Journal of Biomedical Informatics 45 (2012) 45–60

Contents lists available at SciVerse ScienceDirect

Journal of Biomedical Informatics

journal homepage: www.elsevier.com/locate/yjbin

Formalization of treatment guidelines using Fuzzy Cognitive Maps and semantic web tools

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ARTICLE INFO

Article history:
Received 12 January 2011
Available online 1 September 2011

Keywords:
Fuzzy Cognitive Maps
Knowledge representation
Decision support
Semantic web
Notation3
Expert systems
Treatment management

ABSTRACT

Therapy decision making and support in medicine deals with uncertainty and needs to take into account the patient's clinical parameters, the context of illness and the medical knowledge of the physician and guidelines to recommend a treatment therapy. This research study is focused on the formalization of medical knowledge using a cognitive process, called Fuzzy Cognitive Maps (FCMs) and semantic web approach. The FCM technique is capable of dealing with situations including uncertain descriptions using similar procedure such as human reasoning does. Thus, it was selected for the case of modeling and knowledge integration of clinical practice guidelines. The semantic web tools were established to implement the FCM approach. The knowledge base was constructed from the clinical guidelines as the form of if-then fuzzy rules. These fuzzy rules were transferred to FCM modeling technique and, through the semantic web tools, the whole formalization was accomplished. The problem of urinary tract infection (UTI) in adult community was examined for the proposed approach. Forty-seven clinical concepts and eight therapy concepts were identified for the antibiotic treatment therapy problem of UTIs. A preliminary pilot-evaluation study with 55 patient cases showed interesting findings; 91% of the antibiotic treatments proposed by the implemented approach were in fully agreement with the guidelines and physicians' opinions. The results have shown that the suggested approach formalizes medical knowledge efficiently and gives a front-end decision on antibiotics' suggestion for cystitis. Concluding, modeling medical knowledge/therapeutic guidelines using cognitive methods and web semantic tools is both reliable and useful.

1. Introduction

Fuzzy Cognitive Maps constitute an extension of cognitive maps, inheriting the main aspects of fuzzy logic and neural networks. They were introduced by Kosko in 1986 [1] as signed directed graphs for representing causal reasoning and computational inference processing, exploiting a symbolic representation for the description and modeling of a system. They describe particular domains using nodes/concepts (variables, states, inputs, outputs) and signed fuzzy relationships between them. Concepts are utilized to represent different aspects of the system, as well as, their behavior. The dynamics of the system is implied by the interaction of concepts. The fuzzy part allows us to have degrees of causality, represented as links between the concepts of these graphs. This structure establishes the forward and backward propagation of causality, admitting the knowledge base to increase when concepts and links between them are increased [2]. The construction of an FCM requires the input of human experience and knowledge on the system under consideration or input from historical data after training [3,4].

FCMs are simple, yet powerful tools for modeling and simulation of dynamic systems, based on domain-specific knowledge and experience. They present a number of advantages over conventional fuzzy approaches to reasoning. These include handling of incomplete even conflicting information, easy construction and parameterization, and they allow users to rapidly compare their mental models with reality. They have been applied in a number of decision making and support tasks [3–9] showing their efficiency. In the medical and biomedical application domains, FCMs have been used for modeling medical knowledge and analyzing complex medical processes for decision support [10,15–21] and medical diagnosis tasks [11–14].

The task of modeling medical knowledge and making therapy decisions is a complex one as it requires the combinatorial analysis of a number of parameters, symptoms, adverse events, indications and contraindications, stand as decision variables [22,23]. Thus, due to the complexity and vagueness involved in the decision

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doi:10.1016/j.jbi.2011.08.018

making process, physicians need some level of decision support. Guidelines include the description of the various alternatives and of the selector factors that would allow establishing decisions amongst them [24]. In most medical domains, there is a substantial body of knowledge prescribed by guidelines that can be used to model that domain. However, because of the sheer volume of one such guideline and the rigid structure of such guidelines it is very difficult for the treating physician to apply and strictly follow the workflow presented by them. Thus, there is a need to create a computerised system that dynamically guides the physician through the workflow of clinical practice guidelines for making decisions [23,25,26].

This paper describes and evaluates a new innovative method to create a therapy model framework for decision support based on semantic web approaches and the soft computing technique of FCMs for medical reasoning. FCM was selected for modeling and knowledge integration of clinical practice guidelines due to its simplicity in knowledge representation and appropriateness for knowledge management in complex medical tasks. The knowledge base was constructed from the practice guidelines and the knowledge facts were represented in the form of fuzzy if-then rules. These fuzzy rules were transferred to FCM modeling technique and, through the semantic web tools, the whole formalization was accomplished. The advantage of using semantic web is to enable the sharing and reuse of knowledge from databases of guidelines and simplify maintenance. The notation 3 (N3), which is a shorthand non-XML serialization of Resource Description Framework (RDF) models [27], and the Euler sharp reasoning engine [28] were established to implement the FCM approach, taking into account the patient's clinical settings.

The urinary tract infection (UTI) treatment management in adult community was selected to examine the proposed methodology as it is an important and complex task that demands a special attention. From the literature, to model medical knowledge and assign treatment suggestions for UTI, probabilistic networks and fuzzy logic based methodologies have been employed by some researchers [31,32]. Leibovici et al. tried to model bacterial infections by proposing a causal, probabilistic network for optimal treatment of these infections [31]. Although, the probabilistic network was a convenient way to combine data from databases collected at different locations and times with published information, its calibration to new sites requires data that are available in most modern hospitals. Kao & Li tried to exceed the above limitations by proposing an optimal treatment model for bacterial infections with fuzzy information using influence diagrams [32]. The influence diagrams were conducted two kinds of reasoning simultaneously: diagnostic reasoning and treatment planning [33–36].

This research study is focused on the formalization of medical knowledge using cognitive process implemented in semantic web. Since the cognitive mapping seems to be an efficient technique for modeling knowledge based on medical guidelines/treatment suggestions, its implementation in notation 3 (N3) semantic web technique [27,37] helps in reasoning with it.

The proposed methodology was validated on a pilot-evaluation study of 55 real patient cases. The produced results for each individual patient were compared with the clinical practice guidelines (which were considered as the "gold standard"). The success rate of the proposed approach, giving treatment suggestions for UTI caused by *Escherichia coli*, was assigned to 91%, which shows the functionality of the model and its future usefulness in clinical practice. The results have shown that the suggested approach formalizes medical knowledge efficiently and gives a front-end decision on antibiotics' suggestion for first and second line schemes of uncomplicated UTI.

The paper is structured in the rest five sections. Section 2 provides the formalization of FCMs, its reasoning process and the basic aspects of semantic web tools as well as the FCM implementation in notation 3. Section 3 describes the treatment recommendations of the examined case problem and the construction of FCMs for the case problem of uncomplicated UTIs. A pilot-evaluation study was accomplished and the results for the decision support problem of UTI caused by *E. coli* are presented in Section 4, whereas the discussion and conclusions derived are summarized in the last two sections.

2. Fuzzy Cognitive Maps and semantic web approaches

2.1. Fuzzy Cognitive Map description

Fuzzy Cognitive Map (FCM) is a method for analyzing and depicting human perception of a given system. The method produces a conceptual model which is not limited by exact values and measurements, and thus is well suited to represent relatively unstructured knowledge and causalities expressed in imprecise forms [2]. The FCM is defined as a collection of nodes-concepts (events, actions, values, goals, etc.) that influence each other through cause-effect relationships, which are quantified and usually normalized to the $[-1,1]$ interval. Fuzzy Cognitive Maps can be conveniently represented by a graph, which is easily understood by a human, where concepts are represented as nodes and relationships are depicted by directed edges between the nodes. Each edge is also associated with a number (weight) that quantifies the strength of the corresponding relationship [38].

FCM is a dynamic tool because cause-effects relations and feedback mechanisms are involved [39]. Furthermore, the emergent properties in the system can be investigated by asking "what-if" questions regarding the system [40]. FCM focuses on the components and features in the system and is fairly easy to understand for the participants, which opens up the possibility for involving lay people as well as planners, managers and experts [41].

For the purposes of this paper, we define FCM as an order pair $\langle C, W\rangle$, where C is the set of labels and W is the connection matrix. Every label $Ai \in C$ its mapped to its activation value Ai E $[0,1]$, where 0 means no activation, and 1 means full activation. The labels from C can be interpreted as linguistic terms [38] that point to fuzzy sets. In such case, the activation value a_i is interpreted as the value of fuzzy membership function that measures the degree in which an observed value belongs to the fuzzy set pointed by the related term. The other, simplified interpretation of C can be such that the labels C_i denote the real valued variables, the domains of these variables are assumed as normalized into the $[0,1]$ interval. Note that the latter, simplified interpretation of C is applied by many researchers [5–8,20,42] and in most cases does not influence the computational methods that stand behind the reasoning process based on FCM.

The binary causal relationship within the set C will be represented by the matrix W. The matrix W does not change in time and stores the weights assigned to the pairs of concepts. The weights represent the generalized (over a given period of time) causal dependency between the concepts. The weights assume the values $w_{ij} \in [-1,1]$, where the value of weight $w_{ij} = 1$ expresses the full positive and $w_{ij} = -1$ full negative impact of ith causal-concept on jth effect-concept respectively. The intermediate values of weight refer to partial causality.

The construction of an FCM for the modeling of a medical decision making task is implemented in two steps:

1. The *concepts* (N) have to be provided by medical experts and/or guidelines that sufficiently describe the decision making task, including the input and the output knowledge. Each concept

is modeled as a *variable* C_i, $i = 1,2,\ldots,N$ that can take fuzzy or discrete values according to the problem data. The fuzzy values express the degree to which the concepts occur.

