A Many-Valued Empirical Machine for Thyroid Dysfunction Assessment

Sofia Santos[1], M. Rosário Martins[2], Henrique Vicente[3,4](✉), M. Gabriel Barroca[5], Fernando Calisto[5], César Gama[5], Jorge Ribeiro[6], Joana Machado[7], Liliana Ávidos[8], Nuno Araújo[8], Almeida Dias[8], and José Neves[4]

[1] Departamento de Química, Escola de Ciências e Tecnologia, Universidade de Évora, Évora, Portugal
[2] Departamento de Química, Escola de Ciências e Tecnologia, Laboratório HERCULES, Universidade de Évora, Évora, Portugal
[3] Departamento de Química, Escola de Ciências e Tecnologia, Centro de Química de Évora, Universidade de Évora, Évora, Portugal
hvicente@uevora.pt
[4] Centro Algoritmi, Universidade do Minho, Braga, Portugal
jneves@di.uminho.pt
[5] SYNLAB Alentejo, Évora, Portugal
[6] Escola Superior de Tecnologia e Gestão, ARC4DigiT – Applied Research Center for Digital Transformation, Instituto Politécnico de Viana do Castelo, Viana do Castelo, Portugal
[7] Farmácia de Lamações, Braga, Portugal
[8] CESPU, Instituto Universitário de Ciências da Saúde, Gandra, Portugal

Abstract. *Thyroid Dysfunction* is a clinical condition that affects thyroid behaviour and is reported to be the most common in all endocrine disorders. It is a multiple factorial pathology condition due to the high incidence of hypothyroidism and hyperthyroidism, which is becoming a serious health problem requiring a detailed study for early diagnosis and monitoring. Understanding the prevalence and risk factors of thyroid disease can be very useful to identify patients for screening and/or follow-up and to minimize their collateral effects. Thus, this paper describes the development of a decision support system that aims to help physicians in the decision-making process regarding thyroid dysfunction assessment. The proposed problem-solving method is based on a symbolic/sub-symbolic line of logical formalisms that have been articulated as an *Artificial Neural Network* approach to data processing, complemented by an unusual approach to *Knowledge Representation and Argumentation* that takes into account the data elements entropic states. The model performs well in the thyroid dysfunction assessment with an accuracy ranging between 93.2% and 96.9%.

Keywords: Thyroid dysfunction · Knowledge Representation and Reasoning · Artificial Neural Networks · Entropy · Logic Programming · Many-Valued Empirical Machine

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1 Introduction

Thyroid is an endocrine gland that produces *Tri-iodothyronine* (*T3*), *Thyroxine* (*T4*) and *Calcitonin*. The *Thyroid Stimulating Hormone* (*TSH*), released by pituitary gland, controls the thyroid secretion [1]. Thyroid hormones play a key role in most tissues, including maintenance of cognitive, cardiovascular, bone healthiness, metabolism and body energy balance functions [2]. Main representative thyroid diseases include hypothyroidism, hyperthyroidism, goiter, and autoimmune diseases such as Hashimoto's thyroiditis or Graves' disease, and thyroid cancer [3].

Thyroid Dysfunctions (*TDs*) are the most common of all endocrine disorders. On average, about 30% to 40% of TD patients are silent and affect more than one million Portuguese and 300 million people worldwide [4, 5]. About 11% of Europeans have *TDs* and only 50% are aware of their condition [5]. The causes of *TDs* are diverse and often associated with genetic factors and iodine levels that play an important role in thyroid hormone regulation, often with a geographical pattern [1]. *TDs* have a higher incidence in female individuals aged 20–75 years old, a tendency that increases with age [5]. *Nutrition* also affects *TDs*, namely legumes such as cabbage, cauliflower, broccoli, goitrogens and soy enriched feed, once reduce *T4* absorption [6]. Thyroid function can also be influenced by green tea high doses intake [7]. Thyroid pathologies quickly change the patient's emotional state, which can be overactive, with anxiety or underactive, with depression. Sleep disorders with poor concentration and short-term memory can occur, most commonly with hypofunction of the thyroid gland. These disorders can cause differences in appearance, such as weight gain or weight loss that may affect self-esteem [1, 3]. Other risk factors may include race differences, cigarette smoking or ambient temperature, namely cold weather, just to name a few [8].

