Artificial Neural Networks in Diagnosis of Liver Diseases

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Abstract. Liver diseases have severe patients' consequences, being one of the main causes of premature death. These facts reveal the centrality of one`s daily habits, and how important it is the early diagnosis of these kind of illnesses, not only to the patients themselves, but also to the society in general. Therefore, this work will focus on the development of a diagnosis support system to these kind of maladies, built under a formal framework based on Logic Programming, in terms of its knowledge representation and reasoning procedures, complemented with an approach to computing grounded on Artificial Neural Networks.

Keywords: Liver disease · Healthcare · Logic Programming · Knowledge representation and reasoning · Artificial neuronal networks

1 Introduction

Liver disease stands for one of the main causes of premature death, with high treatment costs, and the lost of working times [1]. Several factors may be associated to this illness, namely genetic factors, environmental and lifestyle issues (e.g. dietetic, exercise), viruses, obesity, and alcohol [2], or, in other words, alcoholism, autoimmune diseases, hereditary conditions, drugs and exposure to toxins through ingestion, inhalation, or skin absorption, long-term use of certain medications, diabetes, obesity, and even high levels of triglycerides in blood [3, 4]. Indeed, alcoholic disorder and non-alcoholic fatty syndromes are significant causes of chronic liver disease worldwide, i.e., histological lesions that can include steatosis, which may evolve to cirrhosis, and may lead to liver failure. Nonalcoholic steatohepatitis stands for the more severe end of this

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spectrum and is associated with infection progression and the development of liver fibrosis, cirrhosis and hepatocellular carcinoma [5–7].

Physicians usually start with the patient health history, ask about lifestyle habits and may recommend physical examinations, which may include blood, imaging, and/or tissue analysis. Regarding the former one, since liver contains thousands of enzymes, where a few of them are routinely used as indicators of its behaviour, namely ALkaline Phosphatase (ALP), ALanine aminoTransferase (ALT), ASpartate aminoTransferase (AST), Gamma-Glutamyl TransPeptidase (GGTP), 5'-NucleoTidase (5NT), Lactate DeHydrogenase (LDH), serum bilirubin test, albumin test, and even the prothrombin time test [8]. This test may help in measuring the liver's ability to synthesize cells, since most blood clotting factors are produced in the liver. Another commonly test used in this context is the Mean Corpuscular Volume (MCV). It is a measure of the average volume of red blood cells and their increase (macrocytosis) may point out to alcohol abuse and/or other problems [9].

Concerning imaging tests, several modalities are available, like computed tomography, magnetic resonance imaging and endoscopic ultrasonography [8]. Regarding tissue analysis, it consists in collecting a liver tissue sample in order to perform a laboratorial analysis. Liver biopsy remains as the definitive test to confirm the diagnosis of particular liver diseases like the Wilson one. However, this technique is absolutely contra-indicated in patients with inexplicable bleeding history, prothrombine time higher than 3 to 4 s over control, platelets less than 60000/mm^3, prolonged bleeding time, unavailability of blood transfusion support, suspected hemangioma and uncooperative patient behavior [8, 10].

Liver disease is typically asymptomatic until the development of clinical complications. Unfortunately, these snags appear at a relatively late stage of the progression of the disease. Furthermore, most risk factors for liver disease are also risk features for other ones (e.g., excess of alcohol consumption is associated with an increased risk of alcoholic liver disease and breast cancer [11]; obesity is associated with an increased risk of both non-alcoholic fatty liver disease and the coronary heart one [12]).

The stated above shows that it is difficult to make an early diagnosis of liver disease, since it needs to consider different conditions with intricate relations among them, where the available data may be incomplete, contradictory and even unknown. In order to overcome these drawbacks, the present work reports the founding of a computational framework that uses knowledge representation and reasoning techniques to set the structure of the information system and the associate inference mechanisms. We will centre on a Logic Programming based approach to knowledge representation and reasoning [13, 14], and look at a Soft Computing approach to data processing based on Artificial Neural Networks (ANNs) [15].

