Knowledge-Based Interpretation of Toxoplasmosis Serology Test Results Including Fuzzy Temporal Concepts— The ToxoNet System

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Abstract. *Transplacental transmission of Toxoplasma gondii from an infected, pregnant woman to the unborn that occurs with a probability of about 60 percent [1] results in fetal damage to a degree depending on the gestational age. The computer system ToxoNet processes the results of serological antibody tests performed during pregnancy by means of a knowledge base containing structured medical knowledge on how to interpret toxoplasmosis serology tests. By applying this knowledge, ToxoNet generates interpretive reports consisting of a diagnostic interpretation and recommendations for therapy and proposals for further testing. For that purpose, it matches the results of all serological investigations of maternal blood with the content of the knowledge base returning complete textual interpretations for all given findings. The concluded stage of maternal infection is used to infer the degree of fetal threat. In order to consider varying immune responses of particular patients, certain time intervals have to be kept between two subsequent tests to guarantee a correct interpretation of the test results. These time intervals are modelled as fuzzy sets, since they allow the formal description of temporal vagueness. ToxoNet comprises the knowledge base, an interpretation system, and a program for the definition and modification of the knowledge base and is available through the World Wide Web. Thus ToxoNet supports the physician in toxoplasmosis diagnostics and, in addition, allows to adopt the way of making decisions to the characteristics of the particular laboratory by modifying the underlying knowledge base.*

1. Introduction

1.1. Medical Background

Primary infection with Toxoplasma gondii after conception often leads to fetal infection with serious complications for the unborn if not treated properly. While a preconceptual maternal infection (denoted as latent), or rather the associated raised antibody concentration, prevents transplacen-

tal transmission of the parasite, those women who have acquired the infection after conception (denoted as acute) require immediate treatment. Since early recognition enables commencement of maternal drug therapy, the risk of transplacental transmission of the parasite—that occurs with a probability of about 60 percent in case of no drug therapy—can be reduced, resulting in prevention of fetal infection or at least in a decrease of fetal damage.

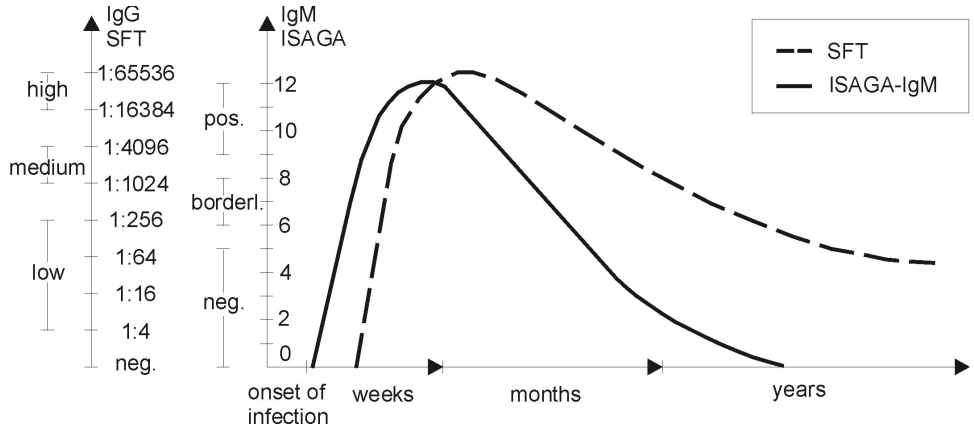

Figure 1: Idealized course of SFT and ISAGA-IgM.

Detection of an infection with Toxoplasma gondii is based on serology 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 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.

1.2. Objectives

The main goal in the development of ToxoNet was to support the clinician in analyzing the results of routinely performed toxoplasmosis tests with the objective of not only facilitating routine laboratory work but also assuring quality by setting standards for therapy. Since the diagnostic process is based solely on observation and interpretation of serological data, it seemed reasonable to employ a knowledge-based system for automatic interpretation of the results obtained from serological investigations. Two further aims of the development of ToxoNet were the possibility to access the system from the World Wide Web on the one hand and the availability of a graphical knowledge acquisition system on the other hand.