The development of decision support systems for predicting, analyzing and evaluating *TDs* may be an asset to medical personnel, particularly in order to define the finest type of treatment. Such systems are based on features derived from parameters of thyroid markers according to a series of historical data that fed a Proof Theoretical problem-solving line [9], leading to real procedures that pass through *Artificial Neural Networks* (*ANNs*) approaches to computing [10, 11]. Thus, the present work describes the development of a decision support system that aims to assess the thyroid dysfunction and help physicians in the decision-making process. Behind a technical component, (e.g., issues related with symptomatology, risk factors and the levels of the thyroid biomarkers) such system also includes the behavioral and the psychological dimensions. It is grounded on a *Logic Programming* (*LP*) approach to *Knowledge Representation* and *Reasoning* (*KRR*) [9], and complemented by a computer framework centered on *Artificial Neural Networks* (*ANN*s).

The article is divided into four sections. The former one defines the goals and the context of the work, followed by a section where one's approach to *KRR* is the object of attention. The next section presents the case study and a possible solution to the problem using *ANNs*. Finally, a conclusion is set and guidelines for future work are outlined.

2 Theoretical Fundamentals

2.1 Knowledge Representation and Reasoning

Knowledge Representation and Reasoning aims to understand the complexity of the information and the associated inference mechanisms. In this study, a data item is to be understood to be slightly smaller in the interior, when it disassembles something, i.e., it is formed mainly of different elements, namely its *Entropic State Range* (*ESR*), *ESR's Quality-of-Information* (*QoI*), *Degree-of-Confidence* (*DoC*) that the unknown *Entropic State Value* (*ESV*) fits into the *ESR*, and the *ESR Potential of Empowerment* (*PE*). These are just a set of over an endless item number. It is put in terms of a set of predicates that elicit the universe of discourse, whose extensions are given as productions of the type, viz.

$$\{$$

$$\neg\, p \leftarrow not\ p, not\ exception_p$$

$$p \leftarrow p_1, \cdots, p_n, not\ q_1, \cdots, not\ q_m$$

$$?\,(p_1, \cdots, p_n, not\ q_1, \cdots, not\ q_m)\ \ (n, m \geq 0)$$

$$exception_{p_1}, \ \cdots \ , exception_{p_j}\ \ (0 \leq j \leq k),\ \ being\ k\ an\ integer\ number$$

$$\} :: entropic\ state$$

where the p_s and q_s are makings of the kind, viz.

$$predicate_{1 \leq i \leq n} - \bigwedge_{1 \leq j \leq m} clause_j \left(\left([ES_{x_1}, ES_{y_1}](QoI_{ESR}, DoC_{ESR}, PE_{ESR}) \right), \cdots \right.$$

$$\left. \cdots, \left([ES_{x_m}, ES_{y_m}](QoI_{ESR}, DoC_{ESR}, PE_{ESR}) \right) \right) :: QoI_j :: DoC_j :: PE_j$$

where n, Λ and m stand for, respectively, the cardinality of the predicates' set, logical conjunction, and predicate's extension cardinality. The items $[ES_{x_m},\ ES_{y_m}]$, QoI_{x_m}, DoC_{x_m} and PE_{x_m} show the way to data item dissection [12, 13], i.e., a data item is to be understood as having an atomic structure. It consists of identifying not only all the sub items that make up an item, but also to investigate the rules that oversee them, i.e., how $[ES_{x_m},\ ES_{y_m}]$, QoI_{x_m}, DoC_{x_m} and PE_{x_m} are kept together and how much added value is therefore created. Indeed, the *ESR* stands for a measure of the unavailable energy in a closed thermodynamic system, i.e., a process of degradation, running down or a trend to disorder, and is given by dark colored areas in Fig. 1. Areas with a gray color indicate a relaxation in the central values, i.e., the corresponding energy values may or may not have been spent. Finally, the *PE* is given by the white areas, and represents an energetic potential that may be available.