This paper is organized into five sections. In the former one an introduction to the problem presented is made. Then the proposed approach to knowledge representation and reasoning is introduced. In the third and fourth sections is introduced a case study and presented a solution to the problem. Finally, in the last section the most relevant conclusions are termed and the possible directions for future work are outlined.

2 Knowledge Representation and Reasoning

Many approaches to knowledge representation and reasoning have been proposed using the Logic Programming (LP) epitome, namely in the area of Model Theory [16, 17], and Proof Theory [13, 14]. In this work it is followed the proof theoretical approach in terms of an extension to the LP language. An Extended Logic Program is a finite set of clauses, given in the form:

$$\begin{aligned}\{\ & p \leftarrow p_1, \cdots, p_n, not\ q_1, \cdots, not\ q_m \\ & ?(p_1, \cdots, p_n, not\ q_1, \cdots, not\ q_m)(n, m \geq 0) \\ & exception_{p_1}, \cdots, exception_{p_j}(j \geq 0)\} :: scoring_{value}\end{aligned}$$

where "*?*" is a domain atom denoting falsity, the p_i, q_j, and p are classical ground literals, i.e., either positive atoms or atoms preceded by the classical negation sign ¬ [13]. Under this formalism, every program is associated with a set of abducibles [16, 17], given here in the form of exceptions to the extensions of the predicates that make the program. The term $scoring_{value}$ stands for the relative weight of the extension of a specific *predicate* with respect to the extensions of the peers ones that make the inclusive or global program.

In order to evaluate the knowledge that stems from a logic program, an assessment of the *Quality-of-Information* (*QoI*), given by a truth-value in the interval [0, 1], that stems from the extensions of the predicates that make a program, inclusive in dynamic environments, aiming at decision-making purposes, was set [18, 19]. Indeed, the objective is to build a quantification process of *QoI* and measure one's confidence (here represented as *DoC*, that stands for *Degree of Confidence*) that the argument values of a given predicate with relation to their domains fit into a given interval [20].

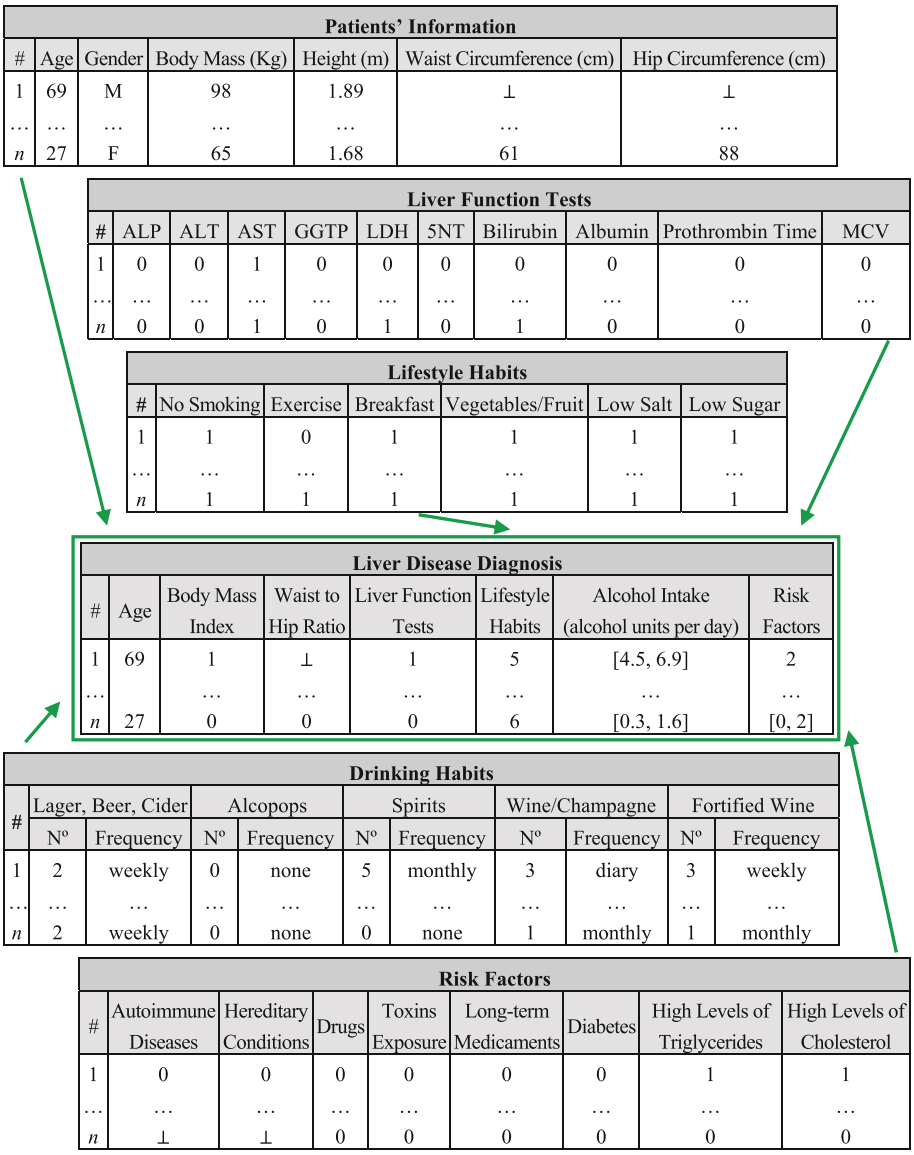
Therefore, the universe of discourse is engendered according to the information presented in the extensions of a given set of predicates, according to productions of the type:

$$predicate_i - \bigcup_{1 \leq j \leq m} clause_j(x_1, \cdots, x_n) :: QoI_i :: DoC_i \tag{1}$$

where ∪ and m stand, respectively, for *set union* and the *cardinality* of the extension of $predicate_i$.

3 A Case Study

As a case study, consider a database given in terms of the extensions of the relations (or tables) depicted in Fig. 1, which stands for a situation where one has to manage information about patients who may suffer from liver diseases. Under this scenario some incomplete and/or default data is also available. For instance, in the *Liver Disease*



Patients' Information

#	Age	Gender	Body Mass (Kg)	Height (m)	Waist Circumference (cm)	Hip Circumference (cm)
1	69	M	98	1.89	⊥	⊥
…	…	…	…	…	…	…
n	27	F	65	1.68	61	88

Liver Function Tests

#	ALP	ALT	AST	GGTP	LDH	5NT	Bilirubin	Albumin	Prothrombin Time	MCV
1	0	0	1	0	0	0	0	0	0	0
…	…	…	…	…	…	…	…	…	…	…
n	0	0	1	0	1	0	1	0	0	0

Lifestyle Habits

#	No Smoking	Exercise	Breakfast	Vegetables/Fruit	Low Salt	Low Sugar
1	1	0	1	1	1	1
…	…	…	…	…	…	…
n	1	1	1	1	1	1

Liver Disease Diagnosis

#	Age	Body Mass Index	Waist to Hip Ratio	Liver Function Tests	Lifestyle Habits	Alcohol Intake (alcohol units per day)	Risk Factors
1	69	1	⊥	1	5	[4.5, 6.9]	2
…		…	…	…	…	…	…
n	27	0	0	0	6	[0.3, 1.6]	[0, 2]

Drinking Habits

#	Lager, Beer, Cider		Alcopops		Spirits		Wine/Champagne		Fortified Wine	
	Nº	Frequency	Nº	Frequency	Nº	Frequency	Nº	Frequency	Nº	Frequency
1	2	weekly	0	none	5	monthly	3	diary	3	weekly
…	…	…	…	…	…	…	…	…	…	…
n	2	weekly	0	none	0	none	1	monthly	1	monthly

Risk Factors

#	Autoimmune Diseases	Hereditary Conditions	Drugs	Toxins Exposure	Long-term Medicaments	Diabetes	High Levels of Triglycerides	High Levels of Cholesterol
1	0	0	0	0	0	0	1	1
…	…	…	…	…	…	…	…	…
n	⊥	⊥	0	0	0	0	0	0

Fig. 1. An extension of the relational model for liver diseases diagnosis.