2. Methods

2.1. General Considerations

In general a reliable diagnosis of a patient's state regarding Toxoplasma infection cannot be derived from a single examination since it would be impossible to decide whether the antibody concentra-

tions are currently on the rise or on the decrease (see Figure 1). In contrast, a sequence of test results sheds light on the degree of threat for the unborn.

Moreover the fact, that immune reactions vary from individual to individual and therefore the corresponding antibody concentrations do so too, complicates the determination of a correct diagnosis. And so it is usually not possible to infer a certain diagnosis from particular test results without uncertainty, since it takes time until an immune reaction to a primary infection is initiated by the immune system. Therefore, these uncertainties have to be considered in the knowledge representation [4,5].

2.2. Knowledge Representation

The knowledge of ToxoNet is represented as a directed decision graph (see Figure 4). 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 (generated from a sequence of Boolean "AND" combined 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 belongs to one of the following four interpretive categories: (a) acute (postconceptual) infection with high risk of fetal infection, (b) latent (preconceptual) infection and thus no risk of fetal damage, (c) no infection, or (d) contradictory serological test results. While states correspond to medical interpretations, the decision criteria that are equivalent to the serological preconditions for a particular interpretation are attached to transitions as conditions.

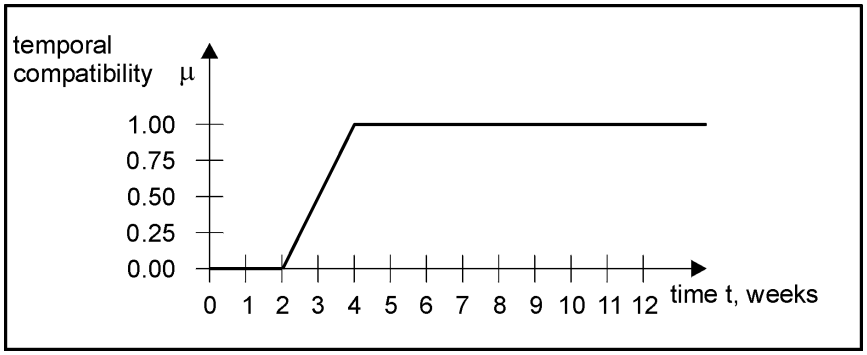

Figure 2: Membership function of a fuzzy set with a fuzzy boundary between no and full temporal compatibility. Fuzzy temporal compatibility between 2 and 4 weeks, full temporal compatibility $\mu_{temp} = 1\ \forall t,\ t \geq 4$ weeks.

In order to deal with varying immune responses of individuals to a Toxoplasma infection, minimum time intervals between two and four weeks have to be kept between subsequent tests to ensure their correct application. These spans that have to be kept between the examinations are modelled as

fuzzy sets and have been 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]—called temporal compatibility—that expresses how close the time difference between two tests agrees with the prescribed interval [4,7]. An example of a membership function used in ToxoNet is given in Figure 2.

2.3. The TOXOPERT Inference Mechanism

The actual inference process is based on the formerly described automaton and is called TOXOPERT. For each given finding of a patient consisting of one IgG and one IgM test result, inference is performed step-by-step by feeding the automaton with the results of particular examinations. If no more test results are available, the last state reached becomes the result of the inference procedure and corresponds to the final interpretation. All affected states and transitions constitute the inference path.

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 levels, i.e., the multiplication operator is used for computing the fuzzy AND operator. This process finally yields an overall temporal compatibility that expresses the total temporal membership of the sequence of findings. This value gives information of how close this sequence agrees with temporal restrictions required for a reliable interpretation [4,5].

