Formalization of Clinical Practice Guidelines: Nonalcoholic Steatohepatitis Diagnosis Model-Related Personalized Medicine

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Abstract

Objective: Non-alcoholic fatty liver disease (NAFLD) is a recently recognized entity related to modern lifestyle and with expanded clinical importance because of the rising incidence of obesity and diabetes.

Methods: We have developed a framework for interacting with patient's heterogeneous data (omics, clinical and biological information) and formalizing medical knowledge.

Results: In this paper we present new diagnosis model to predicate NASH. We extracted 18 clinical concepts and these concepts are annotated with SNOMED CT concepts.

We tested our diagnostic model with database of 36 patients. We have a performance of 91%.

Conclusion: This work represents a preliminary step in developing a CDSS and we'll use a clinical database to test this system and to compare it with others statistic reasoning methods.

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1 Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease in the world [1]. NAFLD is a clinical syndrome and is pathologically characterized by diffuse macrovesicular fatty change in the hepatocytes. NAFLD includes simple nonalcoholic fatty liver disease, nonalcoholic steatohepatitis (NASH) and hepatic cirrhosis [2]. NAFLD is a recently recognized entity related to modern lifestyle and with expanded clinical importance because of the rising incidence of obesity and diabetes. NAFLD is an increasingly recognized cause of liver-related morbidity and mortality and it is frequently associated with insulin resistance. While insulin resistance and hyperinsulinemia, are, in large part, metabolic consequences of obesity, the basis of diversity in severity and progression of inflammation and fibrosis is not known [3].

The presence of fat in the liver means the accumulation of triglycerides. This accumulation determines the evolution of the disease. Infiltration of 30% of hepatocytes is an incipient form, the moderate form means that 60% of hepatocytes were infiltrated and severe form induces over 60% of infiltration hepatocytes [4].
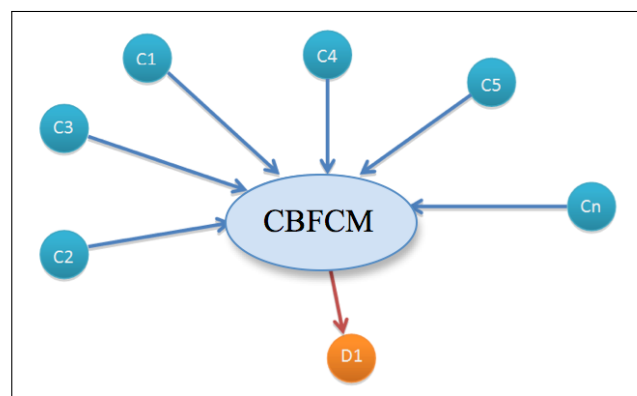

Figure 1: Diagram representing the CBFCM method.

NASH is a disease evolving under the influence of various stimuli still poorly understood. However in this disease, it is well know that insulin resistance is largely implied [5]. Risk factors for NASH/ Fibrosis are: Old over 45 years, Obesity, Diabetes/Insulin resistance, low platelets, low albumin, AST > ALT and imaging signs of hyper portal hypertension.

Several biological Nash prediction tests are developed [6, 7]. The evolution of NAFLD and NASH is variant for each patient and it is important to use all relevant information to diagnose the disease: clinical information, biological test, genomic information and imaging. In this paper we describe a new diagnosis support system based on validated knowledge from scientific literature and clinical practice guidelines (CPG) to diagnose NASH. We tested our diagnostic model with database of 36 patients generated randomly.

2 Methods

We have developed a framework for interacting with patient's heterogeneous data (omics, clinical and biological information) and formalizing medical knowledge.

2.1 CPG Formalization

In the present work we used not only CPG[1] but also scientific literature as sources of knowledge. We have developed a Fuzzy Semantic Web Reasoning approach using the RDF/N3 language to express the rules from the knowledge sources [8]. This approach was previously tested for Infectious diseases diagnosis decision support [9].

