Discriminating Exanthematic Diseases from Temporal Patterns of Patient Symptoms

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Abstract. The temporal dimension is a characterizing factor of many diseases, in particular, of the exanthematic diseases. Therefore, the diagnosis of this kind of diseases can be based on the recognition of the typical temporal progression and duration of different symptoms. To this aim, we propose to apply a temporal reasoning system we have developed. The system is able to handle both qualitative and metric temporal knowledge affected by vagueness and uncertainty. In this preliminary work, we show how the fuzzy temporal framework allows us to represent typical temporal structures of different exanthematic diseases (e.g. Scarlet Fever, Measles, Rubella et c.) thus making possible to find matches with data coming from the patient disease.

1 Introduction

The necessity for the recruitment of symbolic approach to solve medical problems arises from the understanding that medical problems are often too complex to be modeled analytically [21].

An important contribution to symbolic approach is given by fuzzy methodologies that can be regarded as a formalism particularly suitable to deal with the imprecision intrinsic to many medical problems and useful to build models for biological systems when a precise model doesn't exist or it is difficult to realize [16].

The claim that fuzzy logic is a useful theoretical, methodological, and design tool for addressing some of the problems found in developing intelligent patient-supervision systems can be widely found in the literature concerning medical AI [9, 1]. In [9] where a patient supervision system for intensive and coronary care units is described, the role of fuzzy logic is strongly emphasized. In fact, uncertainty and impreciseness pervade system input information as well as the representation of knowledge, and the *modus operandi* of human expert. The model proposed for developing this supervision system allows the integration of knowledge on the evolution of a set of parameters into a knowledge representation scheme in which time plays a fundamental role [9, 13].

More in general, taking into account also the temporal dimension, the development of hybrid systems combining the two notions of fuzziness and time

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makes possible to perform fuzzy temporal reasoning particularly useful in many medical applications [22, 15]. Medical diagnosis is a field in which imprecise information about symptoms and events can appear; for example this happens when the physician must interpret the description of a patient, or when a new disease appears and typical patterns have to be discovered.

Moreover, there are diseases characterized by a typical temporal evolution and duration of different symptoms such as fever, appearance of skin rush et c., that is the occurrence of symptoms follows a typical temporal behavior. In these cases, the study of the temporal evolution of a set of physical parameters may be a way for discriminating among a set of diseases. Then the diagnosis can be based on the recognition of typical temporal structures. This is the case of exanthematic diseases.

This paper deals with representation and reasoning on information concerning the evolution of physical parameters by means of a model based on Fuzzy Temporal Constraint Networks [12, 14]. Temporal information coming from the domain may be both qualitative such as "the interval I_1 with fever precedes the interval I_2 with skin rush" or metric such as "fever lasts one day" or mixed such as "symptom m_2 follows symptom m_1 and starts at 8pm". Moreover the information is often affected by imprecision and uncertainty. For this reason, crisp relations both qualitative and metric are not adequate and fuzzy temporal relations have to be introduced [15, 22].

The aim of this paper is the application of our system capable of handling fuzzy temporal knowledge in a very general way [5] to recognize different patterns typical of diseases in order to build a first step towards an automated tool for medical diagnosis to be applied in all those cases in which these temporally-based features are relevant.

2 Qualitative and Quantitative Fuzzy Temporal Constraints

The most famous approach to deal with qualitative temporal constraints is the Allen's Interval Algebra [2]; in this algebra each constraint is a binary relation between a pair of intervals, represented by a disjunction of *atomic relations*:

$$I_1 \ (rel_1, \ldots, rel_m) \ I_2$$

where each rel_i is one of the 13 mutually exclusive atomic relations that may exist between two intervals (such as *equal*, *before*, *meets* etc.).

Allen's Interval Algebra has been extended in [3, 4, 7] with the Possibility Theory by assigning to every atomic relation rel_i a degree α_i, which indicates the *preference degree* of the corresponding assignment among the others

$$I_1 \ R \ I_2 \text{ with } R = (rel_1[\alpha_1], \ldots, rel_{13}[\alpha_{13}])$$

where α_i is the preference degree of rel_i ($i = 1, \ldots, 13$); preferences can be defined in the interval $[0, 1]$. If we take the set $\{0, 1\}$ the classic approach is obtained.

Intervals are interpreted as ordered pairs $(x, y) : x \leq y$ of $\Re^2$, and soft constraints between them as fuzzy subsets of $\Re^2 \times \Re^2$ in such a way that the pairs of intervals that are in relation rel_k have membership degree α_k.

Temporal metric constraints have been extended to the fuzzy case starting from the traditional TCSPs [11] in many ways [17, 14]. To represent fuzzy temporal metric constraints we adopt trapezoidal distributions [5], since they seem enough expressive and computationally less expensive than general semi-convex functions [19].

