

Temporal Features in Biological Warfare

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Abstract. No matter how prepared a population may be, bioterrorism cannot be prevented: the first clues will always be given by ill people. Temporal analysis applied to this type of scenarios could be an additional tool for limiting disruption among civilians allowing for recognizing typical temporal progression and duration of symptoms in first infected people. We propose the application of a fuzzy temporal reasoning system we have developed for biomedical temporal data analysis in different scenarios after a hypothetical attack. The system is able to handle both qualitative and metric temporal knowledge affected by vagueness and uncertainty, taking into account in this way the vagueness of patients reports expressed in natural language.

1 Introduction

In case of biological attacks, the effects of a deliberate release will be obvious if a large number of troops become ill with similar symptoms at the same time. It may be less clear in a civilian population [1], supposed to be in a period of peace. For this reason establishing a diagnosis is critical to the public health response to a bioterrorism-related epidemic, since the diagnosis will guide the use of vaccinations, medications, and other interventions [2]. Moreover, new or reemerging infectious diseases have relevant implications: during the past 20 years, over 30 new lethal pathogens have been identified; for example the emergence of Severe Acute Respiratory Syndrome (SARS) in South-east Asia rapidly spread to 29 countries in less than 90 days [3]. Emerging disease outbreaks may be difficult to distinguish from the intentional introduction of infectious diseases for nefarious purposes, when considering that Genetic Engineering of biological warfare agents can alter their pathogenicity, incubation periods, or even the clinical syndromes they cause. For this reason, it is important to develop automatic Syndromic Surveillance Systems [2] able to notify as soon as possible the early manifestations of bioterrorism-related diseases from population monitoring. A preliminary step towards the design of a component of such a System could be based on the use of temporal reasoning techniques in order to identify typical temporal progression of diseases.

Taking into account that medical data relative to temporal evolution of diseases are often affected by vagueness and uncertainty, the temporal reasoning model that seems to be more adequate for such real application could be the Fuzzy Temporal Reasoning System (FTR in the following) that we developed in a previous research [4].

The system is based on the integration of temporal information both qualitative and metric represented as fuzzy constraints in a network and extends a previously proposed

system [5] that dealt with fuzzy qualitative temporal reasoning. We have applied our System in several diagnostic problems. In [6], we applied it for discriminating exanthematic diseases from temporal patterns of patient symptoms and in [7] we studied how our system could represent temporal evolutions of symptoms in different patients affected by SARS, thus making possible to deduce characteristic periods of a new disease.

Dealing with the study of biological warfare, we address the problem of the automated analysis of temporal medical data in order to obtain information useful for early detection of biological attacks. In particular, we will start from the temporal evolution of five NIAID (National Institute of Allergy and Infectious Diseases) diseases represented as fuzzy constraint temporal networks. Then we will check the consistency of temporal data relative to a set of ten patients reports [8] with respect to the previously considered diseases; we will use the algorithmic methodologies for checking temporal consistency offered by the FTR system. Two are the main objectives:

- to find the most plausible disease and, once found it,
- to exploit the information in order to infer the possible contagion.

The paper is organized as follows. Section 2 describes the problem of identifying biological attacks while Section 3 is dedicated to a brief presentation of the FTR System. In Section 4 the considered diseases are summarized and in Section 5 the results about temporal analysis of patients data is shown.

2 Identifying Biological Attacks

Early symptoms of disease induced by a biological warfare agent may be non-specific or difficult to recognize, for example a simple febrile illness; the disease itself could affect individuals living in widely dispersed areas, who may then present to several different healthcare providers [1]; once the disease has been diagnosed, appropriate prophylaxis, treatment, and other measures to decrease spreading, such as quarantine (for a contagious illness) would be adopted.