Diagnosis table, the *Waist to Hip Ratio* in case 1 is unknown, while the *Alcohol Intake* ranges in the interval [4.5, 12.9].

In *Liver Function Tests* table, 0 (zero) and 1 (one) denote, respectively, *normal* and *abnormal* values. In *Lifestyle Habits* and *Risk Factors* tables, 0 (zero) and 1 (one) denote, respectively, *no* and *yes*. In *Drinking Habits* table *N* stands for the number of beverages consumed.

Table 1. Waist to hip ratio and disease risk related to obesity, stratified by age and gender.

Age (years)	Men				Women			
	Low	Moderate	High	Very high	Low	Moderate	High	Very high
[20,30[	< 0.83	[0.83, 0.89[	[0.89, 0.94[	≥ 0.94	< 0.71	[0.71, 0.78[	[0.78, 0.82[	≥ 0.82
[30,40[	< 0.84	[0.84, 0.92[	[0.92, 0.96[	≥ 0.96	< 0.72	[0.72, 0.79[	[0.79, 0.84[	≥ 0.84
[40,50[	< 0.88	[0.88, 0.96[	[0.96, 1.00[	≥ 1.00	< 0.73	[0.73, 0.80[	[0.80, 0.87[	≥ 0.87
[50,60[	< 0.90	[0.90, 0.97[	[0.97, 1.02[	≥ 1,02	< 0.74	[0.74, 0.82[	[0.82, 0.88[	≥ 0.88
≥60	< 0.91	[0.91, 0.99[	[0.99, 1.03[	≥ 1,03	< 0.76	[0.76, 0.84[	[0.84, 0.90[	≥ 0.90

In the *Liver Disease Diagnosis* table, the domain of *Body Mass Index* column is in the range [0, 2], wherein 0 (zero) denotes $BMI < 25$; 1 (one) stands for a *BMI* ranging in interval [25, 30[; and 2 (two) denotes a $BMI \geq 30$. The *Body Mass Index* (*BMI*) is evaluated using the equation $BMI = BodyMass/Height^2$ [21]. *Waist to Hip Ratio* column ranges in the interval [0, 3] according to Table 1, adapted from [22], wherein 0 (zero), 1 (one), 2 (two) and 3 (three) denote disease risk related to obesity, in terms of a qualification of *low*, *moderate*, *high* and *very high*.

The alcohol units for most common beverage were calculated in terms of Eq. 2, according to what is set in [23, 24], while the values of the *Alcohol Intake* column of *Liver Disease Diagnosis* table was calculated using Eq. 3.

$$Alcohol\ Units = Alcohol\ by\ Volume(\%) * Volume\left(cm^3\right)/1000 \tag{2}$$

$$Alcohol\ Intake = \sum_{\substack{beverage \\ types}} N * Frequency\ Factor * Alcohol\ Units \tag{3}$$

where *N* stands for the number of beverages consumed. The frequency factor is 1, 1/7, 1/30 and 0 depending on the intake frequency, i.e., daily, weekly, monthly or none.

The values presented in the remaining columns of *Liver Disease Diagnosis* table are the sum of the ones of the correspondent tables, ranging between [0, 10], [0, 6] and [0, 8], respectively for *Liver Function Tests*, *Lifestyle Habits* and *Risk Factors* columns.