Each trapezoid is represented by a 4-tuple of values describing its four characteristic points plus a degree of consistency α_i denoting its height.

$$T_k = \ll a_k, b_k, c_k, d_k \gg [\alpha_k]$$

with $a_k, b_k \in \Re \cup \{-\infty\}$, $c_k, d_k \in \Re \cup \{+\infty\}$, $\alpha_k \in (0, 1]$, $\ll$ is either `(` or `[` and $\gg$ is either `)` or `]`.

The points b_k and c_k determine the interval of those temporal values which are likely, whereas a_k and d_k determine the interval out of which the values are absolutely impossible.

The effective translation of $\ll$ and $\gg$ is not completely arbitrary, but it is constrained to well defined rules that lead to build well-formed trapezoids [5].

As an example, let's consider the following sentence:

> "In disease d_1 the symptom m_1 occurs always after about a day. The symptom m_2 follows m_1 rather commonly; it uses to last between 2 to 4 days, though other less possible cases range from 1 day as the lowest bound to a week as the uppest one."

We can model the sentence as shown in Figure 1 and express it as

$$m_1 : \{(0.5, 1, 1, 1.5)\}$$
$$m_2 : \{(1, 2, 4, 7)[0.7]\}$$

in the first constraint an uncertainty of half a day has been added and its degree of preference has been omitted because it is 1.

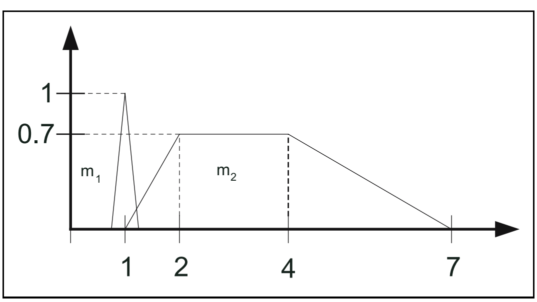

Fig. 1. example of metric constraint

The generalized definition of trapezoid extreme increases the expressivity of the language, therefore the range of allowed trapezoids is augmented with respect to e.g. [8]; for instance, the following trapezoids can be modeled:

$$\text{open triangle:}(a_i, a_i, a_i, d_i)[\alpha_i]$$

$$\text{open trapezoid:}(-\infty, -\infty, c_i, d_i)[\alpha_i]$$

$$\text{closed left semiaxis:}(-\infty, -\infty, d_i, d_i][\alpha_i]$$

Besides, these trapezoids allow us to integrate qualitative constraints.

As far as operations between metric constraints are concerned, the usual operations i.e. inversion, conjunctive combination, disjunctive combination and composition have been defined.

2.1 About the Integration

Dealing with classical crisp constraints a qualitative algebra QA that includes all the combinations that can occur in composition operation between points and intervals is defined in [18]. Considering all the algebrae PA, PI, IP and IA referring to point-point, point-interval, interval-point and interval-interval relations, we have defined the corresponding fuzzy extensions PA^{fuz}, PI^{fuz}, IP^{fuz} and IA^{fuz} [5, 6, 7]. In order to integrate different kinds of fuzzy temporal constraints in a general framework we extend to the fuzzy case the composition operation [18] as shown in Table 1; here the symbol "$\oslash$" denotes illegal combinations. We have defined the fuzzy extension of the involved algebrae IA, PA, IP and PI (tables $T'_1, \ldots, T'_4$), thus obtaining the qualitative algebra QA^{fuz}.

Table 1. Transitivity table of QA^{fuz}

	PA^{fuz}	PI^{fuz}	IP^{fuz}	IA^{fuz}
PA^{fuz}	$[T_{PA^{fuz}}]$	$[T'_1]$	$[\oslash]$	$[\oslash]$
PI^{fuz}	$[\oslash]$	$[\oslash]$	$[T'_2]$	$[T'_4]$
IP^{fuz}	$[T_1'^T]$	$[T'_3]$	$[\oslash]$	$[\oslash]$
IA^{fuz}	$[\oslash]$	$[\oslash]$	$[T_4'^T]$	$[T_{IA^{fuz}}]$

This way, we can manage temporal networks where nodes can represent both points and intervals, and where edges are accordingly labeled by qualitative and quantitative fuzzy temporal constraints.

In particular, we maintain point to point constraints in their metric form, while interval to interval, point to interval, interval to point constraints are qualitative and are given by IA^{fuz}, PI^{fuz} and IP^{fuz} relations.

Moreover, the operations to translate a fuzzy metric constraint C_1 into a fuzzy qualitative one C_2 and vice versa have been defined.

More detailed description of our integrated framework can be found in [5].

