

Antiphospholipid Syndrome Risk Evaluation

João Vilhena¹, Henrique Vicente², M. Rosário Martins³, José M. Grañeda⁴, Filomena Caldeira⁴, Rodrigo Gusmão⁴, João Neves⁵ and José Neves^{6*}

¹ Departamento de Química, Escola de Ciências e Tecnologia,
Universidade de Évora, Évora, Portugal
jmvilhena@gmail.com

² Departamento de Química, Centro de Química de Évora, Escola de Ciências e Tecnologia,
Universidade de Évora, Évora, Portugal
hvicente@uevora.pt

³ Departamento de Química, Instituto de Ciências Agrárias e Ambientais Mediterrânicas,
Escola de Ciências e Tecnologia, Universidade de Évora, Évora, Portugal
mrm@uevora.pt

⁴ Serviço de Patologia Clínica do Hospital do Espírito Santo de Évora EPE, Évora, Portugal
graneda@saop.pt, filomenacaldeira1@gmail.com,
dir.patcli@hevora.min-saude.pt

⁵ Drs. Nicolas & Asp, Dubai, United Arab Emirates
joaocpneves@gmail.com

⁶ Centro Algorithmi, Universidade do Minho, Braga, Portugal
jneves@di.uminho.pt

* Corresponding author: phone: +351-934201337; fax: +351-253604471
e-mail: jneves@di.uminho.pt

Abstract. The antiphospholipid syndrome is an acquired autoimmune disorder caused by high titers of antiphospholipid antibodies, such as anticardiolipin antibodies, lupus anticoagulant and anti- β 2 glycoprotein I, that cause both arterial and veins thrombosis as well as pregnancy-related complications and morbidity, as clinical manifestations. This autoimmune hypercoagulable state has severe consequences for the patients and for the society in general, being one of the main causes of thrombotic disorders and death. Therefore, it is extremely important to be preventive; being aware of how probable is to have that kind of syndrome. This work will focus on the development of a diagnosis support system to antiphospholipid syndrome, 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: Antiphospholipid Syndrome · Logic Programming · Artificial Neural Networks · Knowledge Representation and Reasoning.

1 Introduction

The AntiPhospholipid Syndrome (APS) is an acquired autoimmune disorder defined by the presence of persistently increased titers of antiPhospholipid antibodies (aPL), such as antiCardioLipin antibodies (aCL), Lupus Anticoagulant (LA) and anti- β 2 GlycoProtein I (a β 2GPI) in the presence of one of clinical criteria, such as thromboembolic complications and pregnancy morbidity [1].

The most frequent venous occlusions comprise deep vein thrombosis affecting the veins of the lower members [2]. However, thrombotic events are not only related with the large veins and arteries, small vessels might also be involved causing sporadically superficial thrombophlebitis [3]. Strokes, often preceded by transient ischemic attacks, are the most frequent arterial events in these patients. Therefore, many diverse clinical manifestations due to vascular occlusions in the central nervous system, heart, lungs, liver, adrenal glands, kidneys, skin or eyes, may to be associated with the presence of antiphospholipid antibodies [4]. Pregnancy morbidity in the APS includes recurrent fetal losses and premature births, frequently associated with thrombosis of the placental vessels and subsequent infarction resulting in placental insufficiency, fetal growth retardation, and ultimately fetal loss [2].

AntiPhospholipid antibodies (aPL) comprise a heterogeneous group of autoantibodies that are part of a family which bind *in vitro* not only to phospholipids but predominantly to their complex with plasma proteins [3, 5]. antiCardioLipin (aCL) antibodies and Lupus Anticoagulant (LA) are the main antibodies associated with the antiphospholipid syndrome [6]. The aCL antibodies are strongly associated with venous and arterial thrombosis and require a serum cofactor, β 2-GlycoProtein I (β 2GPI) or apolipoprotein H, for binding to cardiolipin *in vitro* [7]. Updating the Sapporo classification, the laboratory criteria for APS diagnosis maintained both Lupus Anticoagulant (LA) and antiCardioLipin (aCL) Immunoglobulin isotype G (IgG) and M (IgM), and including also IgG and IgM anti- β 2gGlycoProtein-I (a β 2GPI) assays [1]. According to the revised Sidney criteria, the classification of APS syndrome requires the combination of at least one clinical and one laboratory criteria (persistent LA, IgG/IgM aCL or a β 2GPI) [4, 8]. In this classification, the risk stratification of APS patients was divided into four categories: I, more than one laboratory criteria present (any combination); while patients with a single positive test were classified in category II (IIa, if LA is a single positive test; IIb if aCL antibody is a single positive test or IIc, if anti- β 2 glycoprotein-I antibody is present alone assays) [1].

