

## 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 having been performed during pregnancy by means of a knowledge base containing medical knowledge on the interpretation of Toxoplasmosis serology tests. By applying this knowledge ToxoNet generates interpretive reports consisting of a diagnostic interpretation and recommendations for therapy and 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 interpretation algorithm derives the stage of maternal infection from these that is used to infer the degree of fetal threat. To consider varying immune responses of particular patients, certain time intervals have to be kept between two subsequent tests in order to guarantee a correct interpretation of the test results. These time intervals are modelled as fuzzy sets, since they allow

the formal description of the temporal uncertainties. ToxoNet comprises the knowledge base, an interpretation system, and a program for the creation and modification of the knowledge base. It is available from the World Wide Web by starting a standard browser like the Internet Explorer or the Netscape Navigator. 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.

### Keywords:

Decision Support Systems, Toxoplasmosis, ToxoNet, Internet

### Introduction

#### 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

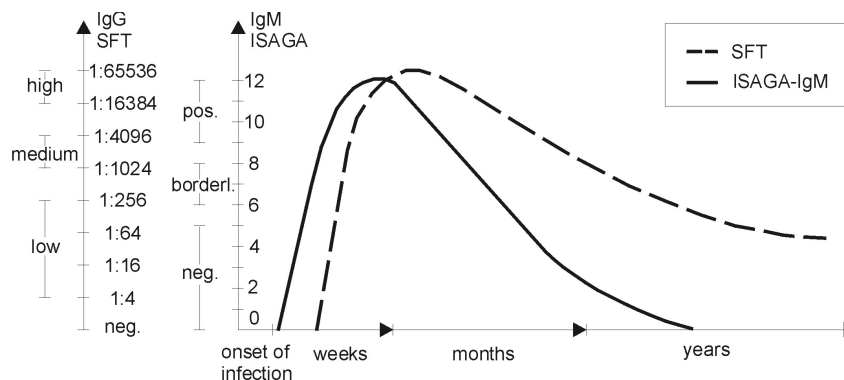


Figure 1 - Idealized course of SFT and ISAGA-IgM

maternal infection (denoted as latent), or rather the associated raised antibody concentration, prevents transplacental 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 transmission of the parasite—that occurs with a probability of about 60 percent in case of no drug therapy [1]—can be reduced, resulting in prevention of fetal infection or at least in a decrease of fetal damage.

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.

### 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.

### Methods

#### 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 concentrations 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 some 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].

#### Knowledge Representation

The knowledge of ToxoNet is represented as a directed decision graph (see Figure 3). This graph may be interpreted as a deterministic final automaton consisting of states (represented by nodes in the graph), transitions (corresponding to edges), and conditions (generated from 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 in addition 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 data for inconsistent 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.

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].

#### Inference Mechanism – TOXOPERT

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 for the patient. 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 an idea of how close this sequence agrees with temporal restrictions required for a reliable interpretation [4,5].

Figure 2 shows a part of the decision graph of ToxoNet in order to explain the rather complicated 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 3<sup>rd</sup>, 2000, as well as the week of gestation at the particular test dates. The processing of the test results according to the mentioned mechanism results in the highlighted path shown in Figure 2. The computation of the temporal compatibility is also presented along the edges in Figure 2. Since the time interval of 4 weeks between the tests on March 3<sup>rd</sup> and March 18<sup>th</sup> and between the tests on March 18<sup>th</sup> and April 3<sup>rd</sup> are too short, the overall temporal compatibility reduces to 0.0.

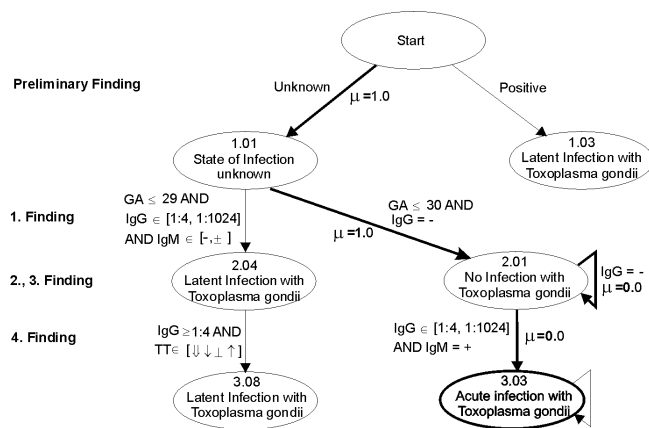


Figure 2 - Visualization of an example inference

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

Date	Test results	GA
2000-03-03	prel. finding unknown	9
2000-03-03	IgG: -, IgM: -	9
2000-03-18	IgG: -, IgM: -	11
2000-04-03	IgG: -, IgM: -	13
2000-05-03	IgG: 1:1024, IgM: +	18

### Interpretation of Reduced Temporal Compatibility

If the inference mechanism results in an interpretation with reduced temporal compatibility this case has to be taken into account in any way. This is due to the fact that on the one hand a physician will not profit from being confronted with a value of for example 0.5 for temporal compatibility, and that on the other hand the presented inference strategy does not yet make any use of the value computed for temporal compatibility. The latter furthermore possibly creates a kind of contradiction as shown in the example above, where the interpretation yields a clear diagnosis although there is no temporal compatibility. Therefore, the knowledge representation formalism has been extended by two mechanisms to do so.