2. The *connections* between the concepts and their *strengths* should be assigned also by medical guidelines and/or physicians' knowledge using if-then *rules*. These rules infer a fuzzy weight from a fuzzy set given in Table 1. These fuzzy sets express the degree to which a concept C_j influences another concept C_i, $i = 1,2,\ldots,N$, $j = 1,2,\ldots,N$.

Table 1
Example of fuzzy sets of Observable "Fever".

Fuzzy membership functions for Fever (means temperature (°C))	Triangular fuzzy sets (°C)	Membership degree of each fuzzy set
Hypothermia	(34,35,36)	0
Normal	(36,37,38.4)	0.1
Low	(38.5,38.7,38.9)	0.3
Moderate	(38.9,39.2,39.5)	0.5
High	(39.5,40.2,40.9)	0.8
Hyperpyrexia	(>41)	1

Once the FCM is constructed, it can receive data from its input concepts, perform reasoning and infer medical decisions as values of its output concepts [10,11,38]. A simple generic example is illustrated in Fig. 1a, whereas in Fig. 1b a concrete example of an elementary FCM for UTI treatment with the antibiotic TMP/SMX is depicted.

The concept *connections* were initially determined by experts following the construction process of FCMs, as linguistic variables. The linguistic variables proposed in [10,19,20] and used for modeling FCMs are: $T(influence) = \{$*negatively very strong*, *negatively strong*, *negatively medium*, *negatively weak*, *negatively very weak*, *zero*, *positively very weak*, *positively weak*, *positively medium*, *positively strong*, *positively very strong*, *positively very very strong*$\}$. These linguistic variables are transferred to the corresponding membership functions depicted in Table 1. These twelve triangular membership functions have been previously described in [4,7,38] showing their functionality. Using more fuzzy sets than 5 or 7, a better description on fuzzy influences among concepts could be assigned [38,45]. The fuzzy influences among concepts are transferred to numerical values of connections, called weights W_{ij}, which are estimated by defuzzification of the aggregated, linguistically expressed, concept connections [43].

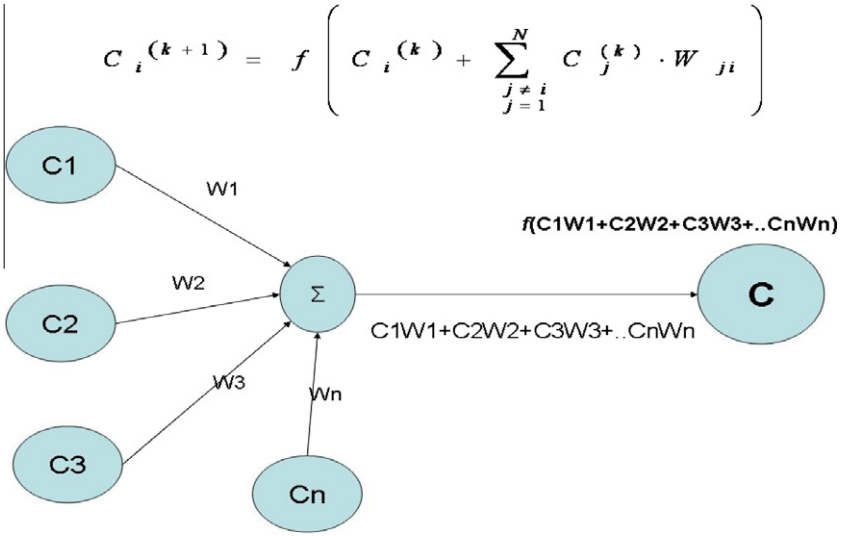


Fig. 1a. Fuzzy cognitive map model for making medical decisions.

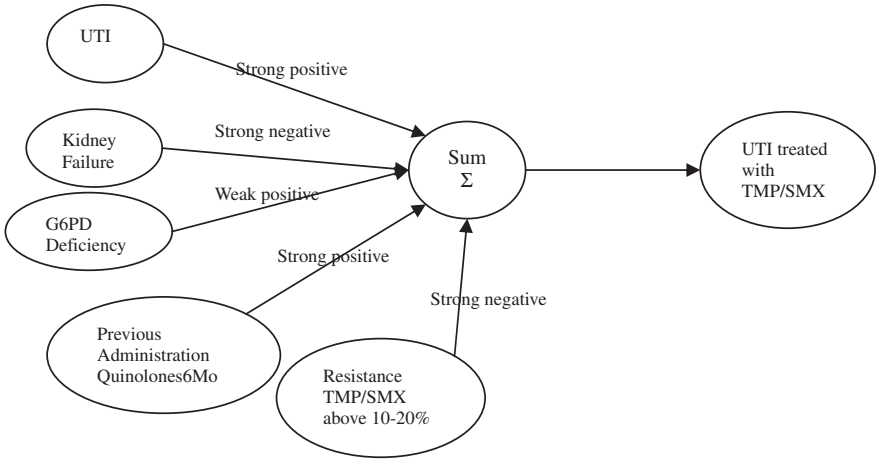


Fig. 1b. Example elementary FCM for UTI treatment with TMP/SMX.

In semantic web, for the notion of N3, the weights W_{ij} are transferred to semantic weights, namely W_{ij}^{semantic} within the range [0,1] that depict the semantic value of numerical weight in N3. The process is described in Section 2.4.

2.2. Fuzzy Cognitive Map inference mechanism

The FCM reasoning process follows a number of steps till the system's equilibrium point. These steps can be found in [20,45] and we briefly present them here. At first step, the initial state of the concepts is given either from experts or from the existing medical database. During reasoning the FCM iteratively calculates its state until convergence. The state is represented by a *state vector* C^k, which consists of real node values $C_i^{(k)} \in [0,1], i = 1,2,\ldots N$ at an iteration k. The value of each node is calculated by the following equation:

$$C_i^{(k+1)} = f\left(C_i^{(k)} + \sum_{\substack{j\neq i \\ j=1}} C_j^{(k)} \cdot W_{ji}\right) \tag{1}$$

where f is a threshold (activation) function:

$$f(x) = 1/(1+e^{-m(x)}) \tag{2}$$

where m is a constant parameter [44]. The parameter m determines how quickly the $f(x)$ approaches the limiting values of 0 and 1. The transformation function is used to reduce unbounded weighted sum to a certain range, which hinders quantitative analysis, but allows for qualitative comparisons between concepts [44].

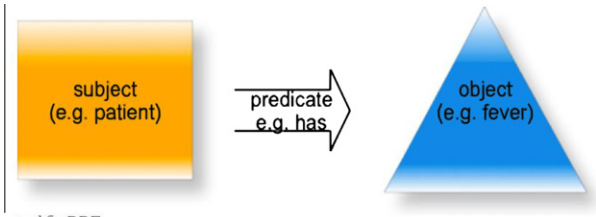
In order to remove the spurious influence of inactive concepts (concepts with zero values) on other concepts, and to avoid the conflicts emerge in cases where the initial values of concepts are 0.5, as well as the missing data, a modified FCM reasoning formalism can be used [20]. Based on this assumption, we reformulated Eq. (1) as:

$$C_i^{(k+1)} = f\left(\left(2C_i^{(k)} - 1\right) + \sum_{\substack{j\neq i \\ j=1}}^{N} \left(2C_j^{(k)} - 1\right) \cdot W_{ji}\right) \tag{3}$$

This Eq. (3) overcomes also the limitation present by the sigmoid threshold function. Thus, the insufficient knowledge and/or missing information for each node can be handled with less deviation from reality [21].

Current FCM-based approaches for decision making assume that nodes with unknown values are set to zero. In that case, the absolute difference between the actual value that is missing and the zero value will be within [0,1], and on average it could exceed 0.5. This rescaled algorithm is implemented especially for the cases where there is no any information about a concept-state or the expert and/or stakeholder can not describe efficiently the initial state of a variable [20,21].

New state vectors showing the effect of the activated concept are computed using method of successive substitution, i.e., by iteratively multiplying the previous state vector by the relational matrix using standard matrix multiplication $\boldsymbol{C}^k = (2\boldsymbol{C}^{k-1} - 1) + (2\boldsymbol{C}^{k-1} - 1) \cdot \boldsymbol{W}$. The iteration stops when a limit vector is reached, i.e., when $\boldsymbol{C}^k = \boldsymbol{C}^{k-1}$ or when $\boldsymbol{C}^k - \boldsymbol{C}^{k-1} \leqslant e$; where e is a residual, whose value depends on the application type (and in most applications is equal to 0.001) [7,45]. Thus, a final vector $\boldsymbol{C\_f}$ is obtained. The conclusions based on FCM should be viewed together with existing scientific knowledge [45]. Conclusions based on an analysis and/or simulations of FCM can be counter-intuitive or against scientific results. If such are encountered, one must further study the assumptions depicted in FCMs, but also be open to insights gained from a systemic approach to problem analysis that FCM is.




```
<rdf:RDF
xmlns="http://wopeg.he.agfa.be/rules/pathFinder#"
xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-
ns#">
<rdf:Description rdf:about=
"http://wopeg.he.agfa.be/rules/pathFinder#Patient">
      <has rdf:resource=
      "http://wopeg.he.agfa.be/rules/pathFinder#Fever"/
>
      </rdf:Description>
</rdf:RDF>
```

Fig. 2. RDF example and its related code.

2.3. Semantic web

In order to understand our techniques in modeling, it is needed the reader be familiar with a few basic concepts that concern the main aspects of N3 and RDFs [27,46]. We do not try here to give a comprehensive overview of these concepts; our only purpose is to give a simple and basic understanding of how N3 is used for formalizing FCMs.

The semantic web approach is based on two notions:

- Develop a common model of integration and use of data from disparate sources.
- Linking data with real world objects, for machines and humans to access data on different bases related by semantic relations.