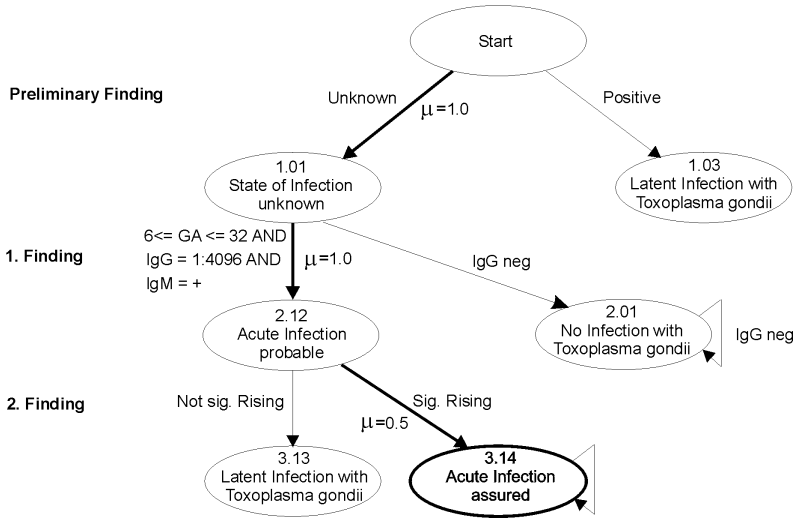

Figure 3: Visualization of an example inference.

date	test results	GA
2000/09/03	preliminary finding: unknown	10
2000/09/03	IgG: 1:4096, IgM: 11	10
2000/30/03	IgG: 1:65536, IgM: 12	13

Table 1: Example sequence of test results (GA is the abbreviation for gestational age).

Figure 3 shows a part of the decision graph of ToxoNet to explain the inference mechanism on behalf of an example. The nodes contain a summary of the diagnostic hypotheses, while the serological preconditions are listed near the edges. Table 1 contains a sequence of test results of a pregnant woman with conception at January 4th, 2000, as well as the week of gestation at the particular test dates. The processing of the test results yields the highlighted path shown in Figure 3. The computation of the temporal compatibility is presented along the edges in Figure 3. Since the time interval between the tests on March 9th and March 30th is too short (three instead of four weeks), the overall temporal compatibility is reduced to 0.5.

2.4. Interpretation of Reduced Temporal Compatibility

If the inference mechanism resulted in an interpretation with reduced temporal compatibility this has to be taken into account, since the physician will not profit from being confronted with a value of, for example, 0.5 for temporal compatibility. Therefore, the knowledge representation formalism has been extended by two mechanisms to do so:

1. It is possible to specify more than one interpretation (consisting of a diagnosis and recommendations for therapy and further testing) for a single node in the decision graph, each of them belonging to a particular range of temporal compatibility. Depending on the temporal compatibility yielded by the inference mechanism the appropriate interpretive text is selected. For instance, for node 3.13 in Figure 3 the two interpretations listed in Table 2 are:

temporal compatibility	**interpretation**
[0.8 – 1.0]	Confirmatory serology did not result in a rising IgG titer. There is latent (preconceptual) infection with persistence of IgM antibodies. The treatment recommended as a precautional measure following the previous test can be discontinued.
[0.5 – 0.8[	Latent (preconceptual) infection with persistence of IgM antibodies is very probable but not confirmed. The treatment shall be continued. For confirmation a serological check at 2 weeks is required.

Table 2: Two possible interpretations for varying values of temporal compatibility.

2. The knowledge engineer can specify for any node in the decision graph that the inference process shall be repeated, if the test having caused the entering of this state yielded a reduced value of temporal compatibility. In addition an explanation may be attached to this node to inform the physician of possible causes for the reduced temporal compatibility. The following inference will not use this particular test and so possibly lead to a more correct result. The user is presented the outcome of both inference processes.

2.5. Knowledge Representation and Error Handling

There arise two special cases in knowledge representation requiring separate treatment:

1. It is in the nature of things that the depth of the decision graph is limited while the number of findings to be evaluated is potentially infinite or at least higher than the depth of the graph. To overcome this problem the knowledge engineer has to take care for introducing cyclical transitions at all end nodes in order to deal with further findings confirming the current diagnosis (see node 3.14 in Figure 3).

2. What happens if the inference mechanism arrives at a diagnosis in an end node and a further finding is inconsistent with the current interpretation? Assume that we have arrived at node 3.14 in Figure 3 and a further IgG test is negative, indicating that an infection with Toxoplasma gondii never existed. Moreover there is no transition meeting this condition and no state defining this situation. This has been made intentionally, since the inference mechanism of ToxoNet in such a case switches to an implicit error state indicating a serum mix-up or any other error that cannot be recovered from. Thus, whenever no corresponding transition is found in an end node, ToxoNet produces an error. Consider that the mechanism is not appropriate to remove states of interpretation group contradictory, since these should be used to guarantee mathematical completeness in the previous levels of the graph and to inform the user about potential causes for the inconsistency. The error mechanism is only intended for errors occurring in end nodes.

