Temporal Information Systems in Medicine

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Overview

1. The role of time in medicine
2. Temporal modeling and temporal reasoning
3. Temporal clinical databases
4. Abstraction of time-oriented clinical data
5. Time in clinical diagnosis
6. Research challenges

1. The role of time in medicine

Science or Art?

Knowledge-intensive to
data-intensive applications

systems that advice to
systems that inform

Medical Tasks

- **Diagnose** the cause of a problem
- **Predict** its development
- **Prescribe treatment**
- **Monitor** the progress of a patient
- **Manage** a patient

computer-based support

Change in Focus

The major challenge is no longer the deployment of knowledge but the **intelligent exploitation of data**

Exploitation of medical data

- Extremely valuable and multifaceted
- Can yield significant new knowledge
- Can provide accurate predictors for critical risk groups based on "low-cost" information
- Enables the intelligent comprehension of individual patients' data
  - Closes the gap (conceptual distance) between raw patient data and medical knowledge

The change in focus has not changed the ultimate objective that still is …

… to aid care providers reach the best possible decisions for any patient, to help them see through the consequences of their decisions/actions and if necessary to take rectifying actions as timely as possible

The change in focus has given rise to ….

- Methods of abstraction, query and display of time-oriented data of relevance to all medical tasks, and
- Has given a new dimension of significance to clinical databases, particularly the intelligent management and comprehension of clinical data

Time plays a major role in Medical Information Systems

- Events occur at some time points
- Certain facts hold during a time period
- Temporal relationships exist between facts and/or events

Abstracting time away means that dynamic situations are converted to static (snap-shot) situations, where neither the evolution of disorders, nor patient states can be modeled

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Temporal Information Systems in Medicine are …

- Information systems able to store, manage and query time-oriented clinical data, and
- Support different inference tasks on these data

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Research Directions

- **Temporal data maintenance** – storage and retrieval of data with heterogeneous temporal dimensions
  - (temporal) database community
- **Temporal data abstraction and reasoning** – supports various inference tasks involving time-oriented data
  - artificial intelligence community
- **Design of medical temporal systems**
  - medical informatics community

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2. Temporal modeling and temporal reasoning

- Modeling temporal concepts
  - modeling time
  - modeling temporal entities
- Temporal reasoning
- General theories of time and the medical domain
- Temporal constraints

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Modeling Temporal Concepts - Modeling Time

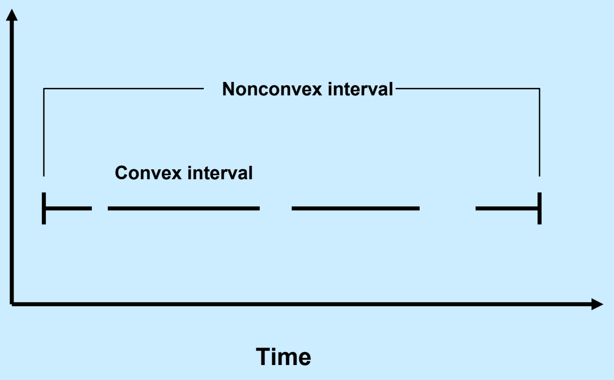
- Modeling time as a **dense** or **discrete** number line may not provide the **appropriate abstraction** for medical applications. Several basic choices have to be made:
  - Time domain
  - Instants and intervals
  - Linear, branching and circular times
  - Relative and absolute times
  - Temporal relationships
  - Granularities
  - Indeterminacy

Time Domain

- (T; ≤), where T is a non-empty set of instants and ≤ is a total order on T
- bounded
  - Contains upper and/or lower bounds w.r.t. to order relationship
- or unbounded?
- dense
  - $\forall\, t_i, t_j \in T$ with $t_i < t_j$, $\exists\, t_k \in T$ s.t. $t_i < t_k < t_j$
- or discrete?
  - Every element has both an immediate successor and an immediate predecessor

Instants and Intervals

- **Time points** represent instantaneous events, e.g. myocardial infarction
- **Time intervals** represent situations lasting for a span of time, e.g. drug therapy
- Often time points are the basic entities, where time intervals are represented by their start and end time points
- **Nonconvex intervals** are intervals formed from a union of convex intervals and might contain gaps – can be used to represent processes or tasks that occur repeatedly over time



Linear, Branching and Circular Times

- In reality, time is linear: the set of time points is completely ordered
- For tasks such as diagnosis, projection or forecasting, a branching time might be necessary: hypothesizing possible past or future events/evolutions
- Circular (or periodic) time is needed to describe times related to recurrent events, e.g. “administration of regular insulin every morning”

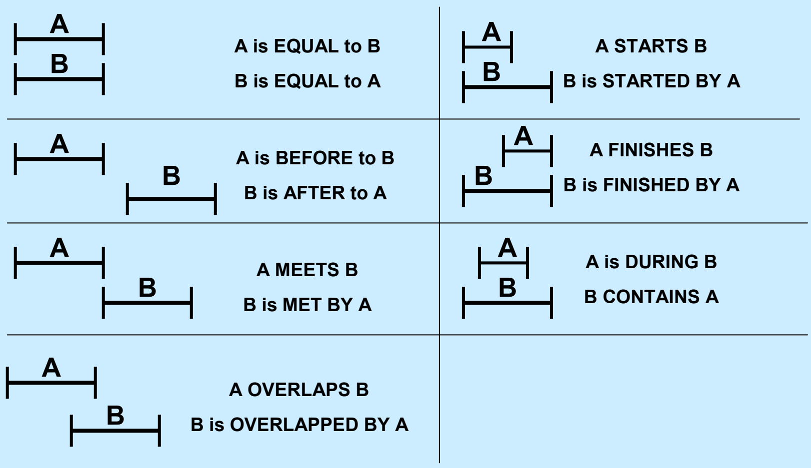
Relative and Absolute Times

- The position on the time axis of an interval or of an instant can be given
  - As an absolute position, e.g. “on July 2, 2007”
  - As a relative position, e.g. “the day after”, or “sometime before now”
- Absolute times are generally associated to a metric, being its position given as a distance from a given time origin, e.g. time origin is “admission to hospital”, metric is “days”, and absolute times could be “-3”, “4”, etc.
- When a metric is defined for the time domain, relative times can be given quantitatively, e.g. “three days after birth”

Temporal Relationships

- **Allen's interval algebra has been widely used in medical informatics**
  - Various extensions have been proposed
- **Two main types of temporal relationships**
  - Qualitative: interval I_1 before interval I_2
  - Quantitative: interval I_1 two hours before interval I_2
- **Can be classified according to the entities involved**
  - Interval/interval, interval/point, point/interval, point/point

Allen's 13 possible relations between time intervals



Granularities

- **Granularity**: level of abstraction at which temporal information is expressed
- Different units of measure allow different granularities
- **Clifford's proposal**
  - Assumes a **chronon** for every temporal domain
  - **Constructive intervallic partitioning**: segment the time line into mutually exclusive and exhaustive intervals
  - **Temporal universe**: hierarchy of time levels and units with defined semantics

Granularities

- **Bettini et al framework:** a granularity is a mapping *G* from the integers (the index set) to subsets of the time domain s.t.
  - If $i < j$ and *G(i)* and *G(j)* are non-empty, then all elements of *G(i)* are less than all elements of *G(j)*, and
  - If $i < k < j$ and *G(i)* and *G(j)* are non-empty, then *G(k)* is non-empty
  - Any *G(i)* is called a **granule** – the set of granules is discrete, irrespective of whether the the time domain is discrete or dense

Granularities

- **Bettini et al framework (cont.)**
  - Besides an index, a granule may have a textual representation, e.g. "July 2007"
  - Relationships between granularities, e.g.
    - A granularity G_1 is finer than another granularity G_2 if for each i, there exists j such that $G_1(i) \subseteq G_2(j)$
- **Time-axes framework**: conceptual modeling of time periods on the universal time line, each with its appropriate time-unit (granularity), e.g. infancy, childhood, puberty, etc.
  - Hierarchical and other relationships between time-axes
  - Spanning time-axes

Indeterminacy

- Often the knowledge of when the considered fact happened is incomplete
- We might not know precisely when a proposition became true and when it ceased to be true, although we might know that it was true during a particular time interval
- The problem may arise because the time units involved have different granularities, or due to the naturally incomplete information in clinical settings
- There is a need to model such vagueness
  - **variable interval** I, is composed of three consecutive convex intervals: *begin(I), body(I), end(I)*

Modeling Temporal Concepts - Modeling Temporal Entities

- A rich model providing a number of interrelated basic temporal entities, different abstraction levels and multiple granularities is often required
- In general, there are two approaches:
  - Adding a temporal dimension to existing objects
    - Database research: simple "atomic" entities
  - Creating model-specific, time-oriented entities
    - AI research: complex, task-specific entities

Example

- Events
  - Instant-based objects
  - E.g. patient visits
- Therapies
  - Time-interval objects
  - E.g. administration of drugs
- Phases (of therapy)
  - Complex objects including events (visits) and therapies
- Objects connected through a network