2.2 Assessing a Qualitative Data Item in Terms of Its Quantitative Counterpart

In present study both qualitative and quantitative data are present. Taking as an example a set of *3* issues regarding a particular subject, where there are *3* possible options (e.g., *low* · *medium* · *high*), which are itemized as a unitary area circle split into 3 (three) slices, being the marks in the axis resembling each of the possible options, viz (Fig. 1).

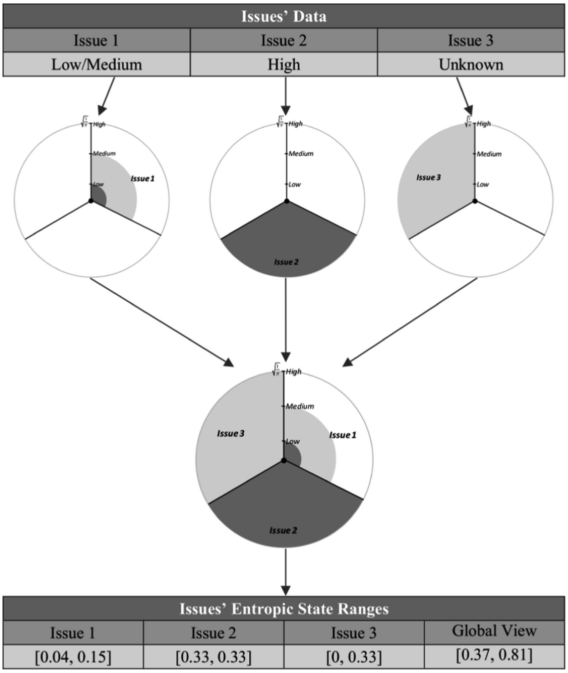


Fig. 1. Going from Qualitative to Quantitative data items.

2.3 Artificial Neural Networks

When one looks to new approaches to problem solving, namely those borrowed from the *Artificial Intelligence* arena which have proven their ability and applicability in terms of prediction, simulation and modeling of physical phenomena, one comes to *ANNs* [11]. *ANNs* are able to capture the embedded spatial and unsteady behavior in the investigated problem, using its architecture and nonlinearity nature, when compared with the other classical problem-solving techniques [10]. Indeed, several decision support systems based on *ANNs* have been applied to various problems in the medical field, namely in cardiovascular diseases, cancer, diabetes or Alzheimer, just to name a few [12–14].

3 Case Study

3.1 Data Collection

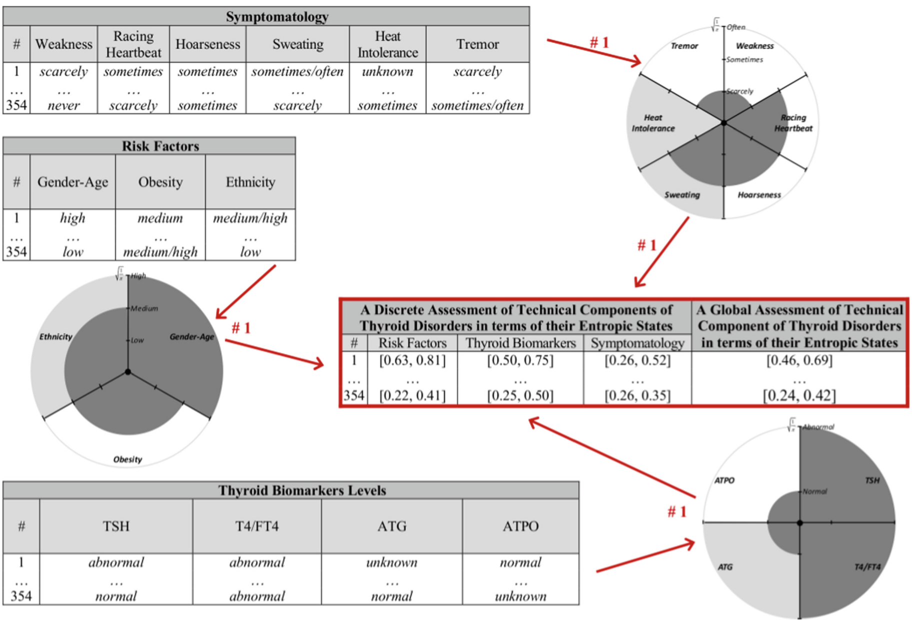
The knowledge base includes 354 patients aged between 17 to 98 years old, with an average of 57 ± 17 years old. The gender distribution was 26.6% and 73.4% for male and female, respectively. It was observed that 7% of the population presented a clinical picture suggestive of *TDs*. The parameters of the thyroid markers used in this study were obtained at the SYNLAB-Évora laboratory from June 1st to December 31st, 2017.