LA was reported to be the most predictive test. LA can be mediated by both anti- β 2GPI and anti-ProThrombin (aPT) antibodies [9]. However, β 2GPI-dependent LA was found to be a stronger risk factor for thrombosis and failures than aPT-dependent LA [10]. An association of aCL antibodies and anti- β 2-GPI (a β 2GPI) in coronary artery disease and recurrent Myocardial Infarction (MI) has been reported in several studies [11]. Clinical events are more robustly associated with aPLs of the IgG isotype [12, 13]. Patients carrying both aCL/anti- β 2GPI antibody isotypes display a higher risk of developing clinical events [4]. Triple positivity, defined by the presence of LA and medium/high titers of aCL and anti- β 2GPI antibodies is the most predictive profile for the APS Syndrome [12, 14].

This work reports the founding of a computational framework that uses knowledge representation and reasoning techniques to set the structure of the information and the associate inference mechanisms. We will centre on a Logic Programming (LP) based approach to knowledge representation and reasoning [15, 16], complemented with a computational framework based on Artificial Neural Networks (ANNs) [17, 18].

ANNs are computational tools which attempt to simulate the architecture and internal operational features of the human brain and nervous system. ANNs can be defined as a connected structure of basic computation units, called artificial neurons or nodes, with learning capabilities. Multilayered feed-forward neural network architecture is one of the most popular ANNs structure often used for prediction as well as for classification. This architecture is molded on three or more layers of artificial neurons, including an input layer, an output layer and a number of hidden layers with a certain number of active neurons connected by modifiable weights. In addition, there is also a bias, which is only connected to neurons in the hidden and output layers. The number of nodes in the input layer sets the number of independent variables, and the number of nodes in output layer denotes the number of dependent variables [19]. Several studies have shown how ANNs could be successfully used to model data and capture complex relationships between inputs and outputs [18, 20, 21].

Solving problems related to APS requires a proactive strategy. However, the stated above shows that the APS assessment should be correlated with many variables and require a multidisciplinary approach. With this paper we make a start on the development of an APS risk assessment system using LP complemented with ANNs.

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 described 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 [22, 23], and Proof Theory [15, 16]. In present 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:

$$\begin{aligned}
 & \{ \\
 & p \leftarrow p_1, \dots, p_n, \text{not } q_1, \dots, \text{not } q_m \\
 & ?(p_1, \dots, p_n, \text{not } q_1, \dots, \text{not } q_m) \quad (n, m \geq 0) \\
 & \text{exception}_{p_1} \dots \text{exception}_{p_j} \quad (j \leq m, n) \\
 & \} :: \text{scoring}_\text{value}
 \end{aligned}$$

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 \neg [15]. Under this formalism, every program is associated with a set of abducibles [22, 23], 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 [24, 25]. 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 [26].

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:

$$predicate_i = \bigcup_{1 \leq j \leq m} clause_j(x_1, \dots, x_n) :: QoI_i :: DoC_i \quad (1)$$

where U and m stand, respectively, for *set union* and the *cardinality* of the extension of $predicate_i$ [26].

3 A Case Study

As a case study consider the knowledge base given in terms of the extensions of the relations depicted in Fig. 1, which stand for a situation where one has to manage information about AntiPhospholipid Syndrome (APS). The knowledge base includes features obtained by both objective and subjective methods, i.e., the physicians may populate some issues while executing the health check. Others may be perceived by laboratorial tests (e.g., this happens with the issues of the *Sydney Laboratory Criteria* table).

Under this scenario some incomplete and/or unknown data is also present. For instance, for patient 1 the parameters regarding the *Sydney Laboratory Criteria (SCC)* are unknown while the *Clinical Manifestations* ranges in the interval $[2, 5]$.

The *Sydney Clinical Criteria*, *Clinical Manifestations* and *Risk Factors* tables are filled with 0 (zero) or 1 (one) denoting, respectively, *absence* or *presence*. The first two columns of the *Sydney Laboratory Criteria (SLC)* table are populated with 0 (zero), 1 (one) or two (2) denoting, respectively, *absence*, *medium-titer* or *high-titer* of aCL or Anti- β_2 GPI antibody. The *LA* column, in turns, is populated with 0 (zero) or one (1) denoting, respectively, *absence* or *presence* of lupus anticoagulants.