Kahn and colleagues
Temporal Network (TNET) concept

- Later evolved to Extended TNET (ETNET)
- A T-node (or an ET-node) models task-specific temporal data (e.g. chemotherapy cycle) at different levels of abstraction
- It is associated with a time interval during which the information represented by the T-node's data is true for a given patient
- Other systems inspired by the TNET model (e.g. M-HTP: monitoring heart-transplant patients)

Associating entities to instants or intervals

- Defining occurrences of temporal entities, i.e. associating time with them:
  - Use both instants and intervals
  - Use just intervals, dealing in a homogeneous way with intervals degenerating to instants
  - Use just instants (time points)

Actual occurrences of temporal entities can be specified in different ways

- **Absolute temporal occurrences**
  - Relative to some fixed time point, by specifying its initiation and termination
  - "*Tachycardia on November 3, 2005 from 6:30 to 6:45 pm*"
  - A common approach in temporal databases
- **Relative temporal occurrences**
  - By referring to other occurrences
  - "*angina after a long walk*", "*several episodes of headache during puberty*" – qualitative relationships
  - "*angina two hours before headache*" – quantitative relationships

Occurrences of temporal entities

- **Absolute vagueness (indeterminacy)**
  - Initiation and /or termination (and thus duration) cannot be precisely specified in a given temporal context – "precision" is relative to the particular temporal context
    - Earliest and/or latest possible time for initiation/ termination
    - Minimum and maximum for duration
    - "*an atrial fibrillation episode occurred on Dec 14th, 2006 between 14:30 and 14:45 and lasted for three to four minutes*"

Occurrences of temporal entities

- **Relative vagueness**
  - An occurrence's temporal relation with other occurrences is not precisely known but can only be expressed as a **disjunction** of primitive relations
  - "*the patient had vomited **before or during** the diarrhea episode*"
  - Incorporating disjunctions within a standard temporal database is still a difficult task
- **Incompleteness** in the specification of occurrences is thus a common phenomenon

Compound occurrences

- **Types**
  - **Periodic**
    - Repetition, in a regular or non-regular fashion
  - **Temporal trend**: describes a change, the direction of change, the direction of change and the rate of change, e.g. "*increasing blood pressure*"
  - **Temporal patterns**, e.g.
    - A sequence of meeting trends
    - Periodic occurrences
    - A set of causally related occurrences
- **Multiple levels of abstraction**, with two basic structural relations
  - **Refinement**: going down to component occurrences
  - **Abstraction**: from components going up to container occurrences

Contexts, causality and other temporal constraints

- **Context**: represents a state of affairs, that when interpreted (logically) over a time interval, can change the meaning of one or more facts which hold within the context time interval
- **Causality**
  - A central relation between occurrences
  - Changes are explained through causal relations, and time is intrinsically related to causality
  - Basic temporal principle: an effect cannot precede its cause
- **Temporal constraints**
  - Causally unrelated occurrences, can also be temporally constrained, e.g. a periodic occurrence could be governed by the constraint "*the repetition occurs every 4 hours*"

Temporal Reasoning

- The ability to reason about time and temporal relations is fundamental to almost any intelligent entity that needs to make decisions
- The real world includes not only static descriptions, but also dynamic processes
  - Evolving situations
  - Taking actions

  } Modeling change thus time

Time is inherently relevant when reasoning about the world

- **Natural-language processing**
  - *"by the time you get home, I would be gone for 3 hours"*
- **Robotics**
  - *Temporal order* of actions, *length of time* to perform actions
- **Causal reasoning**
  - Temporal precedence/equivalence
- **Scheduling tasks in a production line**
  - Serial and concurrent actions – time-intervals
- **Patterns in a baby's psychomotor development**
  - "*walking typically starts when the baby is about 12 months old, and is preceded by standing*"

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Medical Tasks

- **Projection:** hypothesizing the development of the patient's state, e.g. after the application of some therapeutic action
- **Forecasting:** predicting particular future values for various parameters given a vector of time-stamped past and present measured values
- **Planning:** producing a sequence of actions for a care provider, given an initial state of the patient and a goal state
  - Actions are operators with certain or probabilistic effects on the environment
  - May require enabling preconditions

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Medical Tasks

- **Interpretation:**
  - abstraction of a set of time-oriented data, either to an intermediate level of meaningful temporal patterns (e.g. temporal-abstraction or monitoring) or to a level of definite explanation of the findings and symptoms (e.g. diagnosis)
  - Unlike projection and forecasting, interpretation involves reasoning about the present and not the future
- General criterion for classifying temporal-reasoning research: deterministic or probabilistic?

Temporal Reasoning Requirements: Generic Functionalities

- Mapping the existence of occurrences across temporal contexts
- Determining bounds for absolute existences of occurrences
- Consistency detection and clipping of uncertainty
- Deriving new occurrences from other occurrences (temporal-abstraction, decomposition derivations, causal derivations, etc)
- Deriving temporal relations between occurrences
- Deriving the truth status of queried occurrences
- Deriving the state of the world at a particular time

General Theories of Time and the Medical Domain

- Allen's time-interval algebra
- Kowalski and Sergot's Event Calculus
- Dean and McDermott's Time Map Manager

Allen's time-interval algebra

- **Motivation:** expression of natural-language sentences and representation of plans
- **Primitive:** time-interval
  - Propositions interpreted over time-intervals
  - (instantaneous) events are degenerate intervals
- **13 basic binary relations between time-intervals**
  - Incomplete temporal information captured through disjunctions of temporal relations, e.g.
    - I_1 < starts, finishes, during > I_2

Allen's time-interval algebra: Proposition Types

- **Properties** hold over every subinterval of an interval, e.g. "*John had fever during last night*"
  - *holds(p,t) ↔ (∀t' in(t',t) → holds(p,t'))*
- **Events** hold only over a whole interval and not over any subinterval of it, e.g. "*John broke his leg on Saturday at 6 pm*"
  - *occur(e,t) & in(t',t) → ~occur(e,t')*
- **Processes** hold over some subintervals of the interval in which they occur, e.g. "*John had atrial fibrillation during last month*"
  - *occurring(p,t) → ∃t' in(t',t) & occurring(p,t')*

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Allen's time-interval algebra

- **No branching time**, either in the past or the future
- **Two forms of causality**: event and agentive
- **Transitivity table** that defines the conjunction of any two relations
  - R_{ij} & $R_{jk} \rightarrow R_{ik}$
  - sound but incomplete algorithm for propagating transitivity relations

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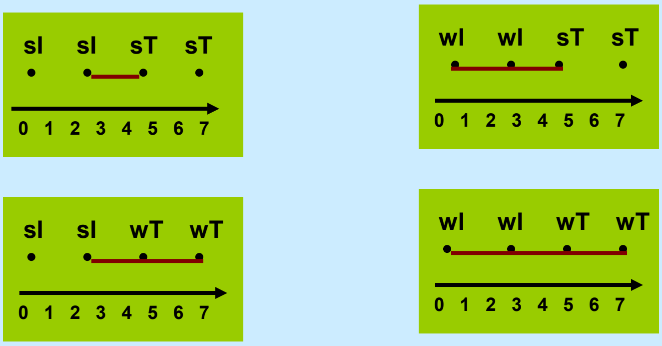
Kowalski and Sergot's Event Calculus (EC)

- A theory of time and change, well founded and formally studied
- Events happen at time points and initiate and/or terminate time intervals over which properties hold
  - *initiates(*ev_1*, prop, t)* ← *happens(*ev_1*, t) & holds(*$prop_1$*, t) & …. & holds(*$prop_N$*, t)*
  - *terminates(*ev_1*, prop, t)* ← *happens(*ev_1*, t) & holds(*$prop_1$*, t) & …. & holds(*$prop_N$*, t)*

Event Calculus (EC)

- default persistence
  - Initiated properties are assumed to persist until the occurrence of an event that interrupts them
- EC is concerned with deriving the maximal validity intervals (MVIs) over which properties hold
  - do not contain any interrupting event for the property
  - are not subsets of any other validity intervals for the property
  - *mholds_for(p, [S,E])*

Weakly and Strongly Initiating and Terminating Events



Interpreting initiating and terminating events

- **Different choices may give different MVIs**
- **The choice depends on the property to be modeled, e.g.**
  - **Weak initiates supports aggregation**
    - **In patient monitoring we need to aggregate similar observed situation, so that a transition in the classification of the patient situation (say ventilatory state) is not caused**
  - **Strong initiates supports omission**
    - **Useful when dealing with incomplete sequences of events, e.g ECG monitoring (connect, connect, disconnect)**

McDermott's temporal logic

- **Goal**: to model causality and continuous change and to support planning
- **Primitive**: *time points*, where time is dense (the time line is the set of real numbers)
- **States**: instantaneous snapshots of the universe (order preserving function: *date*)
- **Intervals**: ordered pairs of states

McDermott's temporal logic Proposition Types

- **Fact**: (T s p) where s, a state, and p, a proposition
  - Interpreted over points: "p is True in s"
  - A proposition, e.g. *(On Patient1 Bed2)*, represents the states where Patient1 is on Bed2
- **Event**, e, is the set of intervals over which the event exactly happens
  - *(Occ s_1 s_2 e)*: event e occurred between the states s_1 and s_2, i.e. over the interval [s_1 s_2]