2.2 Case Based Fuzzy Cognitive Maps (CBFCM)

Case Based Fuzzy Cognitive Map (CBFCM) is a hybrid decision-making computing technique [10]. CBFCM is represented as nodes (concepts) that illustrate the different aspects of the system's behavior. Concepts may represent variables, states, events, inputs and outputs, which are essential to model a system [11]. The value of each node (concept) is represented as Fuzzy Set. Figure 1 is a graphical representation of CBFCM method. A patient N is described by a set of clinical parameters. These clinical parameters can be clinical signs, age, gender or biological results. CBFCM is validated in many medical areas [12, 13, 14, 15].

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[1]World Gastroenterology Organisation Global Guidelines: Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

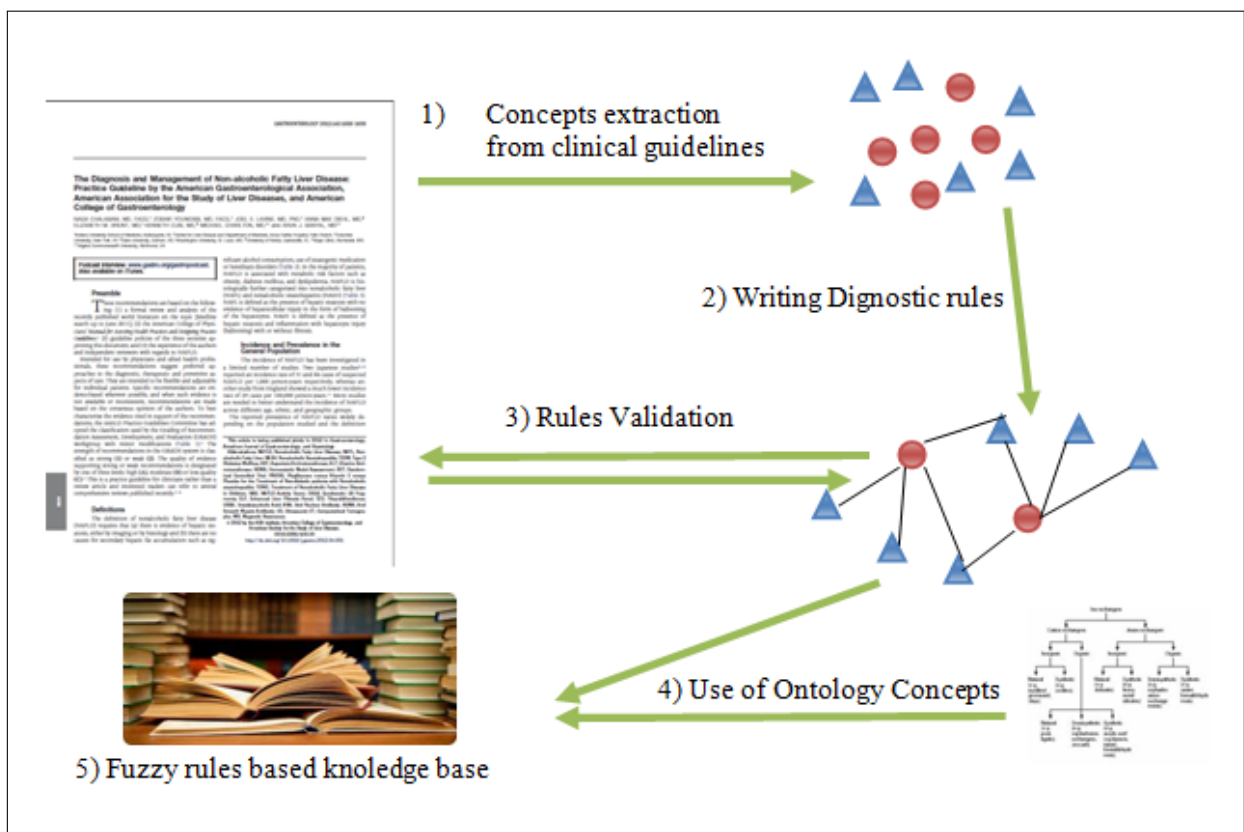http://www.worldgastroenterology.org/assets/export/userfiles/2012 _NASH%20and%20NAFLD_Final_long.pdf

Figure 2: CPG fuzzy formalization method.