The dataset holds information about the factors considered critical in the prediction of *TDs*. These variables were grouped into three takes on, i.e., *Technical*, *Behavioral* and *Psychological* components. The former component considers thyroid biomarkers levels, clinical condition of the patient and relevant risk factors. The second includes issues linked to patients' routines (e.g., dietary and lifestyle) as well as the response to the therapy. Finally, the psychological component comprises mental and emotional features related with the disease and/or treatment.

The Technical Component. This component gathers information related with *Risk Factors*, *Thyroid Biomarkers* and *Symptomatology* (Fig. 2). The issues related with *Risk Factors*, *Thyroid Biomarkers Levels* and *Symptomatology* were valuated according to the scales *low* · *medium* · *high*; *normal* · *abnormal*; and *none* · *scarcely* · *sometimes* · *often*, respectively (Fig. 2).

The evaluation of the $\left[ES_{x_m}, ES_{y_m}\right]$, QoI_{x_m}, DoC_{x_m} and PE_{x_m} parameters to each patient, in terms of the p_s and q_s (Sect. 2.1), is illustrated in Fig. 3 to *patient # 1* for the argument *Sweating* of the relation *Symptomatology*.

The Behavioral Component. This component includes issues regarding *Lifestyle*, *Adherence to Treatment* and *Dietary* (Fig. 4). The items related with *Lifestyle* and *Dietary* were valuated according to the scale *none* · *scarcely* · *sometimes* · *often*, while the scale used to evaluate the *Thyroid Biomarkers Levels* were *low* · *medium* · *high* (Fig. 4). The evaluation of the $\left[ES_{x_m}, ES_{y_m}\right]$, QoI_{x_m}, DoC_{x_m} and PE_{x_m} parameters to each patient followed the procedures described above.



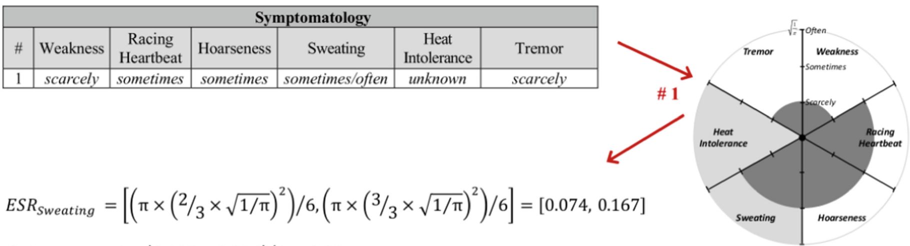
Symptomatology						
#	Weakness	Racing Heartbeat	Hoarseness	Sweating	Heat Intolerance	Tremor
1	*scarcely*	*sometimes*	*sometimes*	*sometimes/often*	*unknown*	*scarcely*
…	…	…	…	…	…	…
354	*never*	*scarcely*	*sometimes*	*scarcely*	*sometimes*	*sometimes/often*

Risk Factors			
#	Gender-Age	Obesity	Ethnicity
1	*high*	*medium*	*medium/high*
…	…	…	…
354	*low*	*medium/high*	*low*

Thyroid Biomarkers Levels				
#	TSH	T4/FT4	ATG	ATPO
1	*abnormal*	*abnormal*	*unknown*	*normal*
…	…	…	…	…
354	*normal*	*abnormal*	*normal*	*unknown*

A Discrete Assessment of Technical Components of Thyroid Disorders in terms of their Entropic States				A Global Assessment of Technical Component of Thyroid Disorders in terms of their Entropic States
#	Risk Factors	Thyroid Biomarkers	Symptomatology	
1	[0.63, 0.81]	[0.50, 0.75]	[0.26, 0.52]	[0.46, 0.69]
…	…	…	…	…
354	[0.22, 0.41]	[0.25, 0.50]	[0.26, 0.35]	[0.24, 0.42]

Fig. 2. The extension of the knowledge base for *Technical Component*.