McDermott's temporal logic chronicles

- states are totally ordered for the past, but are partially ordered and branching into the future
  – This branching captures the notion of a known past, but an indefinite future
- Chronicle
  – A maximal linear path in such a branching tree
  – Represents a complete possible history of the universe, extending to the indefinite past and future, i.e. a totally ordered set of states that extends infinitely in time

Dean and McDermott's Time Map Manager (TMM)

- Temporal primitive: time point (instant)
- Time-token: an interval together with a (fact or event) type
- Time map: a collection of time-tokens represented as a graph
  – Nodes denote instants of time associated with the beginning and ending of events
  – Arcs describe relations between pairs of instants
- Can be applied under a dense or a discrete model of time

Shoham´s Temporal Logic

- Shoham criticized the predicate-calculus semantics of McDermott’s and Allen’s logics
  - Allen’s “properties, events and processes” and McDermott’s “facts and events” seem at times either too restrictive or too general
  - Allen’s avoidance of time points as primitives leads to unnecessary complications

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Shoham´s Temporal Logic

- Time primitive: points, represented as zero-length intervals, < t, t >
- Propositions are interpreted over time intervals
  - Propositions are represented as individual concepts that can have a temporal duration
    - *TRUE(t_1, t_2, p)* – proposition p is true during the interval < t_1, t_2 >
    - Reified first-order-logic propositions, where the temporal and propositional elements are explicit
    - In simple first-order-logic approach, time is used as just another argument without granting it any special status, e.g. ON(Patient1, Bed2, t_1, t_2)

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Shoham´s Temporal Logic Semantic Properties of Propositions

- **Does not distinguish different proposition types, but defines several relations that can exist between the truth value of a proposition over an interval and the truth value of the proposition over other intervals**
  - **downward hereditary**
  - **upward hereditary**
  - **gestalt**
  - **concatenable**
  - **solid**

Example: A simplified description of skeletal dysplasia SEDC

SEDC *presents from birth* and can be lethal. It *persists throughout the lifetime* of the patient. People suffering from SEDC exhibit the following:

- **Short stature, due to short limbs, *from birth***
- **Mild platyspondyly *from birth***
- **Absence of the ossification of knee epiphyses *at birth***
- **Bilateral severe coxa-vara *from birth, worsening with age***
- **Scoliosis, *worsening with age***
- **Wide triradiate cartilage *up to about the age of 11 years***
- **Pear-shaped vertebral-bodies *under the age of 15 years***
- **Variable-size vertebral-bodies *up to the age of 1 year***
- ***Retarded ossification* of the cervical spine, epiphyses and pubic bones**

Representing SEDC in Allen's Logic

occurring(SEDC(P),I) → occur(birth(P),B) & occur(age1yr(P),O) &
occur(age11yrs(P),E) & occur(age15yrs(P),F) &
occur(death(P),D) & started-by(I,B) & finished-by(I,D) &
holds(stature(P,short),I) &
holds(ossification(P,knee-epiphyses,absent),B) &
occurring(coxa-vara(P,bilateral-severe, worsening),I) &
occurring(scoliosis(P,worsening),I) &
holds(triradiate-cartilage(P,wide),W) & started-by(W,B) &
finished-by(W,E) & holds(vertebral-bodies(P,pear-shaped),F') &
started-by(F',B) & before(F',F), &
holds(vertebral-bodies(P,variable-size),V) & started-by(V,B) &
finished-by(V,O) &
occurring(ossification(P,cervical-spine,poor),I) &
occurring(ossification(P,epiphyses,retarted),I) &
occurring(ossification(P,pubic-bones,retarted),I) &

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Representing SEDC in Event Calculus

initiates(birth(P), ossification(P, knee-epiphyses), t)
← happens(birth(P),t) & holds(SEDC(P),t)

initiates(birth(P), stature(P, short), t)
← happens(birth(P),t) & holds(SEDC(P),t)

terminates(death(P), stature(P, short), t)
← happens(death(P),t) & holds(SEDC(P),t)

initiates(birth(P), coxa-vara(P, bilateral-severe, worsening), t)
← happens(birth(P),t) & holds(SEDC(P),t)

terminates(age15yrs(P), vertebral-bodies(P, pear-shaped), t)
← happens(age15yrs(P),t) & holds(SEDC(P),t)

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Representing SEDC in Time-Tokens

The reference point, *ref*, is birth, and the granularity is years

(time-token (SEDCpresent) I)
(time-token (coxa-vara-bilateral-severe) C)
(time-token (coxa-vara-worsening) C')
(time-token (ossification-epiphyses-retarded) E)
(time-token (triradiate-cartilage-wide) W)
(time-token (vertebral-bodies-pear-shaped) V)
………………
(elt (distance (begin C) *ref*) 0 0)
(elt (distance (end C) *ref*) *pos-inf* *pos-inf*)
(elt (distance (begin C') *ref*) ? ?)
(elt (distance (end C') *ref*) ? ?)
(elt (distance (begin V) *ref*) 0 0)
(elt (distance (end V) *ref*) ? 14)
……………

Medical TR Requirements	Allen's TL	EC	TMM
Multiple conceptual temporal contexts	No	No	No
Multiple granularities	No	No	No
Absolute existences	No	Yes	Yes
Relative existences	Yes	No	Partly
Absolute vagueness	No	No	Yes
Relative vagueness	Yes	No	No
Duration	No	Yes	Yes
Point existence	No	Yes	Yes
Interval existence	Yes	Yes	Yes
Periodic occurrences	No	No	No
Temporal trends	No	No	No
Temporal patterns	Partly	No	Partly
Structural relations (temporal decomposition)	No	No	No
Temporal causality	Partly	Partly	Partly

Temporal Constraints

- In the AI community there has been substantial interest in networks of constraints
  - Work on consistency algorithms generally focuses on computational matters and no so much on the constraints themselves
- Clinical temporal constraints could involve fuzziness and different granularities, and could be of mixed types

Abstract Temporal Graph (ATG)

- The ATG is an abstract structure that aims
  - to place different types of constraints within the same unifying framework
  - at the same time enabling the analysis and differentiation of the various types of constraints
- Typical problems:
  - checking the consistency of a set of constraints
  - deciding the satisfiability of some constraint w.r.t. a set of (mutually consistent) constraints

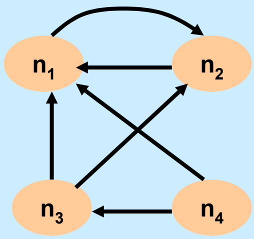
Abstract Temporal Graph (ATG)

- An **ATG** is a directed graph whose nodes represent temporal entities (events, occurrences, etc) and its arcs are labeled with the possible temporal constraints between the given pairs of nodes
  - $\mathcal{T}$ is a (finite or infinite) domain of binary, mutually exclusive, temporal constraints. At a general level, its elements are abstract entities processed by:
    - *id :* $\mathcal{T} \times \mathcal{T} \rightarrow$ *{ true, false}*
    - *inverse :* $\mathcal{T} \rightarrow \mathcal{T}$
    - *transit :* $\mathcal{T} \times \mathcal{T} \rightarrow 2^{\mathcal{T}}$

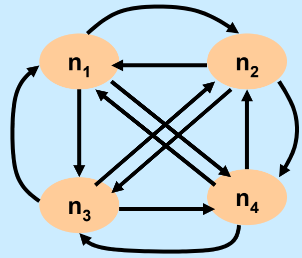
Definition ATG

An Abstract Temporal Graph (ATG) is a graph consisting of a finite set of nodes, $n_1, n_2, .., n_m$, denoting temporal entities (of the same type) and a finite set of directed arcs. A directed arc from n_i to n_j is labeled with a set of temporal constraints, tc_{ij} from $\mathcal{T}$, denoting a **disjunctive constraint** from n_i to n_j

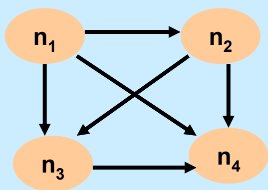
- *match :* $2^{\mathcal{T}} \times 2^{\mathcal{T}} \rightarrow 2^{\mathcal{T}}$
- *propagate :* $2^{\mathcal{T}} \times 2^{\mathcal{T}} \rightarrow 2^{\mathcal{T}}$



