Knowledge-Based Interpretation of Toxoplasmosis Serology Test Results Including Fuzzy Temporal Concepts

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Abstract

Transplacental transmission of *Toxoplasma gondii* from an infected pregnant woman to the unborn occurs with a probability of about 60 percent [1] and results in fetal damage to a degree depending on gestational age. The computer system ToxoNet processes the results of serological antibody tests performed during pregnancy by means of a knowledge base containing medical knowledge concerning the interpretation of toxoplasmosis serology test results. The interpretation algorithm infers the stage of maternal infection to determine the degree of imminent fetal damage. For this purpose, it matches the results of all serological investigations of maternal blood with the content of the knowledge base and generates interpretive reports consisting of a diagnostic interpretation and recommendations for therapy and further testing. In order to take the varying immune responses of individual patients into account, certain intervals between two consecutive tests have to be maintained; this ensures correct interpretation of test results. These time intervals are modelled as fuzzy sets, since they allow the formal description of temporal uncertainty. ToxoNet comprises the knowledge base, an interpretation system, and a knowledge acquisition and modification program. It is available from the World Wide Web by starting it from a standard browser such as Internet Explorer or Netscape Navigator.

1. Medical Background

Primary infection with *Toxoplasma gondii* after conception may lead to fetal infection with serious complications for the unborn if not treated properly. While the elevated antibody levels associated with preconceptional maternal infection (also termed latent) prevents transplacental transmission of the parasite, women who have acquired the infection after conception (denoted as acute) require immediate treatment. By commencing maternal drug therapy immediately after recognition of an acute infection, the risk of transmission of the parasite—that occurs with a probability of about 60 percent in cases of no drug therapy [1]—can be reduced, resulting in prevention of fetal infection or at least in reduction of fetal damage.

Detection of a *Toxoplasma gondii* infection is based on serological tests proving the existence of toxoplasma-specific antibodies in the patient's serum. The Sabin-Feldman dye test (SFT), taken as the reference IgG test, and the immunosorbent agglutination assay (ISAGA) used for the detection of IgM antibodies, are relevant for automation purposes [2–6]. Their idealized courses in response to an acute toxoplasma infection are presented in Figure 1.

2. Objectives

The main purpose of developing ToxoNet was to support the clinician in analyzing the outcome of routinely performed toxoplasmosis tests with the objective of not only facilitating routine laboratory work but also ensuring quality by setting standards for therapy. Since the diagnostic process is solely based on observation and interpretation of serological data, it seemed reasonable to employ a knowledge-based system for automatic interpretation of results obtained from serological investigations.

3. Methods

3.1 General Considerations

A reliable diagnosis of a patient's state with respect to toxoplasma infection cannot be derived from a single examination but must be made from a sequence of test results, since it would be impossible to decide whether the antibody concentrations are currently on the increase or decrease (cf., Figure 1).

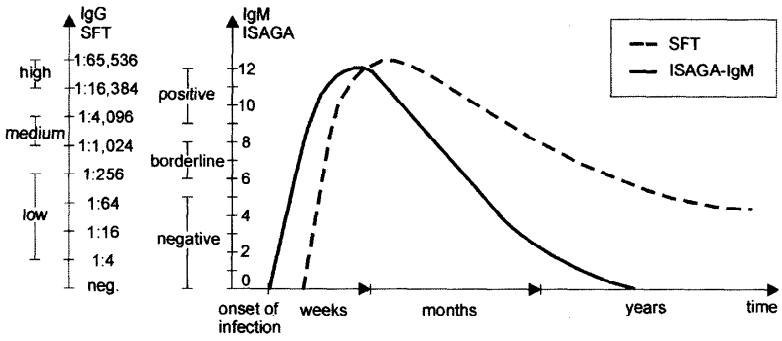

Figure 1: Idealized course of SFT and ISAGA-IgM

Furthermore, two sources of uncertainty have to be considered in knowledge representation [4,5]. Firstly, immune responses and the corresponding antibody levels vary from individual to individual. Secondly, usually it is not possible to infer a certain diagnosis from test results without uncertainty, as it takes some time for an immune response to a primary infection to be initiated by the immune system.