Symptomatology						
#	Weakness	Racing Heartbeat	Hoarseness	Sweating	Heat Intolerance	Tremor
1	*scarcely*	*sometimes*	*sometimes*	*sometimes/often*	*unknown*	*scarcely*

$$ESR_{Sweating} = \left[\left(\pi \times \left(2/3 \times \sqrt{1/\pi}\right)^2\right)/6, \left(\pi \times \left(3/3 \times \sqrt{1/\pi}\right)^2\right)/6\right] = [0.074, 0.167]$$

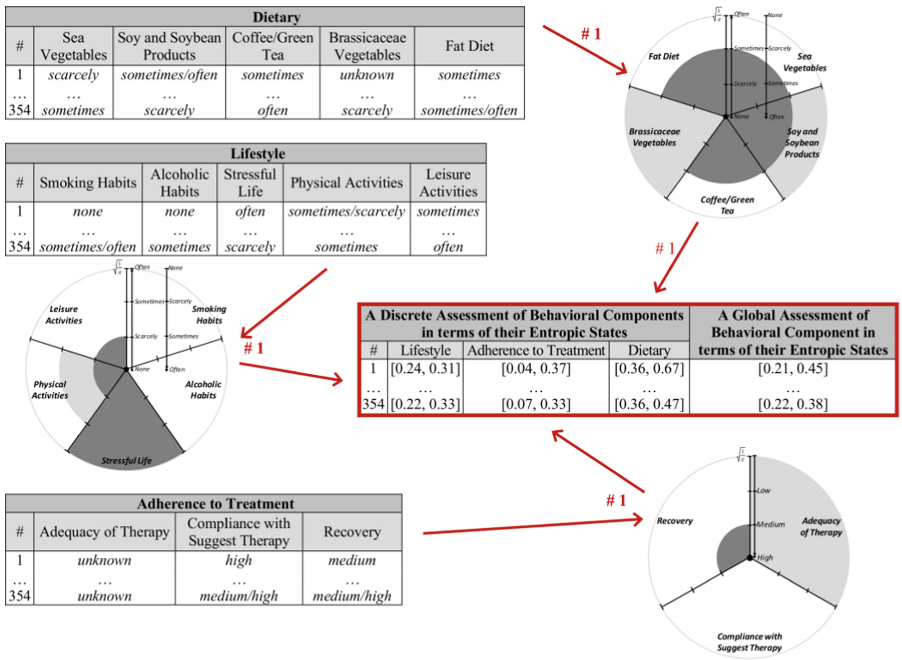
$$QoI_{Sweating} = 1 - |0.167 - 0.074|/1 = 0.91$$

$$DoC_{Sweating} = \sqrt{1 - (0.167 - 0.074)^2} = 0.99$$

$$PE_{Sweating} = \left[1/6 - 0.167, \ 1/6 - 0.074\right] = [0, 0.093]$$

Fig. 3. Evaluation of ESR_{x_m} QoI_{x_m}, DoC_{x_m} and PE_{x_m} parameters to *patient # 1* for the argument *Sweating* of the relation *Symptomatology*.

The Psychological Component. This component comprises psychological features related with *Mental Problems*, *Self-Esteem Damage* and *Emotional Disorders*. *Emotional Disorders* and *Mental Problems* were valuated according to the scale *none* · *scarcely* · *sometimes* · *often*, while the items regarding *Self-Esteem Damage* were valuated according to the scale *low* · *medium* · *high* (Fig. 5). As previously, the $\left[ES_{x_m}, ES_{y_m}\right]$, QoI_{x_m}, DoC_{x_m} and PE_{x_m} parameters were evaluated in the same way.