General ATG



Fully Connected ATG



Ordered ATG

Fully connected, Ordered, and Minimal ATG

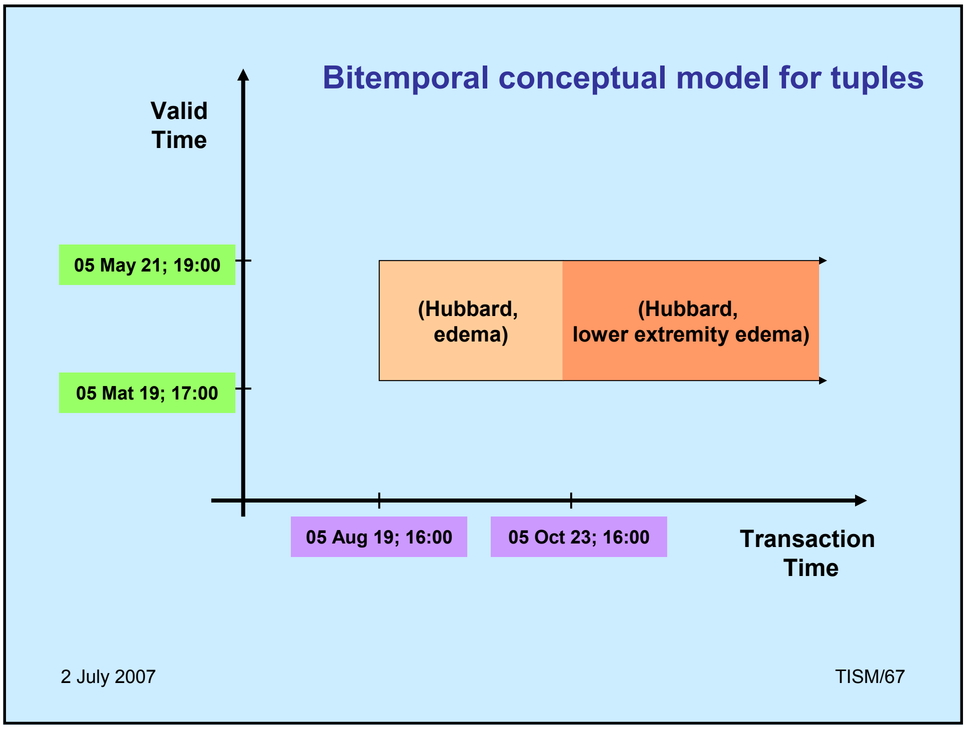
- A **fully connected ATG** is an ATG for which every pair of nodes n_i and n_j such that $i \neq j$ is connected in both directions and each connection is labeled (possibly with τ)
- An **ordered ATG** is an ATG whose nodes n_1, n_2, …, nm form a topological ordering and for every pair of nodes n_i and n_j such that $i < j$, there is a labeled connection from n_i to n_j. Pairs of nodes, n_i, n_j, such that $i \geq j$ are not connected
- A **minimal ATG** is an ordered ATG whose arcs have labels that cannot be further reduced

3. Temporal clinical databases

- Two basic, orthogonal, temporal dimensions have been recognized in the temporal database community
  - Transaction time: the time when a fact is current in the database and may be retrieved (system generated and supplied)
  - Valid time: the time at which the fact is/was true in the modeled reality (user provided)
- There is also user-defined time (not supported by the system)

A Taxonomy of Temporal Databases

- Snapshot database: represents only the current state of the modeled world (no time semantics are supported)
- Valid-time database: Also known as historical database. Supports only valid-time
- Transaction-time database: Also known as rollback database. Supports only transaction-time
- Bitemporal database: Supports both transaction and valid time



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Extending the Relational Model with Time

- **Tuple timestamping**
  - A global temporal dimension is added to each tuple
  - Different temporal dimensions of data defined through **special attributes** managed directly by the DB system
  - Temporal relations are still in 1NF and the classical relational theory can be extended to deal with time
- **Attribute timestamping**
  - Time dimensions are added at the attribute level
  - A more flexible and natural approach to modeling reality but the tuples are no longer in 1NF – attribute domains are complex, composed of couples of values and timestamps
  - The classical (flat) relational theory cannot be directly used

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Tuple timestamping
Time points (chronons)

- **Assumptions**
  - A tuple with a new (more recent) valid time ends the validity of the tuple (if present) with the same key and the closest preceding valid time
  - The insertion of a new tuple makes no more current the possibly existing tuple with the same key and the same valid time
- Suitable for **representing the history** of attribute values for a key
- Useful for **clinical time series**, e.g. the temperature of a patient during a hospitalization or the monitoring of vital signs in ICUs (assume that a measurement for a parameter is significant until a new measurement is performed)

DB of patient's hospitalizations: timestamping with time points

Patient	Ward	VT	TT
Rossi	Cardiology	1	8
Rossi	Cardiology	4	8
Rossi	Intensive Care Unit	2	5
Smith	Internal Medicine	5	8
Smith	Neurology	10	8
Hubbard	Intensive Care Unit	4	4
Hubbard	Cardiology	10	10
Hubbard	Pneumology	10	12
Hubbard	null	12	14

Tuple timestamping
Time intervals

- More complex situations can be modeled this way
- Deletions, multiple values and isolated valid intervals explicitly represented
- Thus data expressiveness is improved
  - Current tuples (identified by the symbol ∞ in the value of transaction time) can be directly observed
  - Valid tuples (identified by the symbol ∞ in the value of the valid time) can also be directly observed – null values for ending the validity of a tuple are avoided
- However the structure of the relation schema is more complex: special symbol ∞ denotes open intervals

DB of patient's hospitalizations: timestamping with time intervals

Patient	Ward	VT	TT
Rossi	Cardiology	[1,1]	[8,+∞]
Rossi	Cardiology	[4,+∞]	[8,+∞]
Rossi	Intensive Care Unit	[2,3]	[5,+∞]
Smith	Internal Medicine	[5,9]	[8,+∞]
Smith	Neurology	[10,+∞]	[8,+∞]
Hubbard	Intensive Care Unit	[4,9]	[4,+∞]
Hubbard	Cardiology	[10,+∞]	[10,11]
Hubbard	Pneumology	[10,+∞]	[12,13]
Hubbard	Pneumology	[10,12]	[14,+∞]

Tuple timestamping
Temporal elements

- Temporal dimensions to tuples are defined as finite sets of disjoint intervals
- Data expressiveness is improved further, since, for example, all hospitalizations of a given patient in the same ward are given in the same tuple, where its valid time is modeled by temporal elements

DB of patient's hospitalizations: timestamping with time elements

Patient	Ward	VT	TT
Rossi	Cardiology	[1,1] U [4,+∞]	[8,+∞]
Rossi	Intensive Care Unit	[2,3]	[5,+∞]
Smith	Internal Medicine	[5,9]	[8,+∞]
Smith	Neurology	[10,+∞]	[8,+∞]
Hubbard	Intensive Care Unit	[4,9]	[4,+∞]
Hubbard	Cardiology	[10,+∞]	[10,11]
Hubbard	Pneumology	[10,+∞]	[12,13]
Hubbard	Pneumology	[10,12]	[14,+∞]

Attribute timestamping

- **Valid time can be separately represented for every single attribute within a tuple**
- **Attribute values are complex**
  - **Atemporal part**
  - **Time dimension, represented as time points, intervals or temporal elements**
- **Attributes may be categorized into time-varying and constant (or all attributes have a temporal dimension)**
- **Usually each tuple is homogeneous**
  - **The time span over which an attribute has (different) value(s) within a tuple is the same for each attribute of the considered tuple**

DB of patient's hospitalizations: attribute timestamping < valid-time, transaction-time >

Patient	Ward
Rossi <[1,+∞], [5, +∞]>	Cardiology < [1,1] U [4,+∞], [8,+∞] > Intensive Care Unit < [2,3], [5,+∞]>
Smith<[5,+∞], [8, +∞]>	Internal Medicine <[5,9], [8,+∞]> Neurology <[10,+∞], [8,+∞]>
Hubbard <[4,12], [4, +∞]>	Intensive Care Unit <[4,9], [4,+∞]> Cardiology <[10,+∞], [10,11]> Pneumology <[10,+∞], [12,13]> Pneumology <[10,12], [14, +∞]>

valid-time: temporal element; transaction-time: time interval

Querying temporal relations

DB of patient symptoms: relation pat_sympt

P_id	symptom	VT	TT
1	headache	[05Oct1,∞]	[05Oct10,05Oct14]
2	vertigo	[05Aug8, 05Aug15]	[05Oct15, 05Oct20]
2	vertigo	[05Aug10, 05Aug15]	[05Oct21, ∞]
1	headache	[05Oct1, 05Oct14]	[05Oct15, 05Oct20]
1	headache	[05Oct1, 05Oct14]	[05Oct21, ∞]

DB of patient therapies: relation pat_ther

P_id	therapy	VT	TT
1	aspirin	[04Oct1, 04Oct20]	[05Oct10, ∞]
2	paracetamol	[05Aug11, 05Aug12]	[05Oct15, ∞]

Querying temporal relations

Example: Determine the symptoms of patients for which the valid time intervals of symptoms and therapies overlap

```
SELECT symptom, S.P_id
FROM pat_sympt S, pat_ther T
WHEN NOT(VALID(S) BEFORE VALID(T)) AND
          NOT (VALID(T) BEFORE VALID(S))
WHERE S.P_id = T.P_id
```


Patient symptoms that overlap therapies

P_id	symptom	VT	TT
2	vertigo	[05Aug11, 05Aug12]	[05Oct21, ∞]

Representations versus Semantics

- Terenziani et al draw a distinction between temporal representations and temporal semantics, pointing out that
- Although in temporal DBs, interval based representations are used, still in the totality of temporal DB approaches "point-based" semantics is implicitly or explicitly assumed (see previous example)