As said before, many diseases caused by bioterrorism present with relatively common features, such as fever or headache, but there are several considerations that can ease the identification of a Bioterrorism-related scenario [9]:

symptoms: a number of patients that abruptly present to care providers or emergency rooms manifesting similar and unexpected symptoms;

zoonoses: most of the agents used in biological warfare are diseases that affect animals, for this reasons sudden deaths between animals can anticipate diffusion among humans;

unexplained factors: whenever an unusual pattern is detected a biological attack may be suspected: unexplained deaths for an usually mild disease, unusual exposure routes for a pathogen, for a geographical area, for a season;

diffusion patterns: higher symptoms manifestations in certain areas, for example buildings, or in short time periods. The abrupt onset and single peak of cases would implicate a point-source exposure without secondary transmission [10].

In this paper only considerations about time will be taken into account.

3 The Fuzzy Temporal Reasoning System

In the present section we will summarize the main characteristics of the FTR System (for a more detailed description cfr. [4]).

In Allen’s Interval Algebra [11] the temporal qualitative knowledge is represented as a binary relation between a pair of intervals in terms of *atomic relations*:

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

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.).

To deal with vague and uncertain temporal information Allen’s Interval Algebra has been extended in [5] 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

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

where α_i is the preference degree of rel_i ($i = 1, \dots, 13$); 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 \mathfrak{R}^2 , and soft constraints between them as fuzzy subsets of $\mathfrak{R}^2 \times \mathfrak{R}^2$ 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 [12] in many ways [13,14,15]. To represent fuzzy temporal metric constraints we adopt trapezoidal distributions [4], since they seem enough expressive and computationally less expensive than general semi-convex functions [16].

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.

$$T_k = \lll a_k, b_k, c_k, d_k \ggg [\alpha_k]$$

with $a_k, b_k \in \mathfrak{R} \cup \{-\infty\}$, $c_k, d_k \in \mathfrak{R} \cup \{+\infty\}$, $\alpha_k \in (0, 1]$, \lll is either **(** or **[** and \ggg 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 generalized definition of trapezoid extreme increases the expressiveness of the language.

As far as integration is concerned, we have defined the fuzzy extensions PA^{fuz} , PI^{fuz} , IP^{fuz} and IA^{fuz} of the corresponding classical algebras PA , PI , IP and IA referring to point-point, point-interval, interval-point and interval-interval relations [17,4,5], we have extended the composition operation and the transitivity table [18]. In the integrated framework 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.

Path-Consistency and Branch & Bound algorithms have been generalized to the fuzzy case adding some relevant refinements that improve their efficiency. Path-consistency has a polynomial computing time and it is used to prune the search space in the

Branch & Bound algorithm; however for real world applications tractable subsets of relations such as those belonging to the Convex Pointizable Algebra SA_c should be used, since in that case Path-consistency is sufficient to find the minimal network [19].

4 Biological Agents

Before presenting the application of the Temporal Reasoning system it is useful to briefly describe the biological agents that will be considered.

4.1 NIAID “Category A” Main Diseases

NIAID (National Institute of Allergy and Infectious Diseases) is the primary Institute at NIH, the US National Institute of Health, for emerging infectious diseases research, including research on agents of bioterrorism. This institute has grouped biological agents in three categories according to their ease of use for a biological attack; the most dangerous are in Category A (Table 1) and are agents that can be easily disseminated or transmitted person to person, that have high mortality and can cause public panic and social disruption, therefore needing special action for public preparedness.

Table 1. Category A agents

● <i>Bacillus anthracis</i> (Anthrax)
● <i>Clostridium botulinum</i> toxin (Botulism)
● <i>Yersinia pestis</i> (Plague)
● <i>Variola major</i> (Smallpox) and other pox viruses
● <i>Francisella tularensis</i> (Tularemia)
● <i>Viral hemorrhagic fevers</i> (VHF)

We have considered the timelines of five diseases: Anthrax, Tularemia, Smallpox, Plague and Ebola. These timelines can be obtained from temporal characteristics of the diseases themselves and are reported in Figure 1. In the following just Anthrax and Plague are described.