2.6. Knowledge Acquisition

The knowledge acquisition process for ToxoNet comprises three essential tasks: (a) the determination of interpretations so that all possible cases are covered, (b) the identification of serological preconditions indicating a particular interpretation, and (c) the analysis of time intervals to be kept between two examinations. Knowledge is indirectly acquired by a knowledge engineer with the help of a graphical knowledge acquisition system (see Figure 4).

The last revision of the knowledge base regarding contents, capacity, and structure resulted in a decision graph consisting of 45 states, 92 transitions, and 53 conditions [4].

3. Results

The need for integrating ToxoNet's database into that of MedFrame, a framework for storing medical data and implementation of client/server-based medical expert systems being developed at the Section on Medical Expert and Knowledge-Based Systems of the Department of Medical Computer Sciences of the University of Vienna Medical School, and the demand for a WWW interface to the inference mechanism led to the decision to implement ToxoNet in Java. The result of this effort was a platform-independent system, that is primarily designed to operate in network environments based on the TCP/IP protocol stack, and can be reached at http://medexpert.imc.akh-wien.ac.at/ToxoNet. It is both runnable as an autonomous program and from inside of any contem-

porary World Wide Web browser. Thus, the operational area ranges from local area networks to the Internet. ToxoNet is originally based on a client/server architecture consisting of three components: ToxoServer, ToxoBuilder, and ToxoApplet. Since the intended area of application is the Internet it is capable of multiple languages, currently of English and German. An HTML-based graphical help system for supporting the user in case of arising difficulties is also available.