2.3.1. RDF/ RDFS (Resource Description Framework/Schema)

The Resource Description Framework (RDF) is a family of World Wide Web Consortium (W3C) specifications originally designed as a metadata data model. The RDF data model idea is based upon the idea of making statements about resources, in particular, Web resources, in the form of subject-predicate-object expressions. These expressions are known as *triples* in RDF terminology. The subject denotes the resource, and the predicate denotes traits or aspects of the resource and expresses a relationship between the subject and the object. For example, one way to represent the notion "The patient has fever" in RDF is as the ***triple***: a **subject** denoting "the patient", a **predicate** denoting "has", and an **object** denoting "fever".

2.3.2. Subject verb/predicate object

Graphically, we can represent RDF as Fig. 2 and its related code is next to the graph:

The subject is a resource identified by a URI (Uniform Resource Identifier), which is described by another resource (object) with a property (Word / Predicate). In the case problem of UTI, an example is given for the "cystitis" diagnosis, where the subject "fever" has the property "symptom" for the object "cystitis".

Example.

```
<rdf:Description about= "http://www.urologie.eu/
  disease/cystitis>"
<prefixe:Symptom>Fever</prefixe:Symptom> </
  rdf:Description>
```

Several syntaxes are used: RDF/XML RDF/N3. RDFS is a language of knowledge representation designed to overcome the limitations of RDF. RDFS is the relationship of "subsumption" and "instantiation" with the respective properties: subClassOf and type [47,48]. RDF is a rating given by Tim Berners Lee as an alternative to RDF/XML [46]. Notation3 (N3) is more compact and human readable RDF/XML.

2.3.3. Reasoning

The chief utility of a formal semantic theory (as mentioned in "Semantic Web") is to provide a technical way to determine when inference processes are valid, i.e. when they preserve truth. This provides the maximal freedom for reasoning engines while preserving a globally coherent notion of meaning.

2.3.4. Eye reasoner

Eye stands for "Euler yap engine" and it is a further incremental development of Euler which is an inference engine supporting logic based proofs. Eye is a backward–forward–backward chaining reasoner design enhanced with Euler path detection.

The backward–forward–backward chaining is realized via an underlying Prolog backward chaining, a forward meta-level reasoning and a backward proof construction. The Euler path detection is roughly "don't step in your own steps" to avoid vicious circles so to speak and in that respect there is a similarity with what Leonhard Euler discovered in 1736 for the Königsberg Bridge Problem [49].

Eye is the latest implementation of the Euler proof engine and is released as open source on http://eulersharp.sourceforge.net. More architectural/technical background for Eye Reasoner is given in [28].

2.3.5. Notation3-N3

N3 is a shorthand non-XML serialization of Resource Description Framework models [27]. This language has been selected on purpose to represent medical knowledge due to its human readability and close relationship to the semantic web. The format is being developed by Tim Berners-Lee and others from the semantic web community.

If you want to compare RDF to N3, you can say that in RDF, information is simply a collection of statements, each with a subject, verb and object - and nothing else where in N3, you can write an RDF triple just like that.

```
:patient :has :fever
```

Thus, formalized medical information can be represented with ontological concepts using N3 format. The previous RDF example describing the "cystitis" diagnosis is translated in N3 at follows, where the triples clearly assigned.

@Prefix MUI: <http://www.urologie.eu/disease#>

```
:Fever :Symptom :Cystitis.
```

2.3.6. N3 logic

It is a logical platform that uses semantic web notation 3 as RDF syntax [50] and expands the vocabulary of predicates. The goal of logic N3 is possible to integrate an RDF data model, logical rules and provide integrated functions that allow access and reason about data [46]. In a rule, premise is the subject and the conclusion is the complement (object). The sign "=>" is a common predicate expression log-rule namely **implies.**

An example of N3 rule is given:

If the patient is pregnant Then TMP/SMX antibiotic treatment is inadequate for UTI (cystitis) caused by *E. coli*.

```
{(?P :Pregnancy) fl:mu l} => {(:UrinaryTractInfection :TMP_SMX) fl:sigma 0}.
```

2.3.7. Web Ontology Language (OWL)

The OWL Web Ontology Language is a markup language in semantics for publication sharing ontologies on the World Wide Web [51]. The OWL Web Ontology Language is intended to provide a language that can be used to describe the classes and relations between them that are inherent in Web documents and applications. It has been designed for use by applications that need to process the content of information instead of just presenting information to humans. OWL facilitates greater machine interpretability of Web content than that supported by XML, RDF, and RDF Schema by providing additional vocabulary along with a formal semantics.

The FCM concepts are included in an ontology repository established for the project needs, namely Debugit Core Ontology (DCO) [52]. DCO is updated continuously in order to contain all relevant clinical concepts. We worked with the Debugit [53] project ontologists to enrich the DCO ontology that can be used with rules produced by therapy guidelines.

2.4. FCM implementation in N3

To implement the FCM formalization and reasoning in N3, we used plug-ins and built-ins of the inference engine EulerSharp developed in Prolog [47,48,54]. In Appendix A, some main aspects of programming FCM approach in N3 are depicted.

The presented implementation method is to write rules in N3 logic for reasoning on data with standardized patients data using the FCM algorithm. The FCM concepts are included in an ontology repository established for the project needs, namely DCO. The DCO repository is updated continuously in order to contain all relevant clinical concepts.

Thus, based on this implementation approach, all the concepts, relationships and fuzzy rules for differential diagnosis are written in N3. Huge effort has been put and is continued to be put in the implementation of an efficient First Order Logic reasoning engine called Eye [28].

2.4.1. Introducing the FCM built-ins

Models are written in a form of T-rules which simplifies the modelling technique to expressing relationships with True or False structures and attaching believes to them. Furthermore the rules expressing medical knowledge make use of built-ins of the Eye reasoner (see above). In the case of FCM modelling the following Eye predicates are used with the Euler built-in `fl:pi`.

- `fl:sigma` is an Eye predicate to express fuzzy set membership, e.g. `(:x :C) fl:mu 0.8` says that :x is a :C to a fuzzy membership degree of 0.8.
- `fl:mu` is an Eye predicate to express fuzzy subsethood e.g. `(:C :D) fl:sigma 0.9` says that :C is a rdfs:subClassOf :D to a degree of 0.9.
- `fl:pi` is an Euler built-in rdf:Property to express the reasoning process of FCM (described in section IIB), referring to a number of iterations as it is expressed in Eq. (3). `fl:pi` is a built-in supplied via plug-in http://eulersharp.sourceforge.net/2006/02swap/fcm-plugin.yap.

In FCM rules and reasoning [http://eulersharp.sourceforge.net/2003/03swap/fl-rules.html], the main aspects of programming FCM approach in N3 are presented.

2.4.2. Representing knowledge in N3 for Fuzzy Cognitive Maps

The formalized medical knowledge in the context of FCMs is represented with ontological concepts using N3 and logic-rules format. The knowledge representation in N3 is accomplished in two steps:

Table 2
Determination of fuzzy weights for semantic languages.

Fuzzy membership functions (triangular)	Fuzzy regions	Deffuzzified value (weight)	Semantic weights
Negative Very very strong influence	[−1, −0.9)	−1	0
Negative Very strong influence	(−0.9 −0.7)	−0.8	0.1
Negative strong influence	(−0.8 −0.6)	−0.7	0.15
Negative medium influence	(−0.7 −0.4)	−0.55	0.225
Negative weak influence	(−0.4 −0.2)	−0.3	0.35
Negative Very weak influence	(−0.2 0)	−0.1	0.45
Positive Very weak influence	(0 0.2)	0.1	0.55
Positive weak influence	(0.2 0.4)	0.3	0.65
Positive medium influence	(0.4 0.7)	0.55	0.725
Positive strong influence	(0.6 0.8)	0.7	0.85
Positive Very strong influence	(0.7 0.9)	0.8	0.9
Positive Very very strong influence	(0.9 1]	1	1

At first, the *concept* $C_i i = 1,2,\ldots,N$ which can represent an observable/symptom/condition/indication or decision is implemented in N3, as :C_i.For example if C_i is an observable for a patient01 and has an initial state value A_i, then this is implemented in N3 as follows: `(:patient01 :Observable) fl:mu 0.XX` says that `:patient01` has : `Observable` (C_i) to a fuzzy membership degree of 0.XX.

The concept C_i can take fuzzy or discrete values according to the problem data and is provided by medical experts and/or guidelines that sufficiently describe the decision making task, including the input and the output knowledge.

The Eye predicate `fl:mu`, was introduced in N3 form to express fuzzy set membership of the initial value of *Ci* concept, namely *Ai*. Let's consider that the patient01 has "high Fever". The observable "Fever" (according to physicians) could take five fuzzy values from the corresponding triangular fuzzy sets {"hypothermia" (34, 35, 36), "normal" (36, 37, 38.4), "low" (38.5, 38.7, 38.9), "moderate" (38.9, 39.2, 39.5), "high" (39.5, 40.2, 40.9), "hyperpyrexia" (>41)}. A fuzzy membership degree for each one fuzzy set is depicted using the fuzzy set theory and, after defuzzification of the center of gravity, a numerical degree is calculated. The respective membership degrees of them are apposed in Table 2.

Thus for "high Fever", the initial value of concept *Ci*-Fever is assigned to 0.8 after defuzzification of the respective fuzzy sets, and in FCMs is represented as *Ai* = 0.8. In N3, the initial value of observable "high Fever" is implemented as: `(:patient01 :Fever) fl:mu 0.8`.

At the second step, the fuzzy *connections* with their *strengths* between the concepts, as they assigned also by medical guidelines, need to be implemented in N3 using the Eye predicate.

The messages of practice guidelines (knowledge facts) are interpreted as rules "If Premise Then Conclusion". The premise takes into account several patient parameters and it consists of several basic premises. Extracting knowledge from these practice guidelines results in fuzzy "if-then" rule base (see Appendix B).