2.2 Algorithms

The notions of local consistency have been extended too [6, 5]. In particular, local consistency has been expressed as the degree of satisfaction which denotes the acceptability of an assignment with respect to the soft constraints involved in the relative sub-network. According to [12], this degree of satisfaction corresponds to the least satisfied constraint.

Moreover, Path-Consistency and Branch & Bound algorithms have been generalized to the fuzzy case adding some relevant refinements that improve their efficiency. Path-consistency allows to prune significantly the search space while having a polynomial computing time.

In our integrated system embedding both qualitative and metric constraints composition and conjunction operations used in the algorithms depend on the type of operands, therefore they change according to the kind of constraints to be processed (qualitative or metric).

3 Temporal Patterns of Diseases

Dealing with an application in the medical domain we focus our attention on the temporal aspects rather than on the atemporal ones.

Let us consider a set of disorders having the manifestations presented by a patient in common but with different temporal progressions and durations. For this, we examine three exanthematic diseases, namely Measles, Rubella and the Sixth Disease (*Exanthema subitum*, also called *Roseola infantum)*, analyzing three characteristic periods (incubation, fever and exanthemata) and the contagion period.

The main idea is to use the temporal evolution of the manifestations which is typical of the disease to select the disease itself in a set of diseases and hence to deduce important advices about the quarantine period.

The sequence can be modeled in a graph whose vertices, labelled by a number, represent:

1. starting of the incubation period;
2. ending of the incubation period;
3. starting of the fever;
4. ending of the fever period;
5. starting of the exanthemata period;
6. ending of the exanthemata period;
7. starting of the contagion period;
8. ending of the contagion period.
9. incubation period.
10. fever period.
11. contagion period.

In the following we report the timelines of the three diseases and the most significant constraints defined for the first networks. In a similar way, the other two networks can be represented. The time unit is hour, and an uncertainty of 33% with respect to the duration is assumed. The possible contagion period is represented by the gray area.

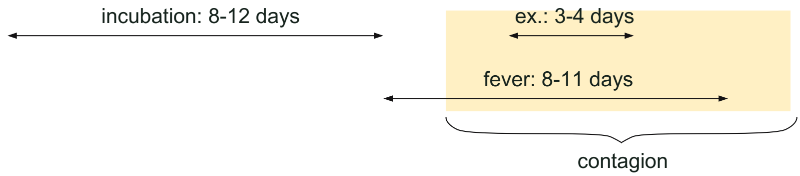

Fig. 2. Measles

3.1 Measles (Paramyxovirus)

– the fever starts when the incubation period ends

$$2\{equals\}3$$

– the **incubation** period lasts 8-12 days

$$1\{(160.0, 192.0, 288.0, 320.0)\}2$$

– the **fever** lasts 8-11 days

$$3\{(168.0, 192.0, 264.0, 288.0)\}4$$

– the **exanthemata** appear 3-4 days after the fever begins and vanish in 3-4 days; they appear after about 14 days

$$3\{(64.0, 72.0, 96.0, 104.0)\}5, 3\{b\}5$$

$$5\{(64.0, 72.0, 96.0, 104.0)\}6$$

$$1\{(240.0, 264.0, 336.0, 360.0)\}5$$

– the **contagion** period begins 1-2 days before the exanthemata and ends 4-5 days after their vanishing

$$7\{(16.0, 24.0, 48.0, 56.0)\}5, 5\{a\}7$$

$$6\{(88.0, 96.0, 120.0, 128.0)\}8$$

$$10\{during\}11$$

3.2 Rubella (Rubivirus)

– the fever starts when the incubation period ends;
– the **incubation** period lasts 14-21 days;
– the **fever** lasts 1-3 days;
– the **exanthemata** last 2-5 days and begin 0-2 days after the fever begins;
– the **contagion** period begins 2-6 days before the exanthemata and ends a week after their vanishing.

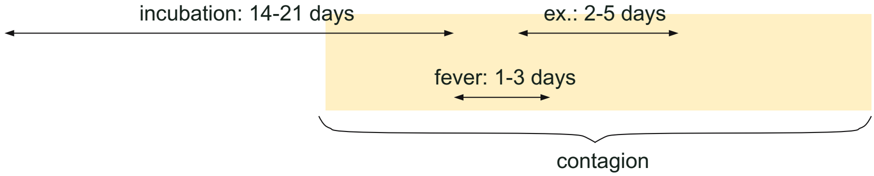

Fig. 3. Rubella

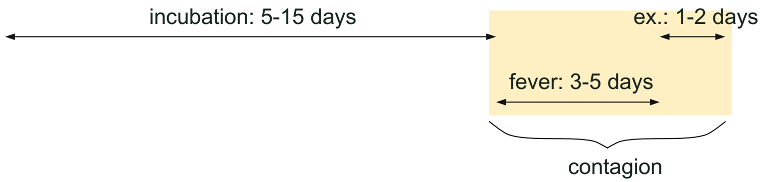

Fig. 4. Sixth Disease

3.3 Sixth Disease (Herpesvirus)

- the fever starts when the incubation period ends;
- the **incubation** period lasts 5-15 days;
- the **fever** lasts 3-5 days;
- then appears the **exanthemata** that last 1-2 days and begin at the end of the fever;
- the **contagion** period is almost during the fever and the exanthemata.

