as age and gender, for the subject class in which the TIRP was found
Automated Classification: Using TIRPs as Features

[Moskovitch & Shahar, IDAMAP 2009]

- The TIRPs discovered by KarmaLego can be used as features for a classification task; a rigorous evaluation was performed in several medical and nonmedical time-oriented domains, with encouraging results
  - Example: An ICU dataset of patients who underwent cardiac surgery at the Academic Medical Center in Amsterdam during April 2002-May 2004
  - Static data include details such as age, gender, surgery type
  - Temporal data (HR, BP, FiO₂…) measured each minute during the first 12 hours
  - Classification task: Determine whether the patient was mechanically ventilated more than 24 hours during her postoperative ICU stay
  - 664 patients; 196 patients were mechanically ventilated for more than 24hrs (29.5%)
  - Multiple aspects were investigated: Epsilon (temporal-relations flexibility factor) value, Discretization method, Feature selection method…
  - Overall accuracy: 79.6% for most combinations involving 5 discrete states using a very simple equal-width discretization method
Summary:
Intelligent Abstraction, Exploration, and Discovery of Temporal-Abstraction Knowledge

- Two categories of tools were presented:
  - **Goal-directed**: Supporting intelligent, interactive visual exploration, by a domain expert, of the contents of the accumulating time-oriented database
  - **Data-driven**: by automated discovery of frequent temporal patterns
- Both enjoy the use of a *temporal-abstraction mediator* that applies temporal-abstraction knowledge to the raw data
- **Quick adaptation** to new patterns is possible, by enabling human experts to easily modify the knowledge base
- Potential support to process mining
- **Provision of concise, meaningful summaries** of large amounts of time-oriented data in terms familiar to domain experts [visually, or by NLG]
- The discovered temporal patterns are useful for clustering, classification, and prediction purposes