Anthrax (*Bacillus anthracis*). Anthrax is one of the most serious diseases: when inhaled it can be quite lethal [9].

Most of the early symptoms of inhalation Anthrax are similar to those for other infectious diseases, making a differential diagnosis difficult during flu season, for example [20]. The distribution of the incubation period for inhalational Anthrax can be relatively broad as observed in Sverdlovsk (2-43 days); in any case, it does not extend more than 60 days. The clinical presentation has been described as a 2-phases illness: the nonspecific prodrome for Anthrax may last from several hours to several days [2]. The second phase develops abruptly, with sudden fever, dyspnea, diaphoresis, and shock.

Case fatality rates of 80% or more, with nearly half of all deaths occurring within 24 to 48 hours, is highly likely to be Anthrax or pneumonic plague. A temporal constraint network for modelling Anthrax can be composed by four vertices: the contagion (1), the first symptom (2), the worsening phase (3) and the death or recovery.

The constraints, deduced from the previous description, are expressed in hours.

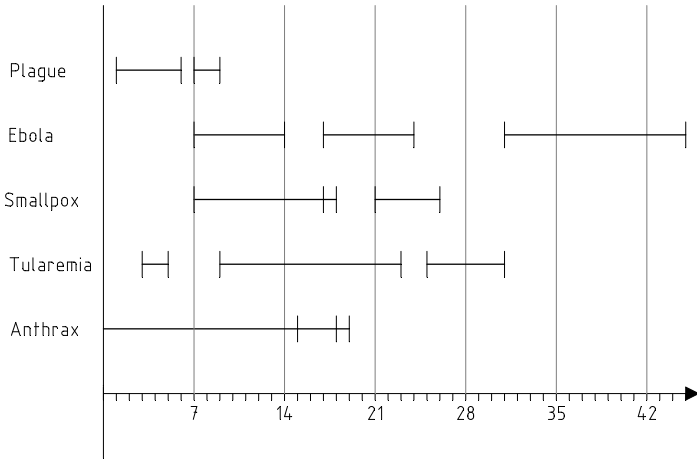


Fig. 1. Timelines for the considered diseases; for each disease the incubation period, the worsening period and the death have been represented (in days)

- Incubation lasts no more than 60 days: 1 $\{(-\infty, -\infty, 1440, 1440)\}$ 2
- First phase lasts from several hours to several days: 2 $\{(6, 12, 24, 96)\}$ 3
- Death occurs within 24 to 48 hours: 3 $\{(12, 24, 48, 60)\}$ 4

Plague (*Yersinia pestis*). Plague is of great concern in a biological attack scenario, since it is available around the world, it is easy to produce and disseminate it through aerosolization; moreover, it causes high fatality rates and can rapidly spread during an epidemic [21]. Vaccine has limited efficacy following aerosol dispersion [9].

A pneumonic plague outbreak would result with symptoms initially resembling those of other severe respiratory illnesses. Exposure to aerosolized *Y. pestis* results in pneumonic plague, which has a typical incubation period of 2 to 4 days (range 1-6 days).

The fatality rate of patients with pneumonic plague when treatment is not commenced within 24 hours of symptoms onset is extremely high [21]. In modelling plague constraint network notice that second phase is almost immediate, therefore, assuming that the same vertices are used for all diseases, the constraint between vertex 3 and 4 could be:

$$3\{before[0.5], meets[1.0]\}4$$

Notice that in the description of Anthrax fuzzy metric constraints were used, while here also a qualitative fuzzy temporal constraint has been specified. This shows that a user can represent the temporal knowledge as it is available.

5 Temporal Analysis

To develop a general framework for automated temporal analysis of biological warfare data different aspects can be considered. Here first we apply the solver to match temporal data coming from patients with the typical evolution of the five diseases previously

cited in order to identify the most plausible disease. Second, when the disease has been selected its characteristic development is used to infer the contagion period.