Point-based semantics for data

- The data in a temporal relation is interpreted as a sequence of states (a state is a conventional relation, i.e. a set of tuples) indexed by points in time. Each state is independent of every other state
- Point-based semantics are appropriate for "atelic facts":
  - downward inheritance applies
  - upward inheritance applies
  - countable
- In an atelic model, overlapping or meeting validity times are "merged" (i.e. coalesced) together

“Telic facts” (accomplishments)

- The point-based semantics do not cover an important class of data, namely **“telic facts”**
- Telic facts have an **intrinsic goal** or **culmination** (from Greek word «τέλος»)
  - downward inheritance does not apply
  - upward ihheritance does not apply
  - not countable
- Telic facts require **“interval-based semantics”** – each interval is interpreted as an atomic, indivisible, one (thus intervals are required not only at the representation level, but also at the semantic level)

Modeling both atelic and telic facts

- There is a debate on whether it is better to model reality as a sequence of different states (**atelic-based representation**, c.f. McCarthy’s Situation Calculus) or as a sequence of different events (**telic-based representation**, c.f. Event Calculus)
  - processes: atelic facts
  - events: telic facts
- The two ways are complementary and both are required

Three-sorted model and a query language to deal with both "telic" and "atelic" medical data

- Proposed **types of relations** in a temporal DB
  - atelic relations – point-based semantics
  - telic relations – interval-based semantics
  - non-temporal relations
- The **query language has to be extended** to allow flexible "casting" operations, to switch from one model to the other and vice versa
- **Object decomposition**
  - An object could be composed of smaller objects at another level of granularity – a telic fact may be composed of atelic ones

Temporal Interpolation is also required

Temporal interpolation techniques derive information for times for which no information is stored on the basis of related information holding at different times

4. Abstraction of time-oriented clinical data

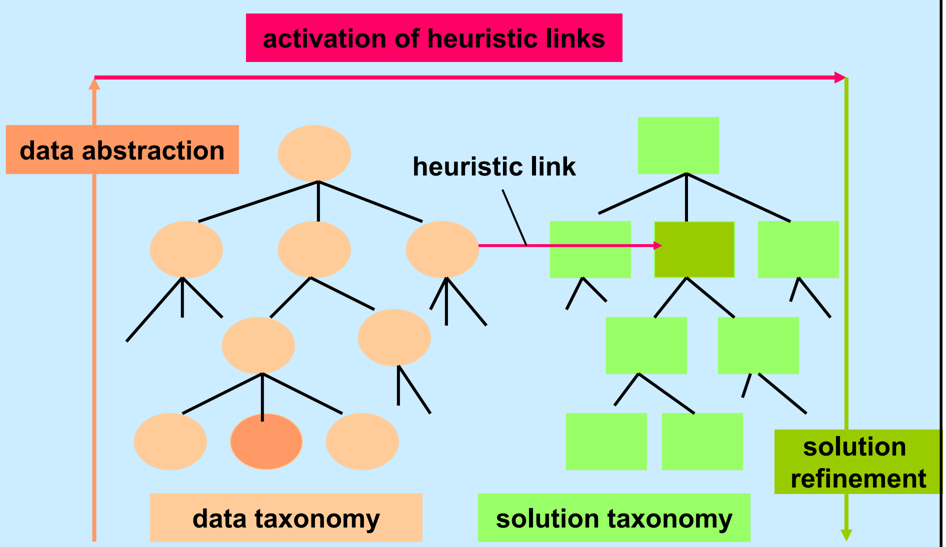
- **Temporal abstraction** is a crucial process, especially in clinical monitoring, therapy planning and exploration of clinical databases.

- General theories of time typically used in AI do not fully address the requirements for temporal abstraction in medical reasoning

Closing the gap between medical knowledge and patient data

- **Medical knowledge, like any kind of knowledge is expressed in as general a form as possible**
  - Association rules
  - Causal models of pathophysiological states
  - Behavior (evolution) models of disease processes
  - Patient management protocols and guidelines
- **Patient data are specific**
  - Numeric measurements of various parameters at different points in time
  - History of the patient (past operations and others treatments), results of laboratory and physical examinations, and the patient's own symptomatic recollections

Clancey's Heuristic Classification



Significance of Data Abstraction

- A knowledge-based system that does not possess data abstraction capabilities requires the user to express the case data at the level of abstraction corresponding to its knowledge
  - Added burden on the user, who might not be a specialist
  - Prone to errors and inconsistencies
  - May be practically impossible due to the sheer volume of raw data

In clinical domains a final diagnosis is not always the main goal

- Often, what is required is a coherent intermediate-level interpretation of the relationships between data and events, and among data
- Goal: abstract the clinical data (time-stamped measurements) into higher-level, interval-based concepts
- Such concepts could be useful for one or more tasks, e.g. therapy planning or summarization of a patient's record

Example

- Origin of time line: external event marking the bone-marrow transplantation
- Granularity: days
- Raw data: platelet and granulocyte counts at different time-points (days) from origin
- External intervention: administration of PAZ protocol for treating patients who have chronic graft-versus-host disease (CGVHD)
- Context interval: Expected CGVHD (open interval)
- Abstractions: bone marrow toxicity of given grade and duration under the given context

Atemporal Data Abstraction

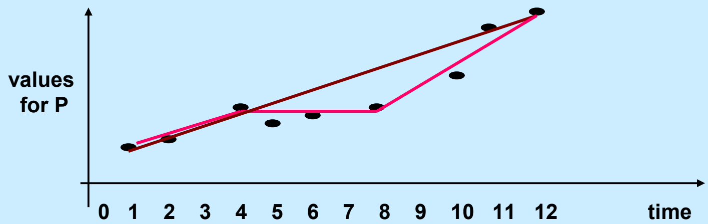
- **Qualitative Abstraction**
  - Converting numeric expressions to qualitative expressions (context-sensitive)
  - e.g. "*a temperature of at least 40º C*" → "*fever*"
- **Generalization Abstraction**
  - Mapping instances into classes
  - e.g. "*halothane administered*" → "*drug administered*"
- **Definitional Abstraction**
  - Mapping across different conceptual categories
  - e.g. "*generalized platyspondyly*" → "*short trunk*"

Temporal Data Abstraction

- **Merge (or State) Abstraction**
  - Deriving maximal intervals for some concatenable property from a group of time-stamped data for that property
  - e.g. three (discrete) consecutive daily recordings of fever → fever for a three-day interval
- **Persistence Abstraction**
  - Applying (default) persistence rules to project maximal intervals for some property, both backwards and forwards in time and possibly on the basis of a single item; context-sensitive
  - Persistence semantics of properties
    - infinitely persisting (e.g. *blindness*)
    - finitely persisting (recurring [e.g. *flu*] , non-recurring [e.g. *chickenpox*])

Temporal Data Abstraction

- **Trend Abstraction**
  - Deriving significant changes and rates of change in the progression of some parameter
  - Employs merge and persistence abstraction
  - Data could be noisy and incomplete
  - Most frequently used type



Temporal Data Abstraction

- **Periodic Abstraction**
  - Deriving repetitive occurrences, usually with some regularity in the pattern of repetition
  - e.g. "headache every morning, for a week, with increasing severity"
  - <repetition element> <repetition pattern> <progression pattern>
    - the repetition element could be of any order of complexity, e.g periodic occurrence
  - The period spanning the extent of a periodic occurrence is nonconvex by default

(Temporal) Data Abstraction

- Basic abstractions can be combined in a multitude of ways to yield complex abstractions
- Distinguishing feature: knowledge-based, heuristic process (statistical analysis, e.g. derivation of trends through time-series analysis, is algorithmic)
  - E.g. in periodic abstractions relevant knowledge can include acceptable regularity patterns, means for justifying local irregularities, etc.
- Atemporal data abstraction is "concept abstraction".
- Temporal data abstraction is "concept abstraction" followed by "temporal abstraction"
  - From time-points to convex/nonconvex time-intervals
  - From fine granularities to grosser granularities
  - Etc.