The rules are formalized as follows:

"If the value of a concept *Ci* (observable) is X then the value of *Cj* (decision) is Y with a degree of influence (weight) W_{ij}". Every relationship between a concept *Ci* and a therapy decision concept *Cj* is defined by a membership function that determines the degree of causality between the two concepts.

The degree of influence can be positive or negative and is determined from the fuzzy set *T*(*influence*) (as described in the previous section). This fuzzy influence is transferred to numerical weight W_{ij}, which in next, due to semantic web compatibility reasons needs to be transferred to a semantic weight, namely W_{ij}^{semantic}.

It is essential to pinpoint that in semantic web, the FCM weights should be transferred in the range 0–1, keeping their meaning. Thus the W_{ij}^{semantic}, which depict the semantic value of numerical weights in [0,1], are calculated by the following mathematical form:

$$W_{ij}^{\text{semantic}} = (W_{ij} + 1)/2 \tag{4}$$

Table 2 depicts the semantic web weights for the related fuzzy and numerical weights of FCMs.

Let's consider an FCM with two concepts, C_i and C_j with a fuzzy influence between them (see Fig. 4a).

In N3 (see Fig. 4b), the influence between two concepts *Ci* (observable) and *Cj* (therapy) is implemented as:

$(:\mathrm{Ci}:\mathrm{Cj})\mathrm{fl}:\mathrm{sigma}\ \mathrm{W}_{\mathrm{ij}}^{\mathrm{semantic}}$

where `fl:sigma` expresses a "subsethood" between the two variables (i.e. therapy and observable) which can be interpreted as how much the observable (which is defined around the domain of a therapeutic process and might be for example indications, contraindications, relative indications, relative contraindications etc.) is contained in the set of therapy.

Medically we approached the problem from the viewpoint of the physician who often applies quantitative descriptors to cases on different scales (consisting of different number of levels). In our case, in order to achieve a higher level of "granularity" and accuracy, we aimed to provide a scale of 12 levels corresponding to mathematical values on the range [−1,1]. Translating negative values to negative effects and positive values to positive effects is straightforward, however, due to compatibility reasons with the performance of the Eye Reasoner, we need to project these values to range of non-negative numbers on [0,1]. Naturally this eliminated all the negative numbers and may not directly translate to logic representation of the negative effect, however from the viewpoint of the Eye Reasoner, anything <0.5 is discouraging decision (therefore acting as a negative effect) and anything >0.5 is encouraging decision (therefore acting as a positive effect). The "distance" from 0.5 determines the "strength" of effect: the bigger the "distance", the stronger the negative (<0.5) or positive (>0.5) effect (or decision).

Thus, each one of the semantic weights (influences between observables and therapy concepts) presents a degree of belief from 0 to 1. Using the Eye predicate fl:sigma, the weights are formalized efficiently in N3.

2.4.3. FCM reasoning in N3

The FCM reasoning is accomplish using the Eye, as described in http://eulersharp.sourceforge.net/2006/02swap/fcm-plugin.yap.

3. Construction of decision support tool for UTI treatment management

3.1. Medical background

UTI refers to inflammation of the urinary tract, which includes the renal parenchyma (pyelonephritis), the bladder (cystitis), the prostate in males (prostatitis) and the urethra (urethritis). The

range of possible symptoms caused by UTI is extremely broad, from no symptoms to symptoms referable the lower urinary tract (e.g. dysuria and frequency), to symptoms indicative of an upper UTI (e.g. loin pain and costo-vertebral angle tenderness), to full-blown septic shock [55,56].

UTI can be classified as uncomplicated (patients with urinary tracts that are normal from both structural and functional perspective) and complicated (that does not fit the uncomplicated category) [56]. Uncomplicated UTIs (uUTI) are most common in young, sexually active women (due to shorter urethra) as well as in hospitalized patients [29]. Because women have a shorter urethra than men, they are 14-times more likely to suffer from an UTI [57]. A United States and Canadian study showed that approximately one half of all women will have a UTI caused mainly by *E.* coli in their lifetimes, and one fourth will have recurrent infections [57–59]. Further a number of studies (guidelines) show the amplitude of this problem and guidelines to be followed [58]. *Escherichia coli* (*E. coli*) is the most common cause of uncomplicated UTI and accounts for approximately 75–95% of all infections [30,55,56].

An extremely large number of uncomplicated UTIs (cystitis) occur every year. The vast majority of acute symptomatic infections occur in young women. Acute symptomatic urinary infections are unusual in men under 50. *Escherichia Coli* (*E. coli)* is a Gram negative rod shaped bacterium that is commonly found in the lower intestine [58]. Also, but more rarely, uncomplicated cases of UTIs may be caused by Klebsiella pneumoniae, Proteus mirabilis, Staphylococcus saprophyticus etc. *E. coli* is responsible for approximately 90% of community-acquired UTIs seen in individuals with ordinary anatomy (no complicating factors) [56]. Also *E.* coli accounts for more than 50% of hospital acquired UTIs [55,57].

Treatment of uUTIs ranges from conservative therapy (abundant fluid intake) to antibiotic therapy. There are several medications available for oral therapy of such as trimethoprim (TMP), cephalosporine, nitrofurantoin, fluoroquinolone. Trimethoprim (also in combined form with Sulfametoxazol, aka TMP/SMX) is one widely used antibiotic for UTIs and suggested as *first line* therapy. Fluoroquinolones (2nd and 3rd generation drugs such as levofloxacin or ciprofloxacin) should be preserved (as backup) for patients with allergies or with underlying diseases that predispose to serious condition as well as for patients where first line drugs fail.

Trimethoprim-sulfamethoxazole (TMP/SMX) for 3 days should be considered the current standard therapy. Trimethoprim alone and ofloxacin are equivalent to TMP-SMX. Fluoroquinolones are more expensive than TMP-SMX and trimethoprim, and, to postpone emergence of resistance to these drugs, we do not recommend them as initial empirical therapy except in communities with high rates of resistance (ie, 10–20%) to TMP-SMX. Nitrofurantoin and fosfomycin may become more useful as resistance to TMP-SMX and trimethoprim increase [58].

The fact is that despite concerns that increasingly widespread use of fluoroquinolones (especially 3rd generation drugs) will promote bacterial resistance, an uncontrolled prescription of these drugs can be observed. Use these drugs for the routine treatment of acute uncomplicated cystitis should be discouraged and the development of resistance carefully monitored. Since the TMP-SMX is devoted to first line therapy in most uncomplicated cases, it is essential to monitor the current setting's resistance profile since above a resistance of about 30% an alternative therapy must be sought. For simplicity we have focused our attention only to the Uncomplicated Bacterial UTI (cystitis) and we have followed the treatment guidelines from AAFP [58].

3.2. Construction of the formalized therapy model

The development of the formal therapy models for the management of uncomplicated bacterial cystitis (uUTI) is introduced using FCMs and semantic web. The therapy models have been designed with the contribution of medical guidelines/treatment suggestions (AAFP) [58] and reasoned following the methodology described in Section 2 (performed by Eye reasoning engine). The medical practice guidelines for the treatment of uUTI were formalized into FCM knowledge model following a number of steps.

Initially, the clinical concepts (i.e. observables, conditions, indications) and therapy concepts, as well as their respective relationships need to be determined. These were extracted manually from medical guidelines using the decision tree approach. Each concept (clinical or therapy) contributes to a node represented in FCM. By this way, all the concepts (clinical and therapy) were defined and we had got them by elementary FCMs. In Appendix B (Fig. B1), we give an example on how from guidelines the respective concepts and rules for the construction of FCM model are extracted. For the examined case problem, forty seven clinical concepts, which represent adverse events, conditions, indications, contraindications, resistances, etc. and eight therapy (decision) concepts that define the antibiotics for uUTI treatment caused by *E. coli* pathogen in adult community were extracted from AAFP guidelines. Table A1 in Appendix gathers all the clinical (input) concepts and Table B1 in Appendix the eight therapy (decision) concepts. It is essential to pinpoint that for each possible treatment of the UTI problem, we constructed elementary FCMs, namely sub-FCMs, which describe each antibiotic therapy according to the initial conditions. Thus, eight (8) sub-FCMs were constructed.

Therefore, the therapy models take as input a set of concepts that respond to the patient's condition and produce the suitable treatments that correspond in the profile of each patient. The concepts within this domain are observables from the scope of a therapy (e.g. indications, contra-indications, relative indications, relative contra-indications etc.). The set of concepts represents the patient's profile, indicating the likely contraindications, side effects or adverse events that a drug/therapy have on patient's organism and harm his health. These concepts are divided in two large categories that describe the patient's health profile. These categories are: the disease that a person can suffer from e.g. kidney insufficient, and conditions that a patient can be; including age, pregnancy, allergies etc.

The impact of a treatment in the patient depends from his diseases and his condition. Each drug has different interaction with the above concepts, which oscillates from very strong positive to very strong negative. The strength of interactions among the concepts (called weights) and the respective treatments/therapies contribute to an interval (from very strong positive to very strong negative) passed from a process of fuzzification where it is judged essential for the knowledge representation and modeling. In this process, we create an escalation of the impact that each concept and therapy has on the patient's health.

For impact assignment of connections from each clinical concept to therapy concepts, IF-THEN rules are needed. This impact between each clinical and therapy concept for each sub-FCM is translated into formal language through the numerical weight produced after defuzzification of the fuzzy weights. These numerical weights in FCM are transferred to semantic weights in N3 in the range [0,1] using Eq. (4), by following the method described in the previous section.