4 Diagnostic Task

In order to do a diagnosis of these types of diseases we can now represent the report of a patient presumably affected by an exanthematic disorder in terms of temporal information about patient symptoms.

By adding new information from the report into the networks built on the basis of standard disease data, the network consistency can be confirmed or it can be lost. The analysis of the changes of the consistency in the networks constitutes a first approach to diagnostic task for exanthematic diseases. In particular, we study how changes the consistency of the three temporal networks by inserting new constraints about the symptoms progression and duration coming from a patient. This kind of model can be very useful since human memory is often little precise about time.

Let's see with an example. If the patient had symptoms that continued for more than a week, the constraint to be added in each of the three networks is:

$$3\{(152.0, 192.0, 312.0, 352.0)\}6$$

By applying the Path-Consistency algorithm, only the Measles network results consistent, while the other two become inconsistent. Setting the present of the patient at the end of the symptoms period, it is also possible to foresee that she/he should stay in quarantine during the next 5-9 days, that is till to the end of the contagion period.

On the other hand, if the patient had symptoms that vanished almost certainly in less than a week, by inserting the constraint

$$3\{(24.0, 48.0, 120.0, 144.0)[0.6]\}6$$

the Rubella network becomes consistent and the Measles one inconsistent. The problem is that in this case also the Sixth Disease network is now consistent. Therefore, in order to make a diagnosis, another clue is needed; this clue must be about time, because the system deals with temporal information. Then, to discriminate between Rubella and the Sixth Disease, further information has to be acquired from the patient asking her/him if the exanthemata appeared shortly after the fever or a few days after. In the first case the Sixth Disease can be diagnosed, while in the latter case Rubella can be identified.

At the moment the system is used to verify at each step the consistency of the constraint networks. Indeed, the system can calculate the degree of consistency of different possible solutions of the networks. This information could be useful to manage more sophisticated and more refined diagnoses.

5 Related Works and Conclusions

An approach which is more directly related with ours is the one proposed in [22] where a system that incorporates fuzzy temporal reasoning within diagnostic reasoning is presented. Disorders are described as a dynamic set of manifestations and fuzzy intervals are used to model their ill-known location in time. As in our case, this approach is based on the work of [14] about FCN (Fuzzy Constraint Networks) and it addresses the problem of diagnosis including not only temporal infomation but also categorical and intensity information. In the present paper we are not concerned with the atemporal aspects of the domain. As far as temporal information is concerned, our system extends the FCN model by allowing multiple constraints that can also be non normalized differently from [22]. Moreover, it allows the integration of fuzzy metric constraints with fuzzy qualitative constraints based on Allen's Interval Algebra [2].

Other works present fuzzy extensions of Allen's Interval Algebra (e.g. [10]) where, instead of attaching preference degrees to qualitative temporal relations as we have done, the indeterminacy of temporal information relative to the patient therapeutic history is dealt with by considering the indeterminacy of period bounds. Even if limited, this method works well for restoring the therapeutic history from prescription data and could be a good basis for an automatic system.

A causal-temporal-action model for clinical diagnoses is proposed in [15] where threee types of ATG (Abstract Temporal Graph) are considered. This model accounts also for uncertainty and for causal links. Again, our work is only devoted to deal with temporal aspects of the domain. Moreover the problem of integration of different types of constraints is tackled in our work in the line of Meiri's classical approach [18].

In this paper we have shown an application of our temporal constraint solver in a medical domain; this application could support the physician to make a diagnosis of the exanthematic diseases on the basis of their temporal patterns. Our solver extends the classic temporal constraints by allowing to specify uncertainty and vagueness; this is fundamental in all those applications where data are gathered from noisy environments or natural language descriptions.

In order to make the system more useful a first enhancement will be the management of constraint classes; in this way, it will be possible to reason about several diseases in parallel.

Moreover, as in [22, 15], a real diagnosis expert system should consider also atemporal aspects of diseases. As future work we intend to enrich our system by addressing also these aspects.

As a final remark, an automated reasoning tool can be useful to find matches against typical patterns of known diseases, but is also interesting the opposite deduction, that is the discovery of the temporal evolution of a disease from the patient data; such an application could be useful for characterizing new diseases, like for example SARS.

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