Deriving Abstractions: Direction of Reasoning

- When hypotheses are explored, the abstraction process is called to corroborate predicted abstractions against raw data; thus it is used in a goal-driven fashion
- For the initial establishment of the hypothesis space, the data abstraction process operates in a non-directed or event-driven fashion (c.f. heuristic classification); in a monitoring system, data abstraction, which is the heart of the system, operates in a largely event-driven way

Example contexts of use of data abstractions

- Summarizing long patient records, e,g. with meaningful trends - visualizations
- Supporting/explaining the recommendations of diagnostic, therapeutic, or other intelligent decision-support systems
- Supporting the monitoring of (therapy) plans during their execution
- Enabling multiple, context-specific, interpretations of the same data, giving hindsight and foresight inferences

Desired computational behavior of a temporal data abstraction method

- Accept as input both numeric and qualitative data, at different levels of abstraction, involving time-points, or time-intervals, etc.
- Input data could arrive out of temporal order – view update or hindsight
- Output abstractions available for query at all levels of abstraction
- All reasonable, alternative, interpretations of the same data, relevant to the task at hand, should be available
- It can cope with uncertainty in the data values and the time
- The method should be reusable in other domains and tasks

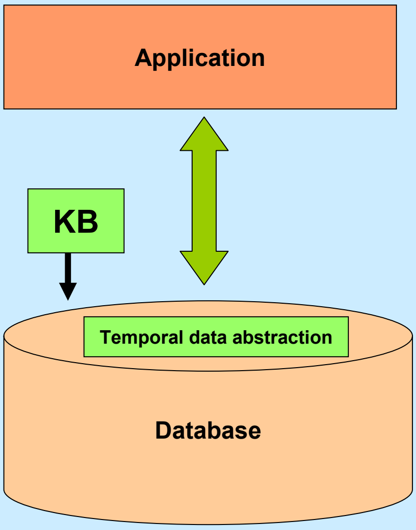
Data Abstraction for Knowledge Discovery

- Data abstraction is primarily used for converting the raw data on a **single patient** to more useful information.
- However temporal abstraction methods can be used **synergistically with machine learning methods** giving added value to knowledge discovery
- An early system, **Blum's Rx system**, aimed to discover possible causal relationships by examining a time-oriented clinical database
- More than a decade now, the **IDAMAP series of international workshops** aims to bring together the machine learning and temporal data abstraction communities interested in medical problems

Temporal Mediators

Merging Temporal Reasoning and Temporal Maintenance

- **Temporal-data maintenance** is equally important to reasoning about time-oriented medical data
- Maintenance of both raw data and abstractions requires an **integration** of the temporal reasoning and temporal maintenance tasks
- Thus we need to consider the **mode of integration** between the application, the data-abstraction process (essentially, a temporal-reasoning task), and the temporal-maintenance aspect of the system



Incorporating the abstraction process within the database

drawbacks: relying on the DBMS's language, tight coupling

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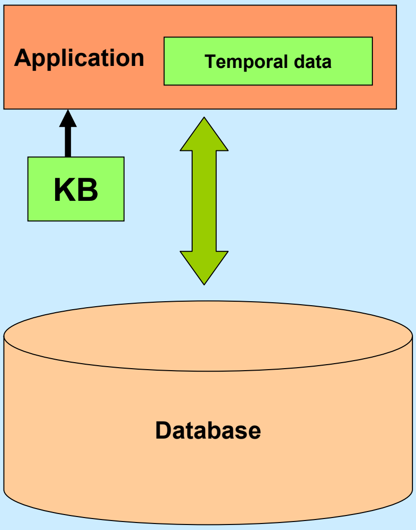

Incorporating the abstraction process within the application

The application system should have a data-management capability, assuming an inherent data-abstraction capability

drawbacks: duplicating in the application of DBMS functions, no reusability, tight coupling

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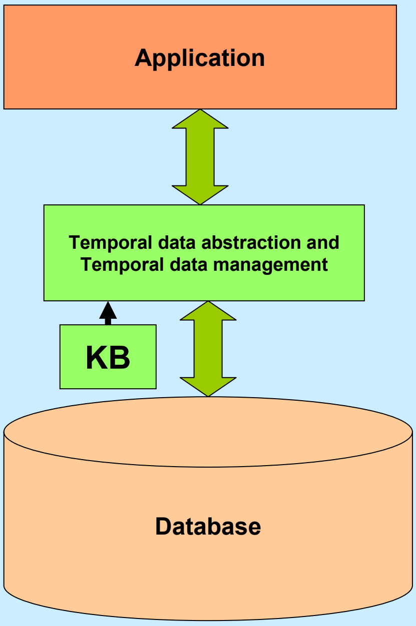

Encapsulating the temporal-data management and the temporal-data abstraction capabilities within an intermediate *mediator* that is independent of both

benefit: enjoying all advantages of the specialized modules

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Shahar's Knowledge-Based Temporal-Abstraction (KBTA) Method

- **Motivation: clinical-data summarization and query for monitoring, therapy, quality assessment and clinical research**
- **Features of KBTA method**
  - **Formal temporal ontology (emphasizes the explicit representation of knowledge for the abstraction)**
  - **A set of computational mechanisms using the ontology, that create abstract, interval-based concepts from time-stamped clinical data**
- **The TA task is decomposed into five subtasks**

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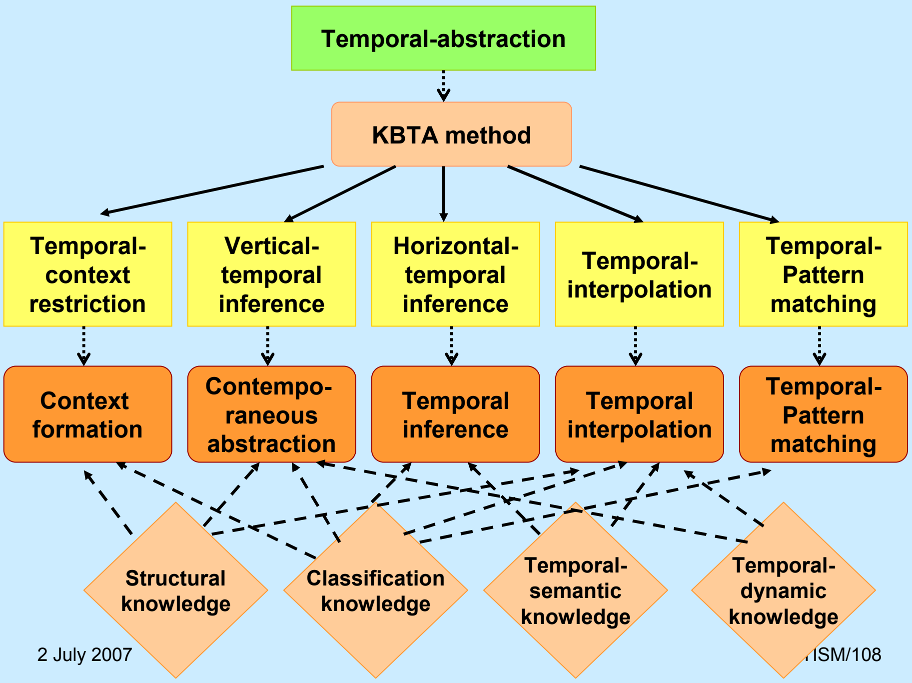
KBTA Method

- Implemented in the **RÉSUMÉ system**
- **Evaluation domains**
  - Guideline-based care of oncology patients
  - Guideline-based care of AIDS patients
  - Monitoring of children's growth
  - Management of patients with insulin-dependent diabetes



The KBTA Ontology: Entity sets

- Time stamps, temporal granularity units, zero-point, time measure
- Time points, time intervals
- interpretation contexts, context intervals
- Event propositions, event schemata, event intervals
- Parameter schemata, parameter propositions, abstract parameters, constant parameters
- Abstraction functions, abstraction types (state, gradient, rate), patterns
- Parameter interval, pattern intervals, abstraction intervals
- Abstraction goals, abstraction-goal intervals
- Dynamic induction relation of a context interval (DIRC)

A domain's TA ontology

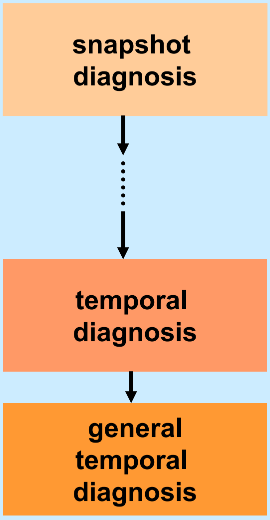
- Event ontology
- Context ontology
- Parameter ontology
- Pattern ontology
- Set of abstraction-goal propositions
- Set of DIRCs

5. Time in clinical diagnosis

- Diagnostic problem solving has attracted and continues to attract considerable interest in the AI community, as it presents a number of challenges – one challenge is the modeling of time
- Pioneering medical diagnostic systems: MYCIN, INTERNIST-1, CASNET, ABEL, MDX/PATREC and many others
- In the early diagnostic systems, time was completely absent or modeled in a rudimentary form

A unified framework for model-based diagnosis

- Proposed by Brusoni et al
- The authors make no commitments regarding an ontology for time
- Time-varying context
  - Observing the behavior of a system at different times
- Temporal behavior
  - The consequences of the fact that a system is in a specific (normal or faulty) mode manifest themselves after some time and for some time
- Time-varying behavior
  - Permitted transitions between faults; if this knowledge is missing any transition is permitted by default



atemporal diagnosis performed at a point in time

considers temporal behavior over a specified time window, but not time-varying behavior – assumption: a fault persists during the given time-window

considers both time-varying and temporal behavior, again over a specified time-Window (a fault does not necessarily Persists during the given time-window)

Paradigms of model-based diagnosis

- **Consistency-based**
  - Models of normal behavior
  - A solution is a (minimal) set of abnormality assumptions
  - The behavior generated when a model of normal behavior is perturbed under the given set of abnormality assumptions, must be consistent with the observed abnormalities
- **Abductive diagnosis**
  - Pointing out, as a sufficiently detailed level, the causes of the observations of abnormality – the diagnosis entails the observations of abnormality
  - More appropriate paradigm for clinical diagnosis