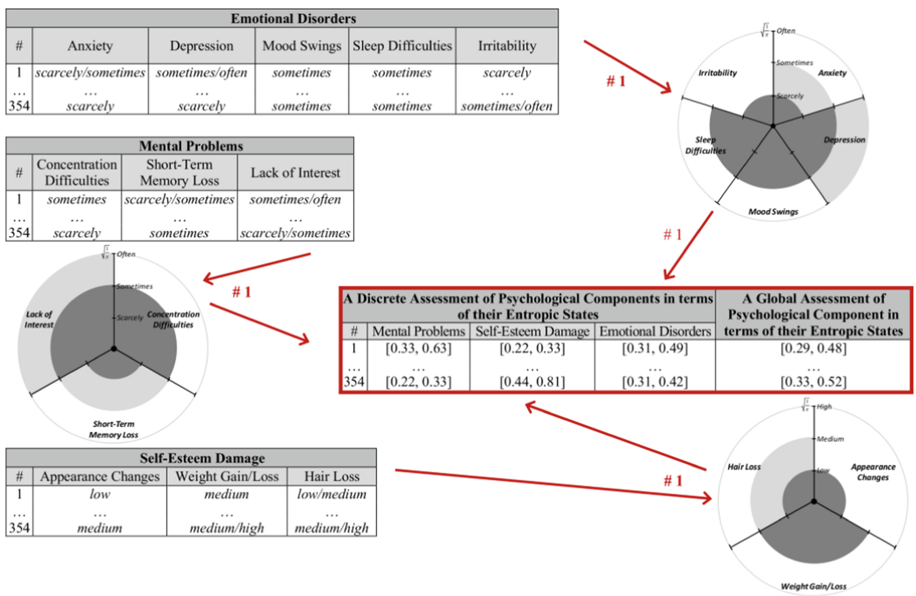
Dietary					
#	Sea Vegetables	Soy and Soybean Products	Coffee/Green Tea	Brassicaceae Vegetables	Fat Diet
1	*scarcely*	*sometimes/often*	*sometimes*	*unknown*	*sometimes*
…	…	…	…	…	…
354	*sometimes*	*scarcely*	*often*	*scarcely*	*sometimes/often*

Lifestyle					
#	Smoking Habits	Alcoholic Habits	Stressful Life	Physical Activities	Leisure Activities
1	*none*	*none*	*often*	*sometimes/scarcely*	*sometimes*
…	…	…	…	…	…
354	*sometimes/often*	*sometimes*	*scarcely*	*sometimes*	*often*

Adherence to Treatment			
#	Adequacy of Therapy	Compliance with Suggest Therapy	Recovery
1	*unknown*	*high*	*medium*
…	…	…	…
354	*unknown*	*medium/high*	*medium/high*

A Discrete Assessment of Behavioral Components in terms of their Entropic States				A Global Assessment of Behavioral Component in terms of their Entropic States
#	Lifestyle	Adherence to Treatment	Dietary	
1	[0.24, 0.31]	[0.04, 0.37]	[0.36, 0.67]	[0.21, 0.45]
…	…	…	…	…
354	[0.22, 0.33]	[0.07, 0.33]	[0.36, 0.47]	[0.22, 0.38]

Fig. 4. The extension of the knowledge base for *Behavioral Component*.



Emotional Disorders					
#	Anxiety	Depression	Mood Swings	Sleep Difficulties	Irritability
1	*scarcely/sometimes*	*sometimes/often*	*sometimes*	*sometimes*	*scarcely*
…	…	…	…	…	…
354	*scarcely*	*scarcely*	*sometimes*	*sometimes*	*sometimes/often*

Mental Problems			
#	Concentration Difficulties	Short-Term Memory Loss	Lack of Interest
1	*sometimes*	*scarcely/sometimes*	*sometimes/often*
…	…	…	…
354	*scarcely*	*sometimes*	*scarcely/sometimes*

Self-Esteem Damage			
#	Appearance Changes	Weight Gain/Loss	Hair Loss
1	*low*	*medium*	*low/medium*
…	…	…	…
354	*medium*	*medium/high*	*medium/high*

A Discrete Assessment of Psychological Components in terms of their Entropic States				A Global Assessment of Psychological Component in terms of their Entropic States
#	Mental Problems	Self-Esteem Damage	Emotional Disorders	
1	[0.33, 0.63]	[0.22, 0.33]	[0.31, 0.49]	[0.29, 0.48]
…	…	…	…	…
354	[0.22, 0.33]	[0.44, 0.81]	[0.31, 0.42]	[0.33, 0.52]

Fig. 5. The extension of the knowledge base for *Psychological Component*.