Table 1: Clinical concepts of NASH diagnosis model.

Clinical concepts	Label Description	SNOMED CT Concepts ID
C1	Hyperglycemia	80394007
C2	Hypertriglyceridemia	302870006
C3	HDL	9422000
C4	Hypertension	38341003
C5	BMI	60621009
C6	Waist circumference	276361009
C7	Fasting insulin	252251004
C8	Index HOMA-IR	237650006
C9	Alcohol consumption	160580001
C10	ALT	250637003
C11	AST	250641004
C12	Apolipoprotein	259599001
C13	GGT	60153001
C14	Haptoglobin	85294008
C15	α-fetoprotein	16236008
C16	Adiponutrine gene profil	413451007
C17	Old-Age	70753007
C18	Sexe	263495000
D1	NASH	197321007

2.3 Case Based Fuzzy Cognitive Map Reasoning Mechanism

The CBFCM reasoning process follows a number of steps till the system's equilibrium point. These steps can be found in [10, 12] 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 CBFCM 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:

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

Where f is a threshold (activation) function:

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

Where m is a constant parameter [13]. 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.

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 CBFCM reasoning formalism can be used. Based on this assumption, we reformulated eq. (1) as:

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

For example, in Figure 1, the value of a concept "DiagnosisN" is obtained by multiplying the value of each of its input concepts, C_i, by their respective weights, W_{ij}, giving values in [0..1]. These values are then summed as in eq. (1) and eq. (3) and the nonlinear function f is used