3.2 Knowledge Representation

The knowledge contained in the knowledge base of ToxoNet is represented by a directed decision graph. This graph may be interpreted as a deterministic finite automaton consisting of states (represented by nodes in the graph), transitions (corresponding to edges), and conditions made up of a sequence of Boolean "AND" combined simple comparisons.

Every state corresponds to a certain interpretation consisting of a diagnosis, recommendations for therapy, and proposals for further testing, if necessary. In order to enable the physician to estimate fetal threat at first glance, every interpretation is additionally assigned to to one of the following four interpretive categories: (a) acute (postconceptional) infection with a high risk of fetal infection, (b) latent (preconceptional) infection and therefore no risk of fetal damage, (c) no infection, or (d) contradictory data from inconsistent serological test results.

The decision criteria that are equivalent to the serological preconditions for a particular interpretation are attached to transitions as conditions.

In order to deal with varying immune responses of individuals to toxoplasma infection, minimum intervals of two to four weeks' duration have to be maintained between tests; this will ensure correct interpretation [4,7]. The intervals also must be maintained between examinations; they are modelled as fuzzy sets and attached to transitions as fuzzy durations. A fuzzy duration denotes a fuzzy variable assigning every possible duration between two examinations to a value in [0,1]—known as temporal compatibility—that expresses how closely the time difference between two tests agrees with the prescribed interval.

The present decision graph consists of 45 states, 92 transitions, and 53 conditions [4].

3.3 Inference Mechanism

The actual inference process is based on the previously described automaton and is known as TOXOPERT. Inference is performed step by step by comparing the findings of a patient, each composed of one IgG and one IgM test result, to the conditions stored in the automaton. If no further test results are available, the interpretation attached to the last achieved state becomes the final interpretation for the patient.

For every step during inference, the fuzzy duration of the involved transition is evaluated. The result of this computation is multiplied by the outcome of the previous level, i.e., the multiplication operator is used for computing the fuzzy AND operator. This process finally yields a value indicating the overall temporal compatibility of the sequence of findings with regard to temporal restrictions required for a reliable interpretation [4,5].

Figure 2 shows a portion of the decision graph of ToxoNet to explain the inference mechanism by means of an example. The nodes contain an abbreviated diagnostic interpretation, while the serological preconditions are listed near the edges. Table 1 contains a sequence of test results of a pregnant woman, the conception date being January 5th, 2001, arranged by increasing date and respective week of gestation. The nodes and edges along the bold path shown in Figure 2 are passed during the processing of the particular test results according to the mentioned mechanism. The particular computed temporal compatibility is presented near the edges in Figure 2.

Table 1: Exemplary sequence of test results (GA is the short form for gestational age)

Date	Test results	GA
2001.03.05	preliminary finding unknown	9
2001.03.05	IgG = –, IgM = –	9
2001.03.20	IgG = –, IgM = –	11
2001.04.05	IgG = –, IgM = –	13
2001.05.08	IgG = 1:1,024, IgM = +	18

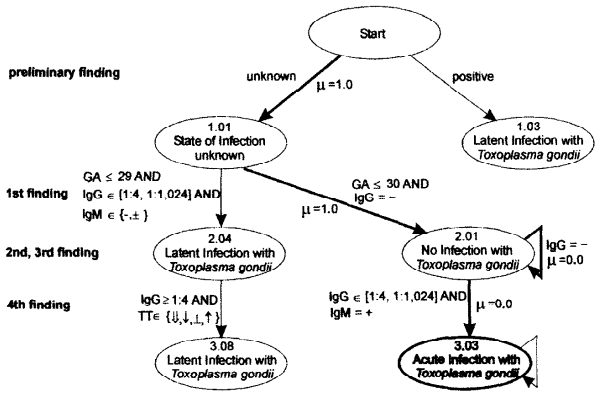

Figure 2: Visualization of an example inference

3.4 Consideration of Temporal Compatibility

Whenever the computed total temporal compatibility is equal to 1.0, the sequence of test results fully agrees with the temporal restrictions required for a reliable diagnosis. Thus, the inferred interpretation needs no modification.