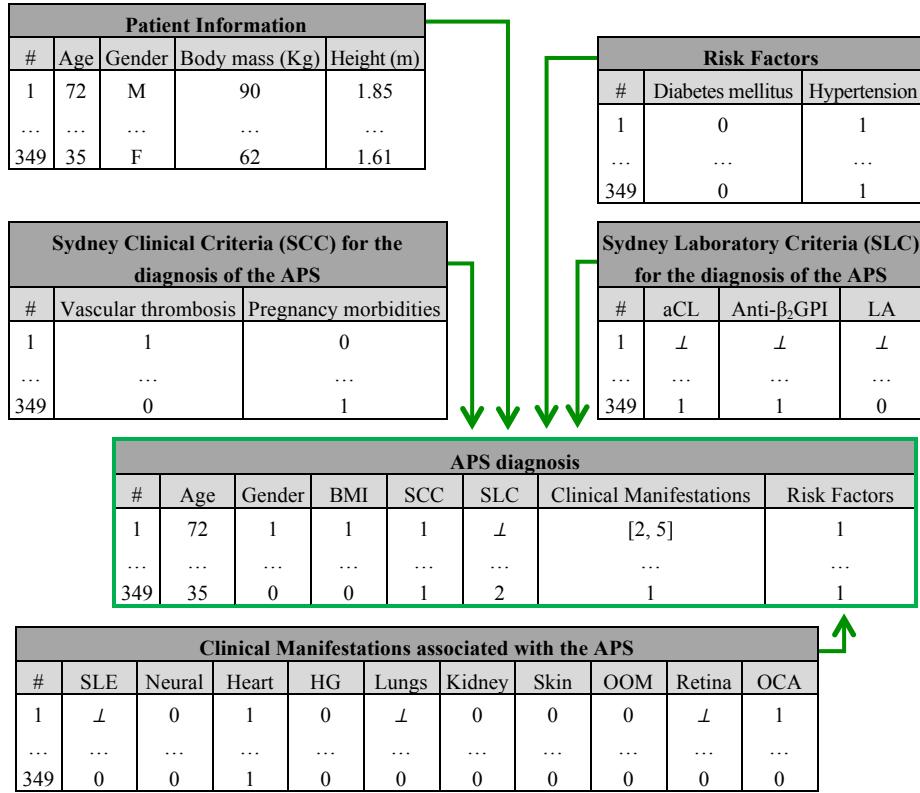


Fig. 1. A fragment of the knowledge base for AntiPhospholipid Syndrome Risk Evaluation.

The values presented in the *SCC*, *SLC*, *Clinical Manifestations* and *Risk Factors* columns of *APS Diagnosis* table are the sum of the attributes values of the correspondent tables, ranging between [0, 2], [0, 5], [0, 10] and [0, 2] respectively. The domain of *Body Mass Index (BMI)* 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 *BMI* is evaluated using the equation $BMI = Body\ Mass/Height^2$ [27]. In the *Gender* column 0 (zero) and 1 (one) stand, respectively, for *female (F)* and *male (M)*.

In *Clinical Manifestations* table (Fig. 1) SLE, Neural, Heart, HG, Lungs, Kidney, Skin, OOM, Retina and OCA stand for Systemic Lupus Erythematosus, neurologic, cardiovascular, hepatic and gastrointestinal, pulmonary, renal, skin, and other organ manifestations, retinal and other coagulation abnormalities, respectively.

Applying the rewritten algorithm presented in [26], to all the fields that make the knowledge base for *APS diagnosis* (Fig. 1) and looking to the DoC_s values obtained in this manner, it is possible to set the arguments of the predicate referred to below, that also denotes the objective function with respect to the problem under analyze.

$aps_diagnosis: Age, Gender, BodyMassIndex, Sydney\ Clinical\ Criteria,$

$Sydney\ Laboratory\ Criteria, Clinical\ Manifestations, Risk\ Factors \rightarrow \{0,1\}$

where 0 (zero) and 1 (one) denote, respectively, the truth values *false* and *true*.