The currently presented formalisms relate solely to the domain of UTI as it has been chosen as proof-of-concept example. For all examined cases and for the proposed therapy module, we have considered that the diagnosis is "acute cystitis" (UTI) and pathogen is "*Escherichia Coli*". Based on these assumptions and on the knowledge facts, a number of fuzzy IF-THEN rules were constructed by available practice guidelines for the treatment management of UTI caused by *E. coli*. 283 rules were extracted from the AAFP guidelines for UTI treatment management. Examples of how the

Table 3
Formalization of Rules using FCMs Implemented in N3.

Knowledge fact	Interpret	Rule form	Formalization in N3
Pregnancy indicates the usage of Nitrofurantoin in UTI	Pregnancy is one of the most important indications of Nitrofurantoin. It is a clear strong positive indication	If the patient is Pregnant Then the proposed therapy is Nitrofurantoin. *The influence between Pregnancy and Nitrofurantoin is pos. very very strong*	`(:Pregnancy:Nitrofurantoin) fl:sigma 0.9`
Neuritis contraindicates the usage of Nitrofurantoin in UTI	Neuritis is a condition whose coexistence with UTI will render the Nitrofurantoin as a possible therapy to not being allowed because it will worsen the symptoms of neuritis. This is a negative outcome. The relationship between Nitrofurantoin and neuritis is not known therefore needs to be estimated using expert opinion. Using the 12 ranges we can determine that it is a strong negative relationship (contra-indication immediately render therapies useless, so they make a strong impact) which can then be estimated according to the given range	If the patient has Neuritis Then the proposed therapy is not Nitrofurantoin. *The influence between Neuritis and Nitrofurantoin is neg. very strong*	`(:Neuritis :Nitrofurantoin) fl:sigma 0.1`
Glucose Metaabsorption contraindicates the usage of TMP/SMX in UTI	Glucose Metabsorption is a condition which does not indicate the use of TMP/SMX due to teratogenic effects that may occur	If the patient has Glucose Metabsorption Then the proposed therapy is not TMP/SMX. *The influence between Glucose Metapsorption and TMP/SMX is neg. very strong*	`(:GlucoseMetabsorption :TMP_SMX) fl:sigma 0.1`
Male gender indicates the usage of Amoxicillin as first line therapy and TMP/SMX as second line therapy	Male is a condition where the Amoxicillin has a very very strong positive indication, and TMP/SMX has a very strong positive indication	If the patient is Male Then the proposed therapy is Amoxicillin (as first line therapy) and the TMP/SMX (as second line therapy). *The influence between Male and Amoxicillin is pos. very very strong. The influence between Male and TMP/SMX is pos. very strong*	`(:Male :Amoxicillin) fl:sigma 1. (:Male :TMP/SMX) fl:sigma 0.9`
Allergy to Amoxicillin contraindicates the usage of Amoxicillin in UTI	This allergy is a condition that excludes the usage of Amoxicillin as therapy. Thus the AllergyToAmoxicillin has a very very strong negative indication to Amoxicillin. Also, AllergyToAmoxicillin has a very very strong positive indication to TMP/SMX	If the patient has AllergyToAmoxicillin Then the proposed therapy is not Amoxicillin. *Actually, the proposed therapies are TMP/SMX as first line therapy and Nitrofurantoin and Fluoroquinolons as second line therapies*	`(:AllergyToAmoxicillin :Amoxicillin) fl:sigma 0. (:AllergyToAmoxicillin :TMP/SMX) fl:sigma 1. (:AllergyToAmoxicillin :Nitrofurantoin) fl:sigma 0.9. (:AllergyToAmoxicillin :Ciprofloxacin) fl:sigma 0.9`

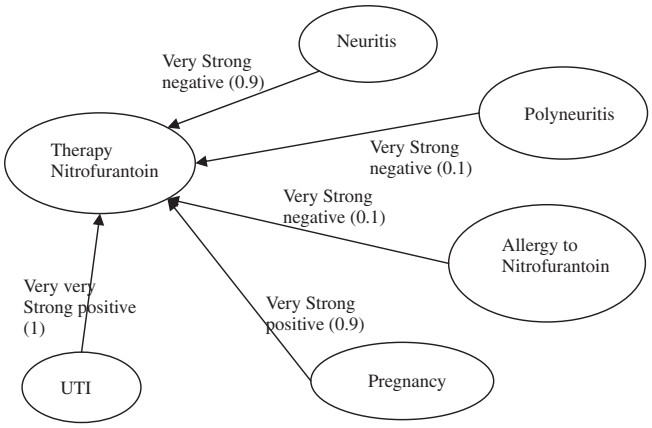


Fig. 3. Urinary tract infection treatment with nitrofurantoin therapy model.

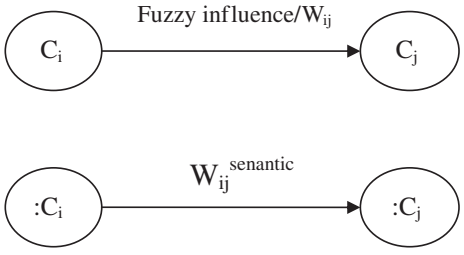


Fig. 4. Fuzzy influences between two concepts (a) in FCM (b) in N3.

rules were extracted from knowledge facts and how they were formalized in N3 are given in Table 4. Table 3 also depicts how the influences between observable and therapy concepts (positive, negative, deterministic, non-deterministic) are implemented in N3. Five examples of knowledge facts and their modeling in semantic web are apposed.

We are going to demonstrate the modelling process for the treatment of UTI with Nitrofurantoin (Fig. 3) by using sub-FCM Nitrofurantoin therapy model as an example. For this therapy case, six observables (which indicate conditions, indications, contra-indications) were considered for the decision of Nitrofurantoin. Each one of the observables has an impact in therapy concept which is interpreted in an IF-THEN rule form and formalized in N3 as established in Table 3.

The N3 code for the formalized Nitrofurantoin model is illustrated at follows:

```
# Nitrofurantoin Therapy Model
@prefix math: http://www.w3.org/2000/10/swap/math#.
@prefix owl: http://www.w3.org/2002/07/owl#.
@prefix fl: http://eulersharp.sourceforge.net/2003/
  03swap/fl-rules#. @prefix : <fcm#>.
(:AgeBelowl2 :Nitrofurantoin) fl:sigma 0.
(:AgeBelowl8 :Nitrofurantoin) fl:sigma 0.4.
(:AgeAbove65 :Nitrofurantoin) fl:sigma 0.4.
(:GenderIsMale :Nitrofurantoin) fl:sigma 0.
(:Neuritis :Nitrofurantoin) fl:sigma 0.01.
(:Polyneuritis :Nitrofurantoin) fl:sigma 0.01.
(:Intersitial_nephritis :Nitrofurantoin) fl:sigma
  0.01.
```

```
(:G6PDDeficiency :Nitrofurantoin) fl:sigma 0.01.
(:KidneyInsufficiency :Nitrofurantoin) fl:sigma
  0.01.
(:KidneyFailure :Nitrofurantoin) fl:sigma 0.01.
(:LungFibrosis :Nitrofurantoin) fl:sigma 0.4.
(:ChronicHepatitis :Nitrofurantoin) fl:sigma 0.4.
(:Cholestasis :Nitrofurantoin) fl:sigma 0.4.
(:AntibiogramAvailab :Nitrofurantoin) fl:sigma
  0.4.
(:PreviousAdministrationOfQuinolones6Mo
  :Nitrofurantoin) fl:sigma 0.6.
(:Pulmonary_fibrosis :Nitrofurantoin) fl:sigma
  0.3.
(:PregnancyBefore28Wk :Nitrofurantoin) fl:sigma
  0.9.
(:PregnancyAfter34Wk :Nitrofurantoin) fl:sigma
  0.9.
(:NursingBabiesWtG6PDDeficiency :Nitrofurantoin)
  fl:sigma 0.
(:NewBornLess3Mo :Nitrofurantoin) fl:sigma 0.
(:AllergyToNitrofurantoin :Nitrofurantoin)
  fl:sigma 0.
(:UrinaryTractInfection :Nitrofurantoin) fl:sigma
  1.
(:EscherichiaColiInfection :Nitrofurantoin)
  fl:sigma 1.
(:resistance_Nitrofurantoinabovel5Pct
  :Nitrofurantoin) fl:sigma 0.
{(?P :resistance_Nitrofurantoinabovel5Pct) fl:mu
  1} => {(:UrinaryTractInfection :Nitrofurantoin)
  fl:sigma 0}.
{(?P :resistance_Nitrofurantoinabovel5Pct) fl:mu
  1} => {(:EscherichiaColiInfection
  :Nitrofurantoin) fl:sigma 0}.
{(?P :AllergyToNitrofurantoin) fl:mu 1} =>
  {(:UrinaryTractInfection :Nitrofurantoin)
  fl:sigma 0}.
{(?P :AllergyToNitrofurantoin) fl:mu 1} =>
  {(:EscherichiaColiInfection :Nitrofurantoin)
  fl:sigma 0}.
```

A concrete example on how the code at the end of the N3 file for this therapy model (Nitrofurantoin) produced is given:

```
IF the patient has Allergy to Nitrofurantoin
THEN Nitrofurantoin is inadequate for UTI caused by
  E. coli infection
```

This rule is translated in N3 using T-rules like:

```
{(?P :AllergyToNitrofurantoin) fl:mu 1} =>
  {(:UrinaryTractInfection :Nitrofurantoin)
  fl:sigma 0}.
{(?P :AllergyToNitrofurantoin) fl:mu 1} =>
  {(:EscherichiaColiInfection :Nitrofurantoin)
  fl:sigma 0}.
```

This is explained as: IF the patient has Allergy to Nitrofurantoin THEN Nitrofurantoin is inadequate for UTI caused by *E. coli* infection, and the most appropriate treatment therapy is TMP/SMX (T7) (however the other therapies except TMP-SMX would be suggested as second-line therapies according to the patients' observables). The tool is investigated to provide therapeutic patterns for first and second line therapies of UTIs. The proposed approach using FCMs establishes the decision for optimal antibiotic selection for patients presenting UTI symptoms and diagnosed for UTI caused only by *E. coli* pathogen [58].