Firstly 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 the appropriate interpretation text will be selected. For instance, for node 3.03 in Figure 2 the two interpretations listed in Table 2 would be appropriate:

Table 2 - Two possible interpretations for varying values of temporal compatibility

Temporal compatibility	Interpretation
[0.5 – 0.8]	Acute (postconceptual) infection with Toxoplasma gondii very probable. We recommend medical treatment as proposed in the attached schema and serological followup at 4 weeks. We suggest to perform PCR (polymerase chain reaction) out of amniotic fluid after completion of week 15 of pregnancy.
[0.8 – 1.0]	There is acute (postconceptual) infection with Toxoplasma gondii, seroconversion. We recommend medical treatment as proposed in the attached schema and serological followup at 4 weeks. We suggest to perform PCR (polymerase chain reaction) out of amniotic fluid after completion of week 15 of pregnancy.

Secondly the knowledge engineer may 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 in order to inform the physician of possible causes for the reduced temporal compatibility. The following inference will not use this particular test and so possibly produce a more correct result. The user is presented the outcome of both inference processes.

In the example in Figure 2 the first run of the inference mechanism would finish in state 3.03, yielding a temporal compatibility of 0.0 and therefore generating the following diagnostic hypothesis: “Acute (postconceptual) infection with Toxoplasma gondii probable”. Thereafter TOXOPERT automatically starts a second inference dropping the test result from March 18<sup>th</sup>, 2000. In this case the inference procedure stops in state 3.03, yielding a temporal compatibility of 1.0 and therefore improving the diagnostic hypothesis to “Acute (postconceptual) infection with Toxoplasma gondii, seroconversion”.

### 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 analyzation 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 3).

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].

## Results

The need for integrating ToxoNet's database into that of MedFrame, a medical consultation system being developed at the Section on Medical Expert and Knowledge-Based Systems of the Department of Medical Computer Sciences of the Univeristy 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. ToxoNet 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 contemporary 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 and comprises a graphical knowledge acquisition system and a module for data entry, inference triggering, and presentation of the interpretation. 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.

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 interface to the inference mechanism 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 ToxoNet as Java Server Pages and therefore required only little additional programming effort.

## Discussion

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. It is also available for other clinics and even external users via the World Wide Web.

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.

In contrast to ToxoNet its precursors—TOXOPERT-I, TOXOPERT-II, and TempTOXOPERT [5,6], that have also been developed at our department—are standalone computer systems. They are based on the same set of serological tests and the same knowledge representation but either do not make use of fuzzy temporal concepts at all or at least temporal compatibility does not have any effects on the interpretations derived. Onset—a system developed for the derivation of the time of onset of infection from serological findings in any field of medicine [8,9]—has also been applied to Toxoplasmosis serology. Onset tries to

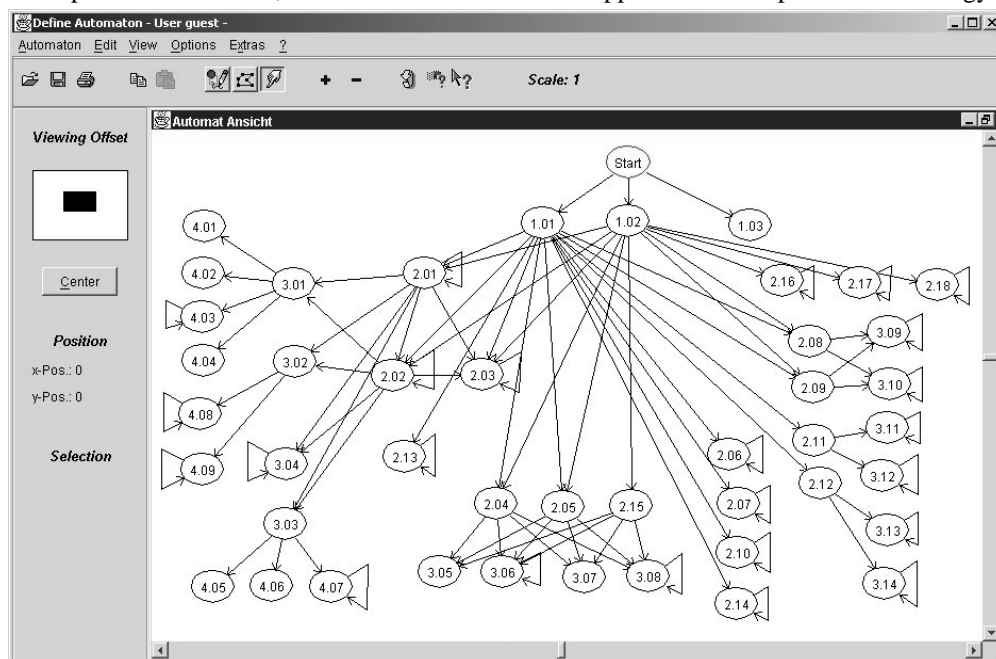


Figure 3 - The knowledge acquisition system and decision graph of ToxoNet

narrow the point of time 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 course of a Toxoplasma infection and concluding to the time of infection from this knowledge. Another two projects in the field of knowledge-based decision support for Toxoplasmosis serology test results make use of a larger set of serological tests and therefore require a better suited laboratory than ToxoNet does. Since these systems are not accessible from the Internet, they are rather targeted to specialized laboratories whereas ToxoNet has to make the compromise between understandability and universality. The first of these two projects was performed at the Johns Hopkins University, Baltimore, and was built on top of neural networks [10]. In the second project a rule-based decision support system derived from Pro. M.D. has been implemented [11].

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.

Table 3 - Results of a retrospective study group of 1606 pregnant women

Physician / ToxoNet	Latent	Acute	No inf.	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
<b>Total</b>	<b>601</b>	<b>152</b>	<b>813</b>	<b>40</b>	<b>1606</b>

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.

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