Diagnosing under the assumption of multiple disorders

- Abductive diagnostic reasoning comprises the **generation** and **evaluation** of diagnostic hypotheses as two distinct but tightly coupled steps

- The reasoning is performed under the assumption of **single** or **multiple disorders**, thus giving rise to simple or complex hypotheses

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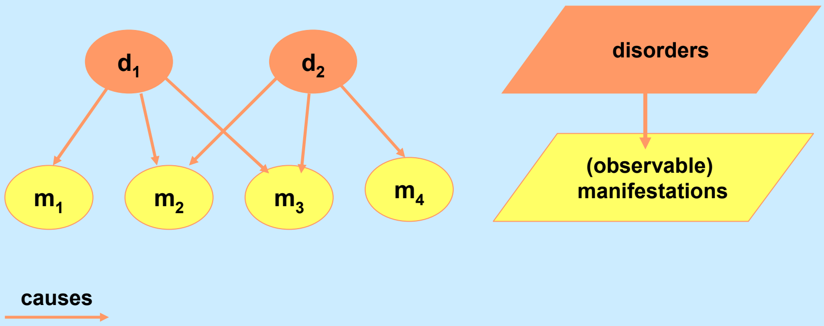

Associational disorder models

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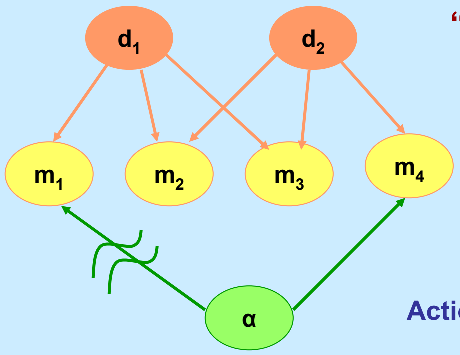
Example

The findings of the patient in question assert the presence of m_2, m_3 and m_4 and the absence of m_1.More specifically, m_2 appeared, then disappeared and then appeared again. The appearance of m_3 followed the start of the second appearance of m_2, the two overlapped and continued together. The appearance of m_4 preceded the first appearance of m_2. It is also known that the patient is currently undergoing treatment α.

Diagnosing under a simple associational disorder model

- **"Best" explanation: disorder d_2**
- **However, temporal and contextual information (application of therapy α) has been ignored**
- **Ignoring temporal information means that a dynamic, moving, picture is replaced with a static one**

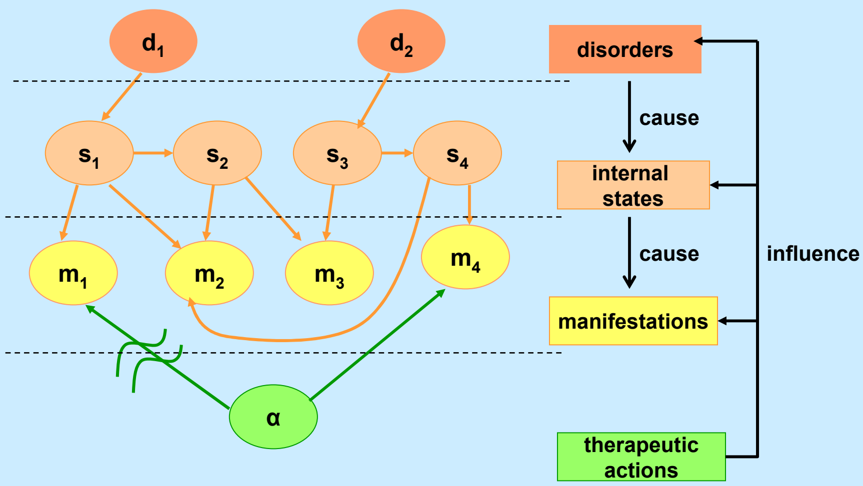
Considering the effects of therapeutic actions



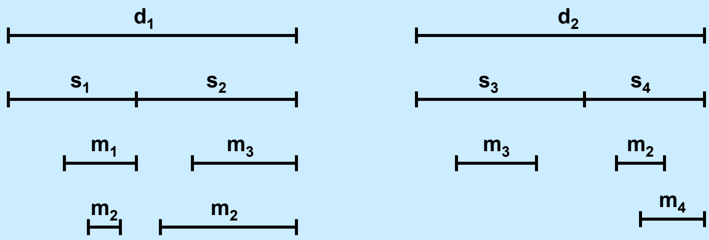
"best" hypothesis: d_1 or d_2 ?

Action α inhibits m_1, but gives rise to m_4

Adding internal states in disorder models and considering the effects of therapeutic actions



Extending disorder models with temporal constraints



Temporal constraints in d_1

Temporal constraints in d_2

Causal-Temporal Disorder Models

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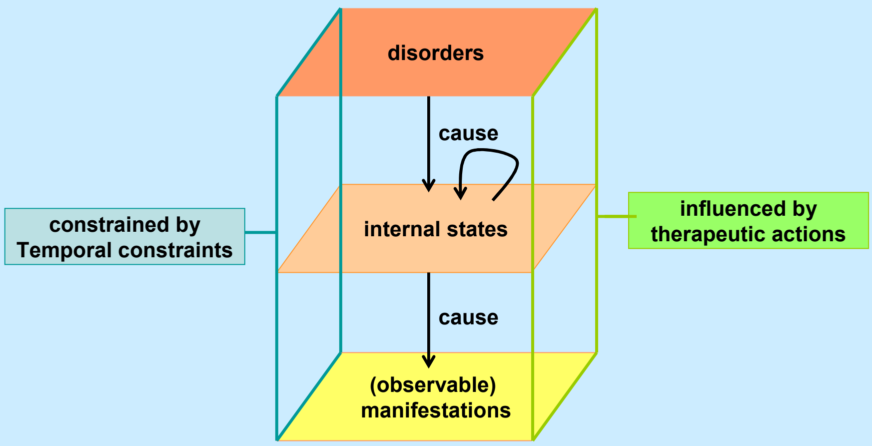
Causal-Temporal-Action (C-T-A) Model



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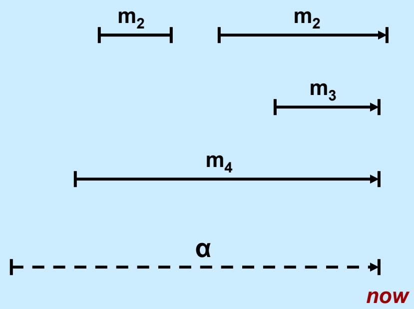
Returning to the Example: Temporal and contextual Information can now be considered

Patient findings



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Best explanation: disorder d_1

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Deriving the ‘Best’ Diagnostic Solution

- Generating potential solutions to a diagnostic problem is one challenge
- Selecting the ‘best’ potential solution is another challenge
  - different evaluation criteria may be used in combination
  - If the *closed world assumption* holds
    - minimality based on cardinality or entailment may be sufficient for selecting the best explanation
  - In clinical domains, diagnostic hypotheses neither entail all observations of abnormality, nor do they exhibit complete consistency with the entire relevant history (past and present) of the patient

Hypothetico-deductive Model of Reasoning

- Hypothesis evaluation involves deductive reasoning in order to discover what is entailed by some hypothesis
- The generation and evaluation of hypotheses (comprising the abductive paradigm) is also referred to as the hypothetico-deductive model of reasoning
- This model is evident in Bayes’ Theorem:

$$P(H/E) = \frac{P(E/H)\,P(H)}{P(E)}$$

Example Clinical Diagnostic Systems

with explicit models of time

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The Heart Disease Program (HDP)

- Diagnoses disorders of the cardiovascular system
  - Patients typically arrive with existing diseases and existing therapies
  - Therapies with both their beneficial effects and side effects are an important part of the domain
- The diagnostic knowledge is modeled as a Bayesian Probabilistic Network, where temporal constraints on the causal relations are explicitly represented
- Patient data are time-stamped entities – available observations are limited

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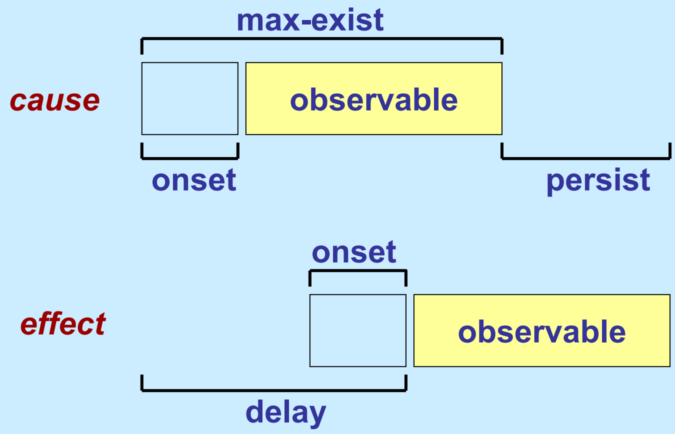
Temporal Semantics of Causal Relation



Self-limiting causality and intermittent states

- **A causal relation is self-limiting if the abnormality ceases by max-exist without any rectification action**
- **A state is intermittent if it is absent over subintervals of the interval in which it is true**

Interpretation rules for temporal constraints

1. When a node is observed, it is assumed to already be producing effects for ***onset time***
2. Effects are observable at a time after the cause given by the ***delay***, if it exists, otherwise by the ***onset***
3. Effects are observable after the cause is observable and overlap the cause
4. Effects continue until the cause ceases, unless the ***max-exist*** is exceeded or the effect is ***intermittent***
5. Effects continue after the cause ceases, in accordance with the ***persist***.