All the input concepts take three discrete values (0, 0.5 or 1) according to the initial patient state. If the patient does not present one or more diseases, conditions, allergies etc. (assigned as input concepts), then the initial values of input concepts are zero (0), in case we do not have knowledge of a specific patient condition (or missing data) then the initial value of its concept is 0.5. In other cases, the initial values of concepts are one (1).

Eye is used by the Decision Support Service for inferring the beliefs in (the need for applying) the therapies given the selected observable. The formalism for describing and inferring on FCM therapy theories is already supported by Eye and has been integrated in the Decision Support Service (see Section 2). In what follows, the therapy model is evaluated depicting the results and providing treatment suggestions of uUTIs caused by *E. coli* for some individual patient cases.

4. Evaluation and results

After the model's construction and implementation in semantic web for UTI treatment management, a number of 55 patient cases on UTI caused by *E. coli* (derived from the General Hospital of Larisa, Greece) were selected from a data set of anonymous patients. More specifically, the fifty five (55) patients were diagnosed with uncomplicated UTI, cystitis, caused by pathogen of *E. coli*. From this data set, 48 patients were female and 7 male, with an average age 48 ± 16 (average ± stdev). Four of the 55 patients had allergy to Ciprofloxacin, two had allergy to Nitrofurantoin, 3 had allergy to Amoxicillin, three were in condition Glucose Metabsorption. Five of 48 female patients were pregnant.

These cases were selected by our doctors/urologists from a 2009-year database of patients diagnosed with different types of UTIs and a medical intervention was given for each one. The criteria that were followed for the selection were the specific type of the disease, which was UTIs, simple cystitis, the type of pathogen, which was *E. coli*, the treatment antibiotic for first or second line therapy, and some conditions, such as known allergies (allergies to TMP/SMX, Fluoroquinolones, Amoxicillin), pregnancy, geriatrics and the route of prescription of antibiotics to be PO (not intravenous).

The decision making capabilities of the technique were presented by simulating these patient cases and finding the predicted treatments (outcomes) according to the available dataset. An important part of fuzzy inference system construction is to check that the obtained treatments' suggestions match the clinical guidelines.

The results presented here follow the steps of the methodology previously described and the inference mechanism of FCMs (link to Eye reasoning engine of eulersharp/plugin). To show how the inference works, let's consider a female patient with age below 18 years old suffers from UTI caused by *E. coli*. The initial state of the patient is described in N3 as follows:

```
@prefix fl: http://eulersharp.sourceforge.net/2003/
  03swap/fl-rules#.
@prefix : <fcm#>.
(:patient001 dco:UrinaryTractInfection) fl:mu 1.
(:patient001 dco:EscherichiaColiInfection) fl:mu
  1.
(:patient001 dco:AgeBelow18) fl:mu 1.
```

The query in N3 is established as follows:

```
@prefix fl:http://eulersharp.sourceforge.net/2003/03swap/
  fl-rules#.
{?X fl:pi ?Y} => {?X fl:pi ?Y}.
```

Then, using the Eye plugin and reasoning engine [http://eulersharp.sourceforge.net/2006/02swap/fcm-plugin.yap], the tool gives the answer for this patient case. We present an overview of the RDF file of the results given by the inference engine supplied via plug-in http://eulersharp.sourceforge.net/2006/02swap/fcm-plugin.yap.

```
#gives the answer for this patient001
(:patient001 :Nitrofurantoin) fl:pi
  0.832018385133924.
(:patient001 :Ciprofloxacine) fl:pi
  0.832018385133924.
(:patient001 :Lomefloxacine) fl:pi
  0.832018385133924.
(:patient001 :Norfloxacine) fl:pi
  0.832018385133924.
(:patient001 :Ofloxacine) fl:pi 0.832018385133924.
(:patient001 :Fosfomycine) fl:pi
  0.832018385133924.
(:patient001 :TMP_SMX) fl:pi 0.3100255188723888.
(:patient001 :Amoxicilline) fl:pi
  0.952574126822433.
```

It is concluded that the patient001 is very likely to receive Amoxicillin as suggested treatment therapy. Amoxicillin is presented as the appropriate therapy for this patient case. Except Amoxicillin as the first line therapy, Nitrofurantoin, Ciprofloxacine, Lomefloxacine, Norfloxacine, Ofloxacine, and Fosfomycin could be also suggested as second-line therapies according to other patient's conditions.

Most of the cases, from the available database were treated with the first line therapy which was the TMP/SMX as it was assigned by clinical practice guidelines. We selected to present seven patient cases with different treatment schemes (see Table 4) to show the validation results of our approach. Two simple (patients #1, #3) and five complex cases were evaluated. The simple scenarios were to demonstrate simple decision behavior of the system while the complex scenarios were to show complicated multi-factorial decision process. Therefore, according to this approach, the rate of "correct" decisions, i.e. the decisions complying with the practice guidelines, were considered as the success rate of the compared models. The success rate of the proposed approach was 91% (50/55 cases).

The proposed therapy models gave an order of possible antibiotic treatments, instead of one, categorizing them to first and second line therapies, as it really happens in clinical practice. The produced therapies from the decision support approach for the antibiotic prescriptions as assigned by guidelines were depicted and compared for the model's validation. A total of 55 simulations for decision making were performed. These simulations run for patients with a certain patient state (for example but certainly not limited to age, conditions, allergies, resistances...) (see Table C1 in Appendix C) together with the selected formal knowledge models leading to the therapy recommendations inferred by the system. Since this work was concerned on the modeling of the treatment guidelines, the results were compared to the recommendations provided by the relevant clinical practice guidelines.

5. Discussion

Aiming to solve the problem of modeling medical knowledge from practice guidelines and to assign antibiotic suggestions, the

Table 4
Results of seven representative patient cases.

Case	Patient observables/conditions	Therapy decisions from FCM		Treatment guidelines	
		Recommend (first line/second line)	No-recommend	Valid recommend	No-recommend
#1	UTI caused by *E. coli* and known allergy to TMP/SMX	**First line** Nitrofurantoin 100 mg PO x 3/day for 5 days Ciprofloxacine 250 mg PO x 2/day during 3 days Lomefloxacine 400 mg PO x 1/day 3 days Norfloxacine 400 mg PO x 2/day 3 days Ofloxacine 200 mg PO x 2/day 3 days **Second line** Fosfomycine trometamol 3 g PO x 1 day Amoxicillin 250–500 mg PO 3/day 10–14 days	TMP/SMX 3 g PO x 2/day 3 days	Nitrofurantoin and Fluoroquinolones as first line therapies, and then Fosfomycin and Amoxicillin as second line therapies	Exclude TMP/SMX due to related allergy

Table 4 (*continued*)

Case	Patient observables/conditions	Therapy decisions from FCM		Treatment guidelines	
		Recommend (first line/second line)	No-recommend	Valid recommend	No-recommend
#2	Pregnant female with UTI caused by *E. coli* and known pregnancy before 14th week	**First line** Nitrofurantoin 100 mg PO x 3/day for 5 days **Second line** Amoxicillin 250–500 mg PO 3/day 10–14 days Alternative second Fosfomycine trometamol 3 g PO x 1 day Ciprofloxacine 250 mg PO x 2/day during 3 days Lomefloxacine 400 mg PO x 1/day 3 days Norfloxacine 400 mg PO x 2/day 3 days Ofloxacine 200 mg PO x 2/day 3 days	TMP/SMX 3 g PO x 2/day 3 days	Nitrofurantoin as first line therapy, Amoxicillin as second line therapy, Fosfomycin and Fluoroquinolones as alternative to second line therapies	Exclude TMP/SMX due to pregnancy and suggest all the other treatments
#3	Male patient with UTI caused by *E. coli*	**First line** Amoxicillin 250–500 mg PO 3/day 10–14 days **Second line** TMP/SMX 3 g PO x 2/day 3 days	Nitrofurantoin 100 mg PO x 3/day for 5 days Fosfomycine trometamol 3 g PO x 1 day Ciprofloxacine 250 mg PO x 2/day during 3 days Lomefloxacine 400 mg PO x 1/day 3 days Norfloxacine 400 mg PO x 2/day 3 days Ofloxacine 200 mg PO x 2/day 3 days	Amoxicillin as first line therapy, TMP/SMX as second line therapy	Exclude Nitrofurantoin, Fosfomycine and four Fluoroquinolones
#4	UTI caused by *E. coli* with allergy Ciprofloxacin and with GlucoseMalabsorbtion	**First line** Nitrofurantoin 100 mg PO x 3/day for 5 days **Second line** Amoxicillin 250–500 mg PO 3/day 10–14 days Lomefloxacine 400 mg PO x 1/day 3 days Norfloxacine 400 mg PO x 2/day 3 days Ofloxacine 200 mg PO x 2/day 3 days Alternative second Fosfomycine trometamol 3 g PO x 1 day	Ciprofloxacine 250 mg PO x 2/day during 3 days TMP/SMX 3 g PO x 2/day 3 days	Nitrofurantoin as first line therapy, Amoxicillin as second line therapy, Fosfomycin as alternative to second line therapies	TMP/SMX must be excluded due to its teratogenic effect Ciprofloxacin is not proper due to the related Allergy. Also the other Fluoroquinolones do not suggested as second line therapies by guidelines **DISAGREEMENT**
#5	UTI caused by *E. coli* with Nursing-AllergyToCiprofloxacine-GlucoseMalabsorbtion-UTI by *E. coli*	**First line** Nitrofurantoin 100 mg PO x 3/day for 5 days	Ciprofloxacine 250 mg PO x 2/day during 3 days	Nitrofurantoin as first line therapy, Amoxicillin as second line therapy, Fosfomycine trometamol as alternative to second line therapy	All the Fluoroquinolones