In contrast, if the inference mechanism results in an interpretation with reduced temporal compatibility, this additional information should be utilized to modify the interpretation, as a physician will not profit from being confronted with a purely numerical value of, for instance, 0.5 for temporal compatibility.

A value less than 1.0 (even 0.0) for temporal compatibility does not vitiate the inference result, but rather dilutes confidence in the interpretation. For instance, in the example in Figure 2, the intervals between the tests on March 5th and March 20th and between the tests on March 20th and April 5th are too short, since a minimum interval of four weeks would have been necessary for correct interpretation in both cases. As a result, the overall temporal compatibility is reduced to 0.0. Nevertheless, the diagnosis "Acute Infection with *Toxoplasma gondii*" is still correct, but its significance should be reduced, for example, to "Acute Infection with *Toxoplasma gondii* is likely". For this purpose, the knowledge representation formalism has been extended by two mechanisms.

Firstly, it is possible to specify more than one interpretation for a single node in the decision graph, each of them applying to a specific range of temporal compatibility. Depending on the temporal compatibility yielded by the inference, the appropriate interpretation text will be selected. For instance, for node 3.03 in Figure 2, the three interpretations listed in Table 2 would be appropriate:

Table 2: Three possible interpretations for varying values of temporal compatibility

Temporal compatibility	Interpretation
[0.0 – 0.5)	Acute (postconceptional) infection with *Toxoplasma gondii* is likely. We recommend medical treatment as proposed in the enclosed plan, and serological follow-up at four weeks. We suggest PCR (polymerase chain reaction) investigation of the amniotic fluid after completion of 15 weeks of gestation.
[0.5 – 0.8)	Acute (postconceptional) infection with *Toxoplasma gondii* is very likely. We recommend medical treatment as proposed in the enclosed plan, and serological follow-up at four weeks. We suggest PCR (polymerase chain reaction) investigation of the amniotic fluid after completion of 15 weeks of gestation.
[0.8 – 1.0]	Acute (postconceptional) infection with *Toxoplasma gondii*, seroconversion. We recommend medical treatment as proposed in the enclosed plan, and serological follow-up at four weeks. We suggest PCR (polymerase chain reaction) investigation of the amniotic fluid after completion of 15 weeks of gestation.

Secondly, the knowledge engineer may specify for any node in the decision graph, that the inference process should be automatically repeated if the test result having caused the onset of the state yielded a reduced value of temporal compatibility. In addition, an explanation may be attached to this node, with a view to informing the physician of the potential causes of reduced temporal compatibility. The subsequent inference process being started automatically will not consider this particular test and thus possibly produce

a more correct result. The user is shown the outcome of both inference processes.

In the example in Figure 2, the first run of the inference mechanism is concluded in state 3.03, yielding a temporal compatibility of 0.0, and the diagnostic hypothesis: "Acute (postconceptional) infection with *Toxoplasma gondii* likely". Thereafter TOXOPERT automatically starts a second inference process, dropping the test result of March 20th, 2001. In this case the inference procedure stops again in state 3.03, now yielding a temporal compatibility of 1.0 and the more reliable diagnostic hypothesis of "Acute (postconceptional) infection with *Toxoplasma gondii*, seroconversion".

4. Results

The intention of integrating ToxoNet's database into that of the medical expert system shell MedFrame [8], and the demand for a WWW interface to the inference mechanism prompted the decision to implement ToxoNet in Java. The outcome of this effort was a platform-independent system that is primarily designed to operate in network environments. ToxoNet can be reached at http://medexpert.imc.akh-wien.ac.at/ToxoNet and can be operated as an autonomous program as well as from within any contemporary World Wide Web browser. ToxoNet comprises a graphical knowledge acquisition system and a module for data entry, inference triggering, and representation of the interpretation. Since the intended area of application is the Internet, it is capable of different languages. It is currently available in English and German. An HTML-based graphical assistance system for supporting the user in case of difficulties is also available.