Now, we may consider the relations given in Fig. 1, in terms of the extension of the *liver disease diagnosis* predicate, depicted in the form:

$$
\begin{aligned}
&\{\\
&\quad \neg liver_{disease\_diagnosis}(Age, BMI, W/H, LFT, LH, AIn, RF)\\
&\qquad\qquad \leftarrow not\ liver_{disease\_diagnosis}(Age, BMI, W/H, LFT, LH, AIn, RF)\\
&\quad liver_{disease\_diagnosis}\Big(\underbrace{1,\ 1,\ 0,\ 1,\ 1,\ 0.99,\ 1}_{attribute`s\ confidence\ values}\Big) :: 1 :: 0.86\\
&\qquad\qquad \underbrace{[0.7,0.7][0.5,0.5][0,1][0.1,0.1][0.8,0.8][0.2,0.3][0.25,0.25]}_{attribute`s\ values\ ranges\ once\ normalized}\\
&\qquad\qquad \underbrace{[0,1]\ [0,1]\ [0,1]\ [0,1]\ [0,1]\ [0,1]\ [0,1]}_{attribute`s\ domains\ once\ normalized}\\
&\ldots\\
&\}:: 1
\end{aligned}
$$

where its argument's values make the training and test sets of the Artificial Neural Network (ANN) given in Fig. 2. Now, let us consider a patient that presents the symptoms $Age = 58$, $BMI = \perp$, $W/H = 2$, $LFT = 2$, $LH = 3$, $AIn = [4.5, 13.1]$, $RF = 3$, to which it is applied the procedure presented in [20]. One may have:

$$
\begin{aligned}
&\{\\
&\quad \neg liver_{disease\_diagnosis}(Age, BMI, W/H, LFT, LH, AIn, RF)\\
&\qquad\qquad \leftarrow not\ liver_{disease\_diagnosis}(Age, BMI, W/H, LFT, LH, AIn, RF)\\
&\quad liver_{disease\_diagnosis}\Big(\underbrace{1,\ 0,\ 1,\ 1,\ 1,\ 0.91,\ 1}_{attribute`s\ confidence\ values}\Big) :: 1 :: 0.84\\
&\}:: 1
\end{aligned}
$$

4 Artificial Neural Networks

It was set a soft computing approach to model the universe of discourse of any patient suffering from liver disease, based on ANNs, which are used to structure data and capture complex relationships between inputs and outputs [25, 26]. ANNs simulate the structure of the human brain, being populated by multiple layers of neurons, with a valuable set of activation functions. As an example, let us consider the case listed above, where one may have a situation in which the diagnosis of liver disease is needed. In Fig. 2 it is shown how the normalized values of the interval boundaries and their DoC_s and QoI_s values work as inputs to the ANN. The output depicts a liver disease diagnostic, plus the confidence that one has on such a happening.

In this study 438 patients were considered with an age average of 65.4 years, ranging from 22 to 93 years old. Liver diseases was diagnosed in 73 cases, i.e., in

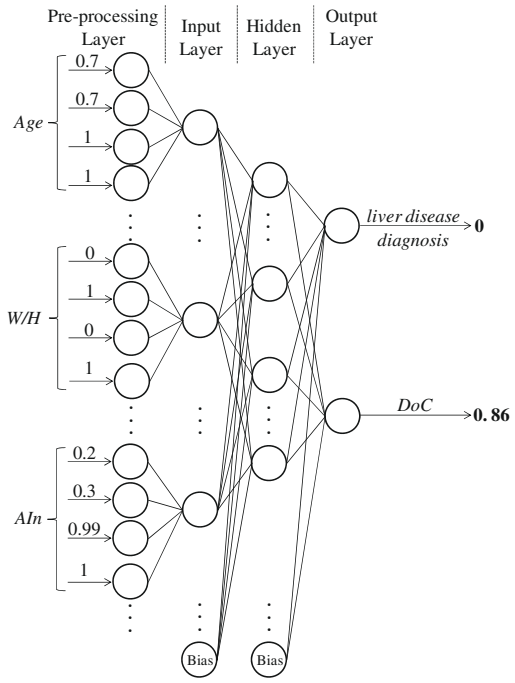


Fig. 2. The artificial neural network topology.

16.7 % of the analysed population. The gender distribution was 41.6 % and 58.4 % for female and male, respectively.