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48 (:PatientId0328 snomedct:266468003) fl:pi 0.999959699696969.
49 (:PatientId0329 snomedct:266468003) fl:pi 0.999912345521133.
50 (:PatientId0330 snomedct:266468003) fl:pi 0.998752019938721.
51 (:PatientId0331 snomedct:266468003) fl:pi 0.997674901812091.
52 (:PatientId0329 snomedct:266468003) fl:pi 0.988729171911901.
```

Figure 3: Example of decision rules.

to limit the range of possible output values. The inference follows an iteration process till the system convergence in a steady state (means a state where all the concepts do not change any more their values).

The simulation stops when a limit vector is reached, i.e., when $C_i^k - C_i^{k-1} \leq e$; where e is a residual, whose value depends on the application type (and in most applications is equal to 0.001) [13]. The conclusions based on CBFCM should be viewed together with existing scientific knowledge [14].

The construction of CBFCM [9] is consisting of three parts: (a) to determine concepts and (b) to determine the strength of cognitive relationships between concepts (c) to explicit fuzzy control rules (see Figure 2).

In the semantic web N3 formalism, the weights W_{ij} are in the range $[0, 1]$, each weight (concepts' influences) presents a degree of influence from 0 to 1 [8].

2.4 Information model

The Semantic Web framework based on CBFCM integrate heterogeneous data: clinical data (signs, symptoms. . .), Biological data (lab test. . .), Imaging and Omics data. To create a patient clinical profile we need to use all these types of data. These data are annotated with SNOMED CT concepts. We extracted a related part of SNOMED CT using UMLS.

3 Results

We extracted 18 clinical concepts and these concepts are annotated with SNOMED CT concepts (Table 1). We tested our diagnostic model with database of 36 patients. We have a performance of 91%.

Figure 3 is an example of result rules. This output is N3 triples:PatienIdxxx is the ID of our patients, snomedct:266468003 is a decision concept (NASH) and fl:pi is the confidence degree of the decision (the range value is (0-1))

4 Discussion and Conclusion

The CBFCM approach allowed us to integrate heterogeneous clinical data to perform a personalized patient profile. This method can identify causal relationships between clinical, biological, genetic concepts and decision concept (Diagnosis of NASH). The use of CBFCM enables to incorporate several sources of knowledge (several CPGs, knowledge from literature), which is of great advantage since all knowledge is rarely embedded in a unique CPG. Indeed, knowledge of a medical field is usually broad, complex and closely related to other areas so that several knowledge sources are needed to cover and modeled the medical domain in question.

We have implemented the knowledge bases, rules and databases in the same environment (RDF, N3, Euler. . .) without compatibility constraints; this is one of the ad-

vantages of using Semantic Web tools. The success rate of 91% shows the functionality of the model and its future usefulness in clinical practice.

The conducted study allowed us to test cognitive approaches reasoning to enable personalized medicine. The advantage of this approach is to enable the sharing and reuse of knowledge and simplify maintenance. This work represents a preliminary step in developing a CDSS and we'll use a clinical database to test this system and to compare it with others statistic reasoning methods.

References

[1] Farrell G.C. and Larter C.Z. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. Hepatology 2006; 43:S99–S112

[2] Sanyal AJ. AGA technical review on nonalcoholic fatty liver disease. Gastroenterology 2002;123:1705-25.

[3] Charlton M. Nonalcoholic fatty liver disease: a review of current understanding and future impact. Clin Gastroenterol Hepatol. 2004. 1048-58

[4] James OFW and Day CP. Non-alcoholic steatohepatitis (NASH): a disease of emerging identity and importance. J Hepatol 1998; 29:495 – 501.

[5] Medina J, Fernandez-Salazar LI, Garcia-Buey L, Moreno-Otero R. Approach to the pathogenesis and treatment of nonalco- holic steatohepatitis. Diabetes Care 2004 ; 27 : 2057-66.

[6] Poynard T, Ratziu V, Charlotte F et al. Diagnostic value of biochemical markers (NashTest) for the prediction of non alcoholo steato hepatitis in patients with non-alcoholic fatty liver disease. BMC Gastroenterology 2006, 6:34

[7] Ratziu V, Massard J, Charlotte F, Messous D, Imbert-Bismut F etall. Diagnostic value of biochemical markers (FibroTest-FibroSURE) for the prediction of liver fibrosis in patients with non-alcoholic fatty liver disease. BMC Gastroenterology 2006, 6:6

[8] Douali N, Papageorgiou E, De Roo J, Jaulent MC. Case Based Fuzzy Cognitive Maps: New method for medical reasoning - Fuzzy Systems (FUZZ), 2011 IEEE International Conference on, 844-850

[9] Douali N, De Roo J, Jaulent MC. Clinical diagnosis support system based on case based fuzzy cognitive maps and semantic web. Stud Health Technol Inform. 2012;180:295-9.

[10] Douali N, De Roo J, Jaulent MC. Decision support system based semantic web for personalized patient care. Stud Health Technol Inform. 2012;180:1203-5.

[11] Douali, N., Jaulent, M.Ch. "Genomic and personalized medicine decision support system." Complex Systems (ICCS), 2012 International Conference on. IEEE, 2012.

[12] Douali, N. et al., Diagnosis Support System based on clinical guidelines: comparison between Case-Based Fuzzy Cognitive Maps and Bayesian Networks, Comput. Methods Programs Biomed. (2013), http://dx.doi.org/10.1016/j.cmpb.2013.09.012

[13] Douali, N. et al. "New Semantic Web rules and new medical reasoning framework." Instrumentation and Measurement Technology Conference (I2MTC), 2013 IEEE International. IEEE, 2013.

[14] Douali, N. et al. "Noninvasive Diagnosis of Nonalcoholic Steatohepatitis Disease Based on Clinical Decision Support System." Studies in health technology and informatics 192 (2012): 1178-1178.

[15] Douali, N., Papageorgiou, E. I., De Roo, J., Sun, H., Colaert, D., Jaulent, M. C. (2013, January). Improve treatment of pneumonia and reduce adverse drug events. In Point-of-Care Healthcare Technologies (PHT), 2013 IEEE (pp. 89-92). IEEE.