5.1 Patients Reports

We consider a set of medical data concerning 10 patients reports [8]. These descriptions contain temporal information that can be modelled using a temporal constraint network according to the FTR representation system.

The timetable of all the ten patients is shown in Figure 2. In the following we report as a detailed example the description and the modelling of the first patient.

Patient 1. *On October 2, 2001, a 63-year-old Caucasian person awoke early with nausea, vomiting, and confusion and was taken to a local emergency room for evaluation. His illness, which started on September 27 was characterized by malaise, fatigue, fever, chills, anorexia and sweats. [...] On hospital day 2, penicillin G, levofloxacin, and clindamycin were begun. He remained febrile and became unresponsive to deep stimuli. His condition progressively deteriorated, with hypotension and worsening renal insufficiency. The patient died on October 5.*

A temporal constraint network for modelling, for instance, Patient1 can be composed by five vertices:

1. the origin of time t_0 ;
2. first symptom (S);
3. worsening (W);
4. hospitalization (H);
5. death / discharge from hospital (D).

The constraints, deduced from the previous reports and expressed in hours from Jan 1 (t_0), can be represented as:

- 1 [6456, 6456, 6480, 6480] 2 (on Sep 27)
- 1 [6576, 6576, 6600, 6600] 4 (on Oct 2)
- 1 [6624, 6624, 6648, 6648] 3 (on Oct 4)
- 1 [6648, 6648, 6672, 6672] 5 (on Oct 5)

Now, to find the most plausible disease we combine the patients networks with the network of each agent. In this way, by means of a consistency analysis, we can have an

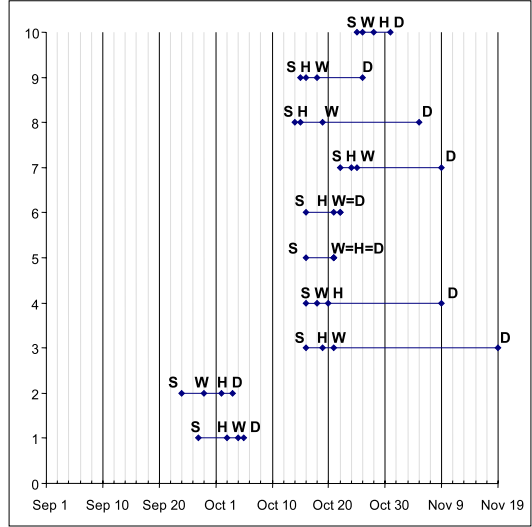


Fig. 2. Timelines for patients (S = first symptom, H = hospitalization, W = worsening, D = death/discharge)

idea of the disease that has the highest compatibility with the considered scenario and then infer the contagion period.

Assuming that the outbreak is located in a single source, all patients should become ill within the incubation period. Applying the FTR system it results that Anthrax is the only disease among the 5 considered which is consistent with all patients; for example the Plague incubation period is too short to fully accommodate a range of 1 month between the appearing of the symptoms in the patients. This inference confirms the hypothesis about Anthrax found by laboratory tests [8].

Then, taking into account that Anthrax incubation lasts no more than 60 days and that symptoms in all patients appeared from September 24 to October 26, the FTR system can deduce that contagion of all these patients could have occurred from the end of July to few days before September 22.

6 Conclusions

In this paper we have studied how to develop a Temporal Reasoner for an automatic Syndromic Surveillance System able to notify as soon as possible the early manifestations of bioterrorism-related diseases from population monitoring. To this aim the detection of temporal characteristic features become an important aspect that we have addressed using the Fuzzy Temporal Reasoning System. This system has allowed inferring information about possible contagion period in an Anthrax attack scenario happened in U.S. in 2001.

As future directions are concerned, we intend to enrich the analysis capabilities of the FTR system for example to identifying clusters in contagion dynamics. In this way we aim to develop a more sophisticated system to face this global threat.

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