In order to provide a means to access the benefits of TOXOPERT from WWW browsers not capable of executing Java Applets and to reduce Applet download time via slow mobile phone connections, we decided to implement an HTML-based interface to the inference mechanism known as TOXOPERT/WWW. It enables the user to enter anonymous test results into standard HTML forms; the respective inference results are immediately presented on traditional HTML pages. From the implementation point of view, TOXOPERT/WWW has been integrated into ToxoNet in the form of Java Server Pages and therefore required little additional programming effort. TOXOPERT/WWW can be reached at http://medexpert.imc.akh-wien.ac.at/toxoWWW.

In a recent study, the data of 1,606 pregnant women taken from the routinely used database of the toxoplasmosis laboratory at the Vienna General Hospital were processed by the TOXOPERT inference mechanism. The results of this study are presented in Table 3.

Table 3: Results of a retrospective study group of 1,606 pregnant women

ToxoNet \ Physician	Latent	Acute	No infection	Contra-dictory	Total
Latent	551	41	0	31	623
Acute	38	110	0	7	155
No infection	0	0	813	0	813
Contradictory	12	1	0	2	15
Total	**601**	**152**	**813**	**40**	**1,606**

All cases belonging to the interpretive category 'no infection' are correctly handled by TOXOPERT.

The number of correctly classified latent and acute infections is also rather high; about 87.8 per cent of the cases (661 of 753) pertaining to these two interpretive categories are classified according to the physician's decision.

1.7 per cent of latent infections and acute infections (13 of 753) being interpreted as contradictory are due to the fact that TOXOPERT yields a contradictory result if no clear decision is possible.

Unfortunately, it is difficult to distinguish between latent and acute infections—10.5 per cent of cases pertaining to one of these interpretive categories (79 of 753) are classified as members of the other category.

We are currently engaged in defining and fixing the problems in the knowledge base and the pool of test cases. These problems are also the reason for the 38 contradictory cases being erroneously classified as latent or acute.

5. Discussion

In contrast to ToxoNet, its predecessors—TOXOPERT-I, TOXOPERT-II, and TempTOXOPERT [5,6] that were also developed at our department—are standalone computer systems. They are based on the same serological tests and similar knowledge representation but either do not make use of fuzzy temporal concepts or temporal compatibility has no effect on the derived interpretations.

ONSET—a system developed for the derivation of the time of onset of infection from serological findings in any field of medicine [9,10]—also has been applied to toxoplasmosis serology. ONSET tries to determine the time point of primary infection by deriving intervals of probable infection onsets from each finding and combining them logically. This is done by determining when the particular test result is possible in the course

of toxoplasma infection and by concluding the time of infection from this knowledge.

Two further projects in the field of knowledge-based decision support for toxoplasmosis serology test results derive their interpretations from a larger set of serological tests usually not conducted in a standard laboratory. Since these systems are not available in the Internet, they are rather confined to specialized laboratories, whereas ToxoNet achieves a compromise between comprehensibility and universality. One of these projects was performed at the Johns Hopkins University, Baltimore, and was constructed on neural networks [11]. In the other project, a rule-based decision support system derived from Pro. M.D. was implemented [12].

In 1975, an obligatory serological screening program to detect *Toxoplasma gondii* infection in pregnant women was introduced in Austria. Since then the incidence of prenatal toxoplasma infections has been reduced from about 50–70 per 10,000 births to less than 1 per 10,000 births [2]. These figures make the costs more acceptable, although additional factors such as improved hygienic standards probably also contributed to this reduction.

ToxoNet contains a knowledge-based system that helps the physician to interpret the results of routinely performed toxoplasmosis serology tests. Thus, it facilitates routine laboratory work and ensures quality by setting standards for therapy. Owing to the way it has been implemented, it is available for other clinics and even external users via the World Wide Web.

6. References

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