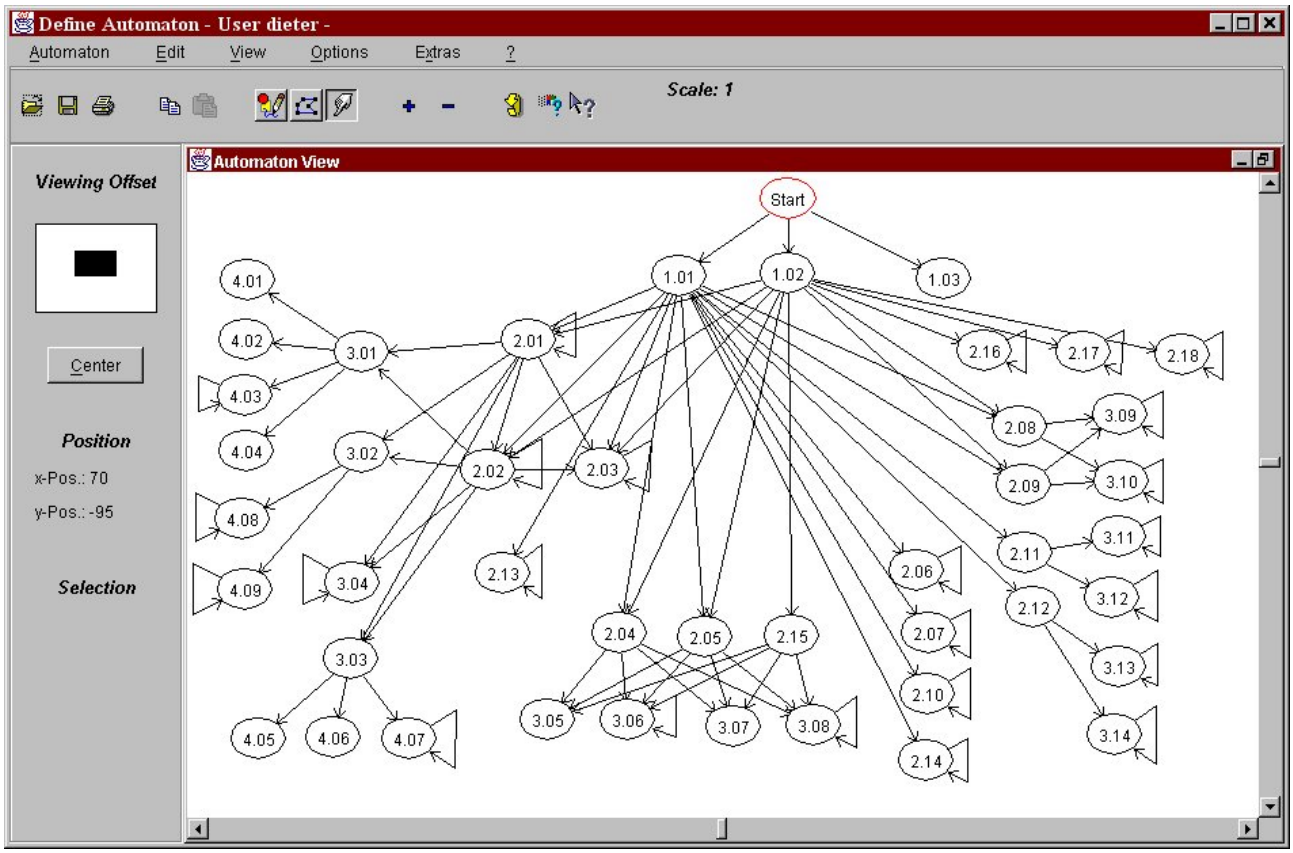

Figure 4: The knowledge acquisition system and decision graph of ToxoNet.

The server's responsibilities, including communication with the MedFrame database as well as the interpretation of patients' data by invoking TOXOPERT, have been implemented in ToxoServer. ToxoApplet is the first of two client modules and provides an interface to the inference mechanism being accessible from anywhere in the Internet. It allows the user to enter a patient's personal data and serological test results, to start the diagnostic process at ToxoServer, and to display the result in a textual and graphical manner. Finally, ToxoBuilder forms a graphical knowledge acquisition system enabling the user to create and modify the knowledge graph in terms of traditional drawing software by a simple point-and-click methodology [4] (see Figure 4).

In order to provide a possibility to access the benefits of TOXOPERT from WWW browsers being not capable of executing Java Applets and to reduce Applet download times via slow mobile phone connections, we decided to implement an HTML-based equivalent to ToxoApplet called

TOXOPERT/WWW. It enables the user to fill anonymous test results into standard HTML forms, the inference results are presented on traditional HTML pages. From the implementation's point of view, TOXOPERT/WWW has been integrated with ToxoServer as Java Server Pages and therefore required only little additional programming effort.

4. Discussion

ToxoNet provides automated knowledge-based decision support for the process of detecting infections with Toxoplasma gondii, not only for a particular laboratory but also for other clinics and even external users via the World Wide Web.

In 1975 an obligatory serological screening program for pregnant women to detect infections with Toxoplasma gondii was introduced in Austria, and therefore every woman is tested for antibodies three times during pregnancy. ToxoNet is a valuable tool for supporting physicians and laboratory assistants in their daily work. Considering that the incidence of prenatal toxoplasma infections has reduced from about 50–70 per 10,000 births to presently below 1 per 10,000 births since the introduction of the screening program [2], the associated costs show themselves under a different but favourable light, although most probably other factors—like improved hygienic standards—also may have contributed to this reduction.

The results of a recently performed study including the data of 1606 pregnant women taken from the routinely-used database of the Toxoplasmosis Laboratory of the Vienna General Hospital are presented in Table 3.

Physician / ToxoNet	**latent**	**acute**	**no infection**	**contradictory**	**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**	**1606**

Table 3: Results of a retrospective study group of 1606 pregnant women.

Obviously the number of correctly classified latent and acute infections is rather high, since about 85 % of latent and acute infections are classified according to the physician's decision. The 5 % of cases being interpreted as contradictory instead of latent or acute are due to the fact, that TOXOPERT yields a contradictory result if no clear decision is possible. Unfortunately there is a problem with distinguishing between latent and acute infections that partly results from errors in the current knowledge base and partly from faulty data. We are currently working on finding and fixing these problems.

5. Conclusion

ToxoNet contains a knowledge-based system supporting the physician in interpreting the results of routinely performed toxoplasmosis serology tests, thus, facilitating routine laboratory work and assuring quality by setting standards for therapy.

On the one hand the inference mechanism is able to categorize the major part of possible cases on its own, thus, relieving the laboratory personnel from tedious routine workload and enabling them to concentrate on contradictory and more challenging cases. On the other hand the inferred interpretations have been formulated in a manner that even people without extensive knowledge about toxoplasmosis are able to comprehend them.

6. References

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