(*continued on next page*)

Table 4 (*continued*)

Case	Patient observables/conditions	Therapy decisions from FCM		Treatment guidelines	
		Recommend (first line/second line)	No-recommend	Valid recommend	No-recommend
		Second line Amoxicillin 250–500 mg PO 3/day 10–14 days Alternative second Fosfomycine trometamol 3 g PO x 1 day	Lomefloxacine 400 mg PO x 1/day 3 days Norfloxacine 400 mg PO x 2/day 3 days Ofloxacine 200 mg PO x 2/day 3 days		
#6	UTI caused by *E. coli* with AgeBelow18-G6PD_Deficiency-ChronicHepatitis-FructoseIntolerance and Allergy ToNitrofurantoin	Amoxicillin, 250–500 mg PO x 3/day 10–14		Amoxicillin is the only recommended therapy for this case	Nitrofurantoin, TMP/SMX, and Fluoroquinolones due to Age constrains
#7	UTI caused by *E. coli* with Kidney_Failure-PregnancyBefore28Wk-Pulmonary_fibrosis and AllergyToAmoxicillin	**First line** Fosfomycine trometamol 3 g PO x 1 day	TMP/SMX 3 g PO x 2/day 3 days	Fosfomycine trometamol as first line therapy, And Fluoroquinolones and Nitrofurantoin as second line therapies	Exclude TMP/SMX due to pregnancy and Amoxicillin due to related allergy
		Second line Ciprofloxacine 250 mg PO x 2/day during 3 days Lomefloxacine 400 mg PO x 1/day 3 days Norfloxacine 400 mg PO x 2/day 3 days Ofloxacine 200 mg PO x 2/day 3 days Nitrofurantoin 100 mg PO x 3/day for 5 days	Amoxicillin 250–500 mg PO 3/day 10–14 days		

FCM approach was investigated and formalized with the use of semantic web tools. The proposed formal therapy models represent therapeutic patterns. They were designed to aid the physician in selecting the most appropriate therapy for his patient. In these models, observables were defined around the domain of a therapeutic process. Since the same therapy might have different scope and features when applied to different medical conditions and diseases, it is necessary to properly identify the model's scope, which in this case is a therapy-disease combo (e.g. Trimethoprim – UrinaryTractInfection combination where UrinaryTractInfection represents the disease the Trimethoprim therapy is applied to). This "combinational representation" of the domain is necessary in order to ensure that the scope of medical therapy is properly covered. The variables within this domain are observables from the scope of a therapy.

The advantage of this approach is to enable the sharing and reuse of knowledge from databases of guidelines and simplify maintenance. The knowledge base of facts and rules was implemented in the same environment (RDF, N3, Euler, OWL.) without compatibility constraint, which we found it advantageous using semantic web tools. Moreover, the proposed decision support method emerges an advantage over other relevant methodologies, such as the artificial neural networks, logistic regression or even other fuzzy logic-based approaches [60,61], which is that, it resembles human decision making, with its ability to perform approximate reasoning and handle incomplete information. It is easily understandable, even by a nontechnical audience and each of its parameters has a perceivable meaning. Furthermore, the formalization using FCM can be easily altered to incorporate new phenomena and thus adjust its behavior in making decisions.

The goal of our research study was threefold. First EYE inference engine for FCMs reasoning was established. Then, as a result, the N3 notation and logic were used for the implementation of our cognitive maps for knowledge formalization of AAFP clinical guidelines. Finally, a patient database on which we applied the reasoning of our cognitive maps was created and tested for the model's validation.

The obtained results from its evaluation lead to the conclusion, that:

- The Fuzzy Cognitive Maps are appropriate for knowledge representation of guidelines as well as for knowledge management in complex medical tasks.
- The semantic web tools enable the implementation of formalized knowledge in Fuzzy Cognitive Maps taking into account the patient's clinical settings.
- The formalization of knowledge allows a better rendering of medical decision support systems.

In our work, only one source of knowledge based on clinical practice guidelines from AAFP was used. The rules we imple-

mented only concern the community UTIs in adults. Thus, the knowledge from guidelines is not sufficient to produce a dynamic and efficient tool for decision support in real clinical practice and integration of other medical guidelines is needed. In upcoming work, the FCM approach will be extended to include more features, conditions and treatment selections for the therapeutic management.

Future work also includes the construction of more dynamic systems based on the proposed methodology that could be integrating more sources of knowledge and data covering other areas of infectious disease which will allow us to support more realistic decisions and diagnosis. Also, we plan to test our rules on a larger number of data and update it by integrating knowledge of experts and of data mining results.

6. Conclusions

This study presents the results of our investigation on the problem of modeling medical knowledge/ treatment guidelines by capturing the system's behavior for decision support in medicine by using a new methodology of FCMs implemented in semantic web notation 3. More specific, this work employs a decision support tool based on FCM formalism and semantic web approach applied in the case of uncomplicated UTI by suggesting the appropriate antibiotic(s) for each patient case. A number of medical guidelines for the therapy of UTI cystitis were formalized into elementary FCMs that constitute the formal knowledge model. Then the FCMs were implemented in N3, which is an open and semantic language.

The produced therapy models calculate the therapy recommendations for uncomplicated UTIs. The decisions of the therapy models coincide with medical recommendations, and thus the proposed formalization approach exhibits more robust performance regardless of the number of the given input concepts as it considers the missing data and incomplete knowledge inherent in this domain. In all examined patient cases, it is observed that the FCM model recommended efficiently the appropriate order of the selected antibiotics for uncomplicated UTI treatment (first and second line therapies), with a success rate 91% for a pilot-evaluation

Table A1
Theory (observables) concepts of the proposed therapy model.

Observables-concepts (theory name)	Category	Type: condition or disease
C1:AgeBelow12	Contraindication	Condition
C2:AgeBelow18	Contraindication	Condition
C3:AgeAbove65	Contraindication	Condition
C4:GenderIsMale	Indication	Condition
C5: Neuritis	Contraindication	Disease
C6=Polyneuritis	Contraindication	Disease
C7=Intersitial_nephritis	Contraindication	Disease
C8=G6PD_Deficiency	Relative_contraindication	Disease
C9=Kidney_Insufficiency	Relative_contraindication	Disease
C10=Kidney_Failure	Relative_contraindication	Disease
C11=PregnancyBefore28Wk	Indication	Condition
C12=PregnancyBetween28_34Wk	Indication	Condition
C13=PregnancyAfter34Wk_	Indication	Condition
C14=NursingBabiesWtG6PD_Deficiency	Contraindication	Condition
C15=Nursing	Contraindication	Condition
C16=NewBornLess3Mo	Contraindication	Condition
C17=LungFibrosis	Adverse event	Disease
C18=ChronicHepatitis	Contraindication	Disease
C19=Cholestasis	Contraindication	Disease
C20=AntibiogramAvailable	Indication	Condition
C21=PreviousAdministrationQuinolones6Months	Indication	Condition
C22=Epilepsy	Contraindication	Disease
C23=Myasteria Gravis	Contraindication	Disease
C24=Fructose Intolerance	Indication	Disease
C25=GlucoseMetabsorption	Contraindication	Disease
C26=IsomaltaseDeficiency	Contraindication	Disease
C27= Pancreatitis	Contraindication	Disease
C28= Photosensitivity/phototoxicity	Contraindication	Condition
C29= toxic epidermal necrolysis (TEN)	Contraindication	Disease
C30= Leukopenia	Contraindication	Disease
C31= Thrombocytopenia	Contraindication	Disease
C32= HIV	Contraindication	Disease
C33= Pulmonary_fibrosis	Contraindication	Disease
C34=Tetracyclines co_administered	Contraindication	Disease
C35=Allergy ToNitrofurantoin	Indication	Condition
C36=Allergy ToCiprofloxacine	Indication	Condition
C37=Allergy ToLomefloxacine	Indication	Condition
C38=Allergy ToNorfloxacine	Indication	Condition
C39=Allergy ToOfloxacine	Indication	Condition
C40=Allergy ToFosfomycine	Indication	Condition
C41=Resistance to TMP > 10–20% (Allergy To TMP/SMX)	Indication	Condition
C42=Allergy ToAmoxicillin	Indication	Condition
C43=UrinaryTractInfection	Indication	Disease
C44=e_coli_infection	Indication	Pathogen
C45=Resistance to TMP/SMX above 10–20%	Resistance to antibiotics	Condition
C46=Resistance to Fluoroquinolones above 30–50%	Resistance to antibiotics	Condition
C47=Resistance to Nitrofurantoin above 15%	Resistance to antibiotics	Condition

study. Of course, more trials and clinical experiences are needed for a large number of patient cases in order to confirm and/or improve this result.

Acknowledgments

The DebugIT Project (http://www.debugit.eu/) is receiving funding from the European Community's Seventh Framework Programme under Grant agreement n° FP7–217139, which is gratefully acknowledged. The information in this document reflects solely the views of the authors and no guarantee or warranty is given that it is fit for any particular purpose. The European Commission, Directorate General Information Society and Media, Brussels, is not liable for any use that may be made of the information contained therein.

Appendix A. Ontological properties defined for the FCM model

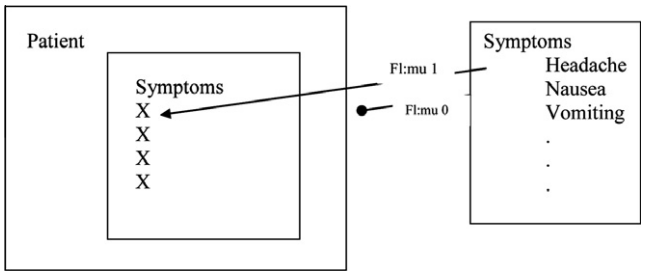
```
### ontology
fl:mu a rdf:Property;
  rdfs:domain rdf:List;
  rdfs:range xsd:decimal;
  rdfs:comment ''to express fuzzy set membership
  e.g. (:x :C) fl:mu 0.8 says
that :x a :C to a degree of 0.8".
```

`fl:mu` is an `rdf:Property` referring to express fuzzy subsethood for each node-concept of the FCM model; (it is also an euler predicate). An example is given:

(:x :C) fl:mu 0.8 says that :x is a :C to a fuzzy membership degree of 0.8.