3.2 Knowledge Base

After being shown how the information was processed it is possible to build up a knowledge base given in terms of the extensions of the relations depicted in Fig. 6. This dataset contained information that must be managed for *Thyroid Dysfunction Assessment*, and it is given in terms of the tables/relations *Technical Component* (*TC*), *Behavioral Component* (*BC*) and *Psychological Component* (*PC*). The extensions of these relations turn into the definition of predicate $\boldsymbol{t}_{hyroid}\ \boldsymbol{d}_{ysfunction}\ \boldsymbol{a}_{\boldsymbol{ssessment}}$ (*tda*), which is used to train the *ANNs* (i.e., it will work out *Thyroid Dysfunction Assessment*) and also denotes the objective function with respect to the problem under analyze, viz.

$$tda : T_{echnical}C_{omponent},\ B_{ehavioral}C_{omponent},\ P_{sychological}C_{omponent} \rightarrow \{true,\ false\}$$

i.e., a *Many-Valued Empirical Machine* for *TDs* assessment is now set in terms of an *ANN* whose topology is given in Fig. 7.

A Discrete Assessment of Psychological Components in terms of their Entropic States				**A Global Assessment of Psychological Component in terms of their Entropic States**
#	Mental Problems	Self-Esteem Damage	Emotional Disorders	
1	[0.33, 0.63]	[0.22, 0.33]	[0.31, 0.49]	[0.29, 0.48]
…	…	…	…	…
354	[0.22, 0.33]	[0.44, 0.81]	[0.31, 0.42]	[0.33, 0.52]

A Discrete Assessment of Behavioral Components in terms of their Entropic States				**A Global Assessment of Behavioral Component in terms of their Entropic States**
#	Lifestyle	Adherence to Treatment	Dietary	
1	[0.24, 0.31]	[0.04, 0.37]	[0.36, 0.67]	[0.21, 0.45]
…	…	…	…	…
354	[0.22, 0.33]	[0.07, 0.33]	[0.36, 0.47]	[0.22, 0.38]

Thyroid Dysfunction Assessment in terms of their Entropic States			
#	Technical Component	Behavioral Component	Psychological Component
1	[0.46, 0.69]	[0.21, 0.45]	[0.29, 0.48]
…	…	…	…
354	[0.24, 0.42]	[0.22, 0.38]	[0.33, 0.52]

A Discrete Assessment of Technical Components of Thyroid Disorders in terms of their Entropic States				**A Global Assessment of Technical Component of Thyroid Disorders in terms of their Entropic States**
#	Risk Factors	Thyroid Biomarkers	Symptomatology	
1	[0.63, 0.81]	[0.50, 0.75]	[0.26, 0.52]	[0.46, 0.69]
…	…	…	…	…
354	[0.22, 0.41]	[0.25, 0.50]	[0.26, 0.35]	[0.24, 0.42]

Fig. 6. The thyroid dysfunction assessment's knowledge base.