In each simulation, the available data was randomly divided into two mutually exclusive partitions, i.e., the training set with 70 % of the available data, used during the modeling phase, and the test set with the remaining 30 % of the cases, used after training in order to evaluate the model performance and to validate it. The back propagation algorithm was applied in the learning process of the ANN. The activation function used in the pre-processing layer was the identity one. In the other layers was used the sigmoid activation function.

A common tool to evaluate the results presented by the classification models is the coincidence matrix, a matrix of size $L \times L$, where L denotes the number of possible classes. This matrix is created by matching the predicted and target values. L was set to 2 (two) in the present case. Table 2 presents the coincidence matrix (the values denote the average of the 30 runs). A perusal of Table 2 shows that the model accuracy was 96.1 % for the training set (296 correctly classified in 308) and 95.4 % for test set (124 correctly classified in 130).

Based on coincidence matrix it is possible to compute sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of the classifier. Briefly, sensitivity and specificity are measures of the performance of a binary classifier. Sensitivity evaluates the proportion of true positives that are correctly identified as such, while specificity translates the proportion of true negatives that are correctly

Table 2. The coincidence matrix for ANN model.

Target	Predictive			
	Training set		Test set	
	True (1)	False (0)	True (1)	False (0)
True (1)	49	3	20	1
False (0)	9	247	5	104

identified. Moreover, it is necessary to know the probability of the classifier that give the correct diagnosis. Thus, it is also calculated both PPV and NPV, while PPV stands for the proportion of cases with positive results which are correctly diagnosed, NPV is the proportion of cases with negative results which are successfully labeled. The sensitivity ranges from 94.2 % to 95.2 %, while the specificity ranges from 95.4 % to 96.5 %. PPV ranges from 80.0 % to 84.4 %, while NPV ranges from 98.8 % to 99.0 %. Thus, it is our claim that the proposed model is able to diagnosis liver diseases properly. The inclusion of other patient's characteristics, like lifestyle and drink habits may be responsible for the good performance exhibited by the presented model.

5 Conclusions and Future Work

Diagnosing *liver disease* has shown to be a hard task. On the one hand, the parameters that cause the disorder are not fully represented by objective data. On the other hand, liver disease is asymptomatic until the development of clinical complications that are manifested at a relatively late stage of the progression of the disease. Therefore, it is mandatory to consider many different conditions with intricate relations among them. These characteristics put this problem into the area of problems that may be tackled by Artificial Intelligence based methodologies and techniques to problem solving.

This work presents the founding of a computational framework that uses powerful knowledge representation and reasoning techniques to set the structure of the information and the associate inference mechanisms. This finding is built on a set of presuppositions, namely:

- Data is not equal to information;
- The translation of the raw measurements into interpretable and actionable read-outs is challenging; and
- Read-outs can deliver markers and targets candidates without pre-conception, i.e., knowing how personal conditions and risk factors may affect the liver disease predisposition.

The knowledge representation and reasoning techniques presented above are very versatile and capable of covering almost every possible instance, namely by considering incomplete, contradictory, and even unknown data, a marker that is not present in existing systems. Indeed, this method brings a new approach that can revolutionize prediction tools in all its variants, making it more complete than the existing methodologies and tools for problem solving. The new paradigm of knowledge

representation and reasoning enables the use of the normalized values of the interval boundaries and their *DoC* values, as inputs to the ANN. The output translates a diagnosis of liver disease and the confidence that one has on such a happening.

The main contribution of this work relies on the fact that at the end, the extensions of the predicates that make the universe of discourse are given in terms of *DoCs* values that stand for one's confidence that the predicates arguments values fit into their observable ranges, taking into account their domains. It also encapsulates in itself a new vision of Multi-value Logics, once a proof of a theorem in a conventional way, is evaluated to the interval [0, 1]. Future work may recommend that the same problem must be approached using others computational frameworks like Case Based Reasoning [27], Genetic Programming [14] or Particle Swarm [28], just to name a few.

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