Distinctly, let's consider a patient with the `SymptomOl` `(:patientOOl :SymptomOl) fl:mu l`

This means that the patient suffers from the `SymptomOl`, and the activation value of FCM concept ''`SymptomOl`'' is 1. The expression `fl:mu` 1 "bridges" the relation between the `SymptomOl` and the `patientOOl` by creating a fuzzy set membership. If the value of the expression `fl:mu` was 0, the entity patient and the subentity `SymptomOl` would be discreet- no relationship between them. This is the way of our system activation, by establishing fuzzy subsethood for each one concept belonging to the FCM model describing patient's disease (see Table A1).



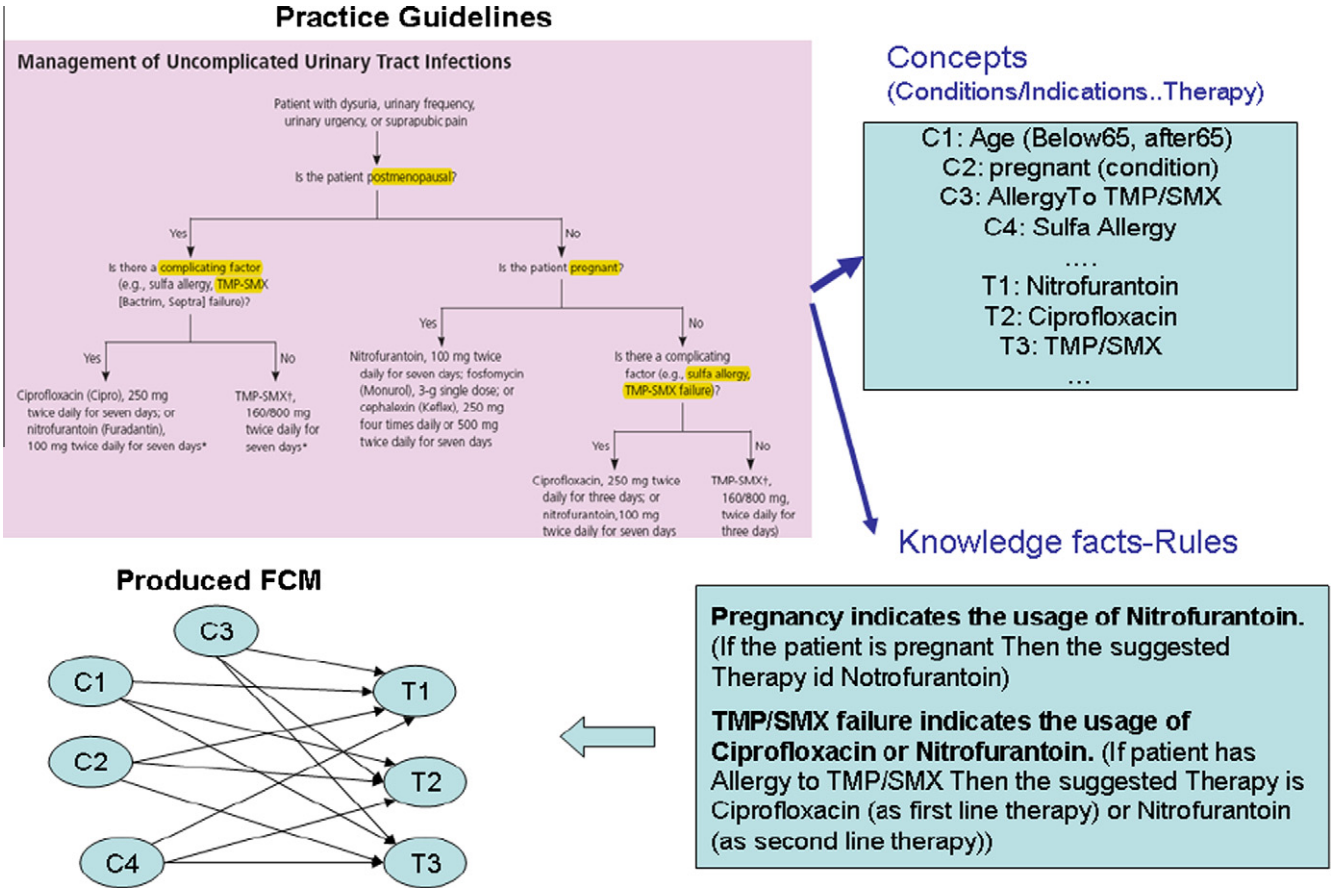


Fig. B1. Knowledge extraction from guidelines∗ using decision tree approach and FCM construction (∗Management of Uncomplicated UTIs derived from the treatment guidelines proposed of the American Academy of Family Physicians [8]).

Table B1
Suggested therapies for UTI based on medical guidelines.

Therapy concept	Theory name	Description
T1-C(45)	T1_Nitrofurantoin_100mg_PO_TID_5D	Nitrofurantoin 100 mg PO x 3/day for 5 days
T2-C(46)	T2_Ciprofloxacin_250mg_PO_BID_3D	Ciprofloxacine 250 mg PO x 2/day during 3 days
T3-C(47)	T3_Lomefloxacin_400mg_PO_UID_3D	Lomefloxacine 400 mg PO x 1/day 3 days
T4-C(48)	T4_Norfloxacin_400mg_PO_BID_3D	Norfloxacine 400 mg PO x 2/day 3 days
T5-C(49)	T5_Ofloxacin_200m_PO_BID_3D	Ofloxacine 200 mg PO x 2/day 3 days
T6-C(50)	T6_Fosfomycin_3g_PO_SingleDose	Fosfomycine trometamol 3 g PO x 1 day
T7-C(51)	T7_TMP_SMX_1Tablet_x2_BID_3D	TMP/SMX 3 g PO x 2/day 3 days
T8- C(52)	T8_Amoxicillin_20_40mg_perKg_perDie_4DivDos	Amoxicillin 250–500 mg PO x 3/day 10–14 days

Table C1
Descriptive Table summarizing the characteristics of all 55 patients together (age, gender, antibiotic, allergy, pathogen, etc.). Columns 2 and 3 display the disease and its MeSH identifier. Column 4 and 5 display the causative pathogen and the treatment. Column 6 is the route of prescription of antibiotic. Column 7 is the dosage of the antibiotic. Column 8 is the frequency of prescription (e.g. q12h means every 12 h). Column 9 is the duration of the treatment (e.g. 5 to 7D means from 5 to 7 days). Column 10 shows additional conditions. Column 11 is the priority of the treatment: 1 for a first choice antibiotic and 2 for an alternative. Column 12 displays the mean age of the patient group.

# Of patients	Gender	Average age	Antibiotic-dosage-route-frequency-duration	Additional conditions, allergies
55 Suffer from Cystitis (MESH D003556) caused by pathogen Escherichia coli	48 female & 7 male	48 ± 16	Nitrofurantoin 100 mg PO x 3/day for 5 days Ciprofloxacine 250 mg PO x 2/day during 3 days Lomefloxacine 400 mg PO x 1/day 3 days Norfloxacine 400 mg PO x 2/day 3 days Ofloxacine 200 mg PO x 2/day 3 days Fosfomycine trometamol 3 g PO x 1 day TMP/SMX 3 g PO x 2/day 3 days Amoxicillin 250–500 mg PO x 3/day 10–14 days	4/55 allergy to Ciprofloxacin, 2/55 allergy to Nitrofurantoin, 3/55 allergy to Amoxicillin, 3/55 were in condition Glucose Metabsorption, 2/55 with chronic hepatitis, 1/55 with kidney failure, 5/48 female were pregnant

```
fl:sigma a rdf:Property;
  rdfs:domain rdf:List;
  rdfs:range xsd:decimal;
  rdfs:comment ‘‘to express fuzzy subsethood e.g.
  (:C :D) fl:sigma 0.9 says
that :C rdfs:subClassOf :D to a degree of 0.9".
```

`fl:sigma` is an `rdf:Property` referring to express fuzzy set membership (that described the strength of relationship), between the interconnected concepts of FCM model; (it is euler predicate). An example is given:

`(:x :C) fl:sigma 0.8`

says that the influence from subject `x` to object `C (:x a :C)` has a degree of 0.8.

A concrete example for FCM diagnosis model is:

`(:SymptomOl :Dl-diagnosis) fl:sigma 0.3.`

This means that the observable ‘‘`SymptomOl`’’ has strength of impact to ‘‘`Dl-diagnosis`’’ equal to 0.3 (which is the numerical value of fuzzy set membership). The value of 0.3 expresses the defuzzified value of weight (strength of relationship) between these two concepts.

```
fl:pi a rdf:Property, e:Builtin;
  rdfs:domain rdf:List;
  rdfs:range xsd:decimal;
  rdfs:comment ‘‘builtin to calculate fuzzy set
  membership according to
Elpiniki Papageorgiou method".
```

`fl:pi` is an euler built-in `rdf:Property` to express the propagation algorithm of FCM (inference process described in section IIB), referring to a number of iterations as it is expressed in Eq. (3). `fl:pi` is a built-in supplied via plug-in http://euler-sharp.sourceforge.net/2006/02swap/fcm-plugin.yap.

Appendix B

See Fig. B1 and Table B1.

Appendix C

See Table C1.

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