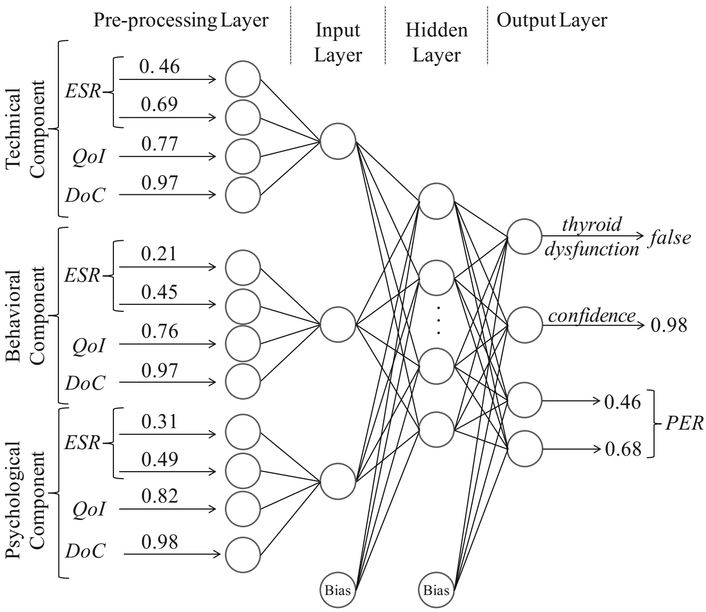


Fig. 7. The *ANN* topology for thyroid dysfunction assessment.

3.3 Computational Model

ANNs were selected due to their dynamic properties such as adaptability, robustness and flexibility. Figure 7 shows how the *ESR*, *ESR's QoI* and *ESR's DoC* values operate as inputs to the *ANN*. The result is the *TDs* assessment as well as a measure of the trust that can be expected from such a prediction and the correspondent *Potential of Empowerment Range* (*PER*).

A set with 354 records were used. The dataset was divided in exclusive subsets through the ten-folds cross validation. In order to guarantee the statistical significance of the attained results 30 (thirty) experiments were applied in all tests. The back-propagation algorithm [15] was used in the learning process of the *ANN*. In the pre-processing layer it was used as activation function the *linear one* (i.e., activation is proportional to input), in the remaining layers the *sigmoid* (i.e., the output of the activation function is going to be in the range [0, 1]; it would not blow up the activations).

Table 1 shows the confusion matrix (the values presented refer to the results obtained in the 30 experiments) for the proposed model. A perusal of Table 1 shows that the model correctly classified [330, 343] of a total of 354 cases, with an accuracy ranging between 93.2% and 96.9%. The values of *Sensitivity*, *Specificity*, *Positive Predictive Value* (*PPV*) and *Negative Predictive Value* (*NPV*) were computed based on the values exhibited in Table 1 [16], presenting a percent in the intervals [93.6, 97.1], [92.8, 96.7], [92.6, 96.9] and [93.9, 97.2], respectively. Such results seem to suggest that the *ANN* model performs well in the thyroid dysfunction assessment. In fact, the inclusion of the *Behavioral* and *Psychological Components* add an essential feature to the proposed model, since some studies point out that such issues (e.g., nutrition, emotional state of patient, mental diseases) can affect the secretion of thyroid hormones and the evolution of *TDs* [1, 6].

Table 1. The confusion matrix regarding proposed model.

Output	Model output	
	True (1)	False (0)
True (1)	TP = [162, 168]	FN = [5, 11]
False (0)	FP = [6, 13]	TN = [168, 175]

4 Conclusions

The early diagnosis of thyroid dysfunction is mandatory to establish patient medication to reverse the disorder. Thus, this paper present a syntheses and characterization of a workable methodology for problem solving that allows for the *TDs* assessment was set as a *Many-Valued Empirical Machine*, i.e., it returns a patient's diagnostic to thyroid dysfunction in terms of a *Truth Value Valuation*. In other words, the proposed approach beyond allowing to obtain the *TDs* diagnosis, also estimate the confidence associated with this finding (98.0% for the example presented above). It must be noted that the word *Empirical* means *based on*, *concerned with*, or *verifiable by observation or experience* rather than theory or pure logic. The model accuracy, sensibility and sensitivity exhibit percentages ranging in the intervals [93.2, 96.9], [93.6, 97.1], and [92.8, 96.7], respectively. In addition, the paper focuses on the uncertainty measures of proposed epitome, i.e., axiomatic definitions for *ESR*, *QoI*, *DoC*, and *PE* were presented. In upcoming work, we intend to move from *Empirical* to *Logic Machines*, showing the way to *Many-Valued Logic Machines* [17].

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