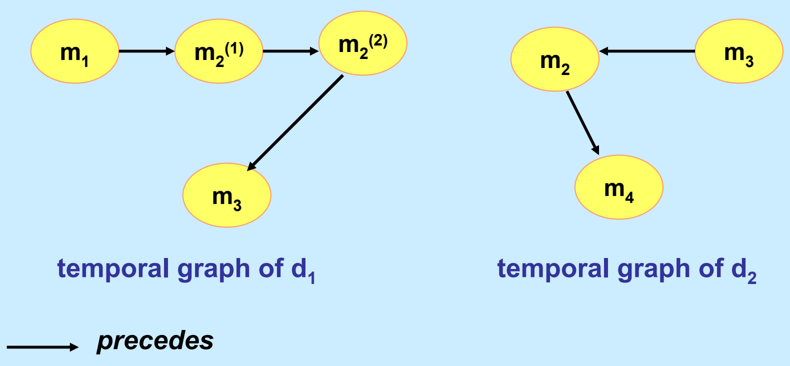
Patterns of Causality

- **immediate**: the effect happens immediately
- **progressive**: the effect, once it takes place, continues and often worsens
- **accumulative**: when a cause is required to exist over a period of time
- **corrective**: when a state causes another state to return to normality

Temporal Parsimonious Covering Theory

- **Temporal extension of Peng and Reggia's PCT:**
  - **Associational disorder models**
  - **Parsimony criteria for diagnostic explanations**
    - ***Relevancy***
    - ***Irredundancy***
    - ***Minimality***

- **In t-PCT each disorder is modeled, separately, as a temporal graph**
  - **Directed arcs represent temporal precedence, and thus a temporal graph is not necessarily a causal graph**
  - **Quantitative information about durations or delays is associated with the relevant nodes or arcs**

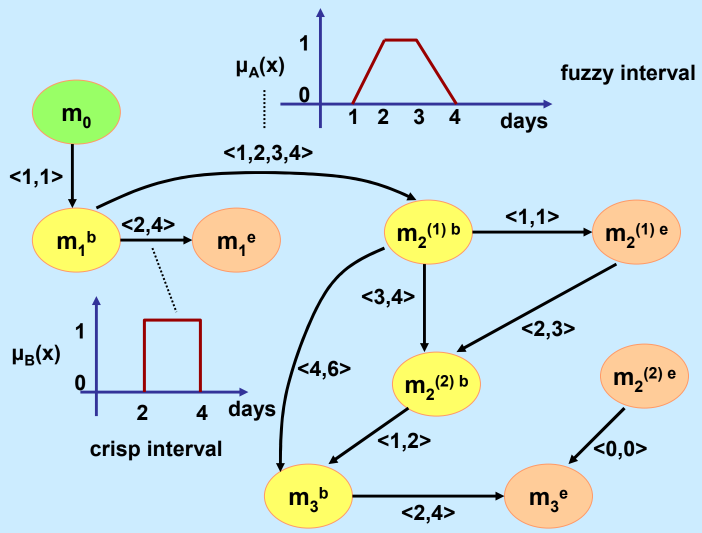


Temporal uncertainty

- An interval, $I=[I^-,I^+]$, is a non-empty, convex, set of time points: $^{I-}$ is the min extent, and I^+ is the max extent (if $I^- = I^+$ there is no uncertainty)
- Operations on time intervals
  - Intersection gives the common subrange
  - Sum propagates delays along a chain of manifestations, or positions a manifestation on the time line
- Temporal inconsistency arises if
  - There is arc inconsistency
  - The actual duration of a manifestation is different from its expected duration under a given disorder

Fuzzy Temporal/Categorical Diagnosis

- t-PCT has been extended using fuzzy sets
- The crisp representation of a time interval as a range of values has been replaced with a fuzzy set giving ranges for typical as well as possible extents
- The intensity of manifestations (disorder models, patient information) is expressed in terms of fuzzy sets – manifestations distinguished into necessary and possible
- The speed of evolution of the 'concluded' disorder is computed on the basis of the patient data – this is used to make predictions about past and future events



temporal graph of d_1

Abductive Diagnosis using Time-Objects

- **Central primitives**: time-axis and time-object
- **Time-axis**
  - Represents a period of valid time from a given conceptual perspective
  - Expressed discretely as a sequence of time-values relative to some **origin**
  - **Types**
    - **Atomic** – single granularity
    - **Spanning** – hybrid granularity

Time-Object

- A **time-object** is a dynamic entity that has **time as an integral aspect**
- It is an association between a property and an existence
- Formally τ is defined as a pair $<\pi_\tau, \varepsilon_\tau>$ where π_τ is the property and ε_τ its existence function
- Time-objects can be **compound**, involving component time-objects
  - Can be **viewed from different temporal perspectives**
  - At gross perspectives some components may not be visible

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Causality

- A central notion of the time-object ontology
- *causes(τ_i,τ_j,cs,cf),* where τ_i and τ_j are abstract time-objects
- *causality-link(τ_i,τ_j),* where τ_i and τj are concrete time-objects
- *cause-spec(ρ_i,ρ_j,μ,TRel,Tabs,cf),* where ρ_i and ρ_j are abstract properties, and μ a granularity

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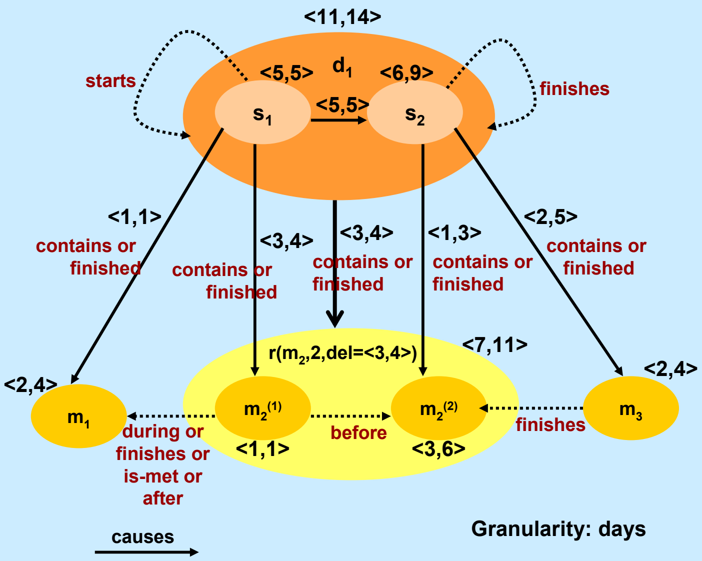
Concrete Time-Object

- Can be viewed as an **agent**
  - **Extinguished**; its existence refers to the past
  - **Alive and active**; its existence refers to the present
  - **Asleep and waiting**; its existence refers to the future
- It's a dynamic entity that exhibits a certain behavior in terms of the **changes it can bring about**, either to itself or to other time-objects
  - **Constructive change** (creates a time-object)
  - **Destructive change** (destroys a time-object)
- Thus a time-object interacts with other time-objects, in a constructive or destructive manner
  - Interactions are modeled through causality

Modeling d_1 as a causal-temporal structure of atomic and compound time-objects



6. Research Challenges

Temporal Reasoning & Data Mining

- **Development of medical models that effectively combine causal, temporal and action knowledge, and enable the dynamic (contextual) derivation of different forms of interactions and the rates of evolution of the operative processes.**
- **Dealing with uncertainty through the effective combination of temporal-probabilistic-fuzzy knowledge – reasoning efficiently with mixed temporal constraints involving different granularities**
- **Bestowing medical systems, with the ability to dynamically and timely change a temporal plan of therapy actions by responding to relevant sensors.**

Temporal Reasoning & Data Mining

- Developing further the concept of a data mediator that facilitates the incorporation of different ontologies in different applications by providing in a task and domain independent way temporal-data management and temporal-data abstraction capabilities.
- Integrating temporal abstraction with machine learning
- Temporal data mining – "information-based medicine"

Health Information Systems

- Incorporating time as an important aspect in the modeling and managing processes within health information systems – temporal data management and workflow systems
- Adopting a temporal DBMS

Temporal Clinical Databases

- **Several challenges remain in making temporal database methods more commonly used by decision-support, data mining and workflow systems – new approaches for temporal representations and querying in database systems are called for**
- **Relational databases lack a standard way to maintain the granularity of time-values – evaluating the expressivity of the TSQL2 model for clinical applications and adopting/extending the most suitable features**
- **Further work is needed to establish and examine the needs of clinical researchers working with large sets of temporal data and to create efficient methods for statistical analysis with temporal representation and reasoning approaches**