Exemplifying the application of the rewritten algorithm presented in [26], to a term (patient) that presents feature vector ($Age = 69$, $Gender = 1$, $BMI = 1$, $SCC = 1$, $SLC = [2, 4]$, $CM = [3, 5]$, $RF = \perp$), and applying the procedure referred to above, one may get:

Begin,

The predicate's extension that map the Universe-of-Discourse for the term under observation is set \leftarrow

{

$\neg aps_{diagnosis}(Age, Gen, BMI, SCC, SLC, CM, RF)$
 $\quad \quad \quad \leftarrow aps_{diagnosis}(Age, Gen, BMI, SCC, SLC, CM, RF)$
 $aps_{diagnosis}(\underbrace{69, 1, 1, 1, [2, 4], [3, 5], \perp}_{\text{attribute's values}}) :: 1 :: DoC$
 $\quad \quad \quad \underbrace{[2, 90][0, 1][0, 2][0, 2] [0, 5][0, 10][0, 2]}_{\text{attribute's domains}}$

$\} :: 1$

The attribute's values ranges are rewritten \leftarrow

{

$\neg aps_{diagnosis}(Age, Gen, BMI, SCC, SLC, CM, RF)$
 $\quad \quad \quad \leftarrow aps_{diagnosis}(Age, Gen, BMI, SCC, SLC, CM, RF)$
 $aps_{diagnosis}(\underbrace{[69, 69], [1, 1], [1, 1], [1, 1], [2, 4], [3, 5], [0, 2]}_{\text{attribute's values}}) :: 1 :: DoC$
 $\quad \quad \quad \underbrace{[2, 90] [0, 1] [0, 2] [0, 2] [0, 5][0, 10][0, 2]}_{\text{attribute's domains}}$

$\} :: 1$

The attribute's boundaries are set to the interval $[0, 1]$ \leftarrow

{

$\neg aps_{diagnosis}(Age, Gen, BMI, SCC, SLC, CM, RF)$
 $\quad \quad \quad \leftarrow aps_{diagnosis}(Age, Gen, BMI, SCC, SLC, CM, RF)$
 $aps_{diagnosis}(\underbrace{[0.8, 0.8], [1, 1], [0.5, 0.5], [0.5, 0.5], [0.4, 0.8], [0.3, 0.5], [0, 1]}_{\text{attribute's values}}) :: 1 :: DoC$
 $\quad \quad \quad \underbrace{[0, 1] [0, 1] [0, 1] [0, 1] [0, 1] [0, 1] [0, 1]}_{\text{attribute's domains}}$

$\} :: 1$

The DoC's values are evaluated \leftarrow

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{
   $\neg \text{aps}_{\text{diagnosis}}(\text{Age}, \text{Gen}, \text{BMI}, \text{SCC}, \text{SLC}, \text{CM}, \text{RF})$ 
   $\leftarrow \text{aps}_{\text{diagnosis}}(\text{Age}, \text{Gen}, \text{BMI}, \text{SCC}, \text{SLC}, \text{CM}, \text{RF})$ 
   $\text{aps}_{\text{diagnosis}}(1, \underbrace{1, 1, 1, 0.92, 0.98, 0}_{\text{attribute's confidence values}} :: 1 :: 0.84)$ 
   $\underbrace{[0.8, 0.8] [1, 1] [0.5, 0.5] [0.5, 0.5] [0.4, 0.8] [0.3, 0.5] [0, 1]}_{\text{attribute's values ranges once normalized}}$ 
   $\underbrace{[0, 1] [0, 1] [0, 1] [0, 1] [0, 1] [0, 1] [0, 1]}_{\text{attribute's domains once normalized}}$ 
}

```

$\} :: 1$

End.

4 Artificial Neural Networks

One's model for APS diagnosis set above displays how the information comes together to shape a diagnosis. In this section, a data mining approach to deal with this information is considered. It was set a hybrid computing approach to model the universe of discourse, based on Artificial Neural Networks (ANNs) [18, 20, 21]. As an example, let us consider the case given above, where one may have a situation in which an APS diagnosis is paramount. In Fig. 2 it is shown how the normalized values of the interval boundaries and their *DoC* and *QoI* values work as inputs to the *ANN*. The output depicts the APS diagnosis, plus the confidence that one has on such a happening.

In this study 349 patients were considered, with an age average of 48 years, ranging from 2 to 90 years old. The gender distribution was 32% and 68% for male and female, respectively. The APS was diagnosed in 38 cases, i.e., in 10.9% of the population.

To ensure statistical significance of the attained results, 30 (thirty) experiments were applied in all tests. In each simulation, the available data was randomly divided into two mutually exclusive partitions, i.e., the training set with 67% of the available data, used during the modeling phase, and the test set with the remaining 33% of the cases, used after training in order to evaluate the model performance and to validate it. The back propagation algorithm was used in the learning process of the ANN. As the output function in the pre-processing layer it was used the identity one. In the other layers we used the sigmoid 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 1 presents the coincidence matrix (the values denote the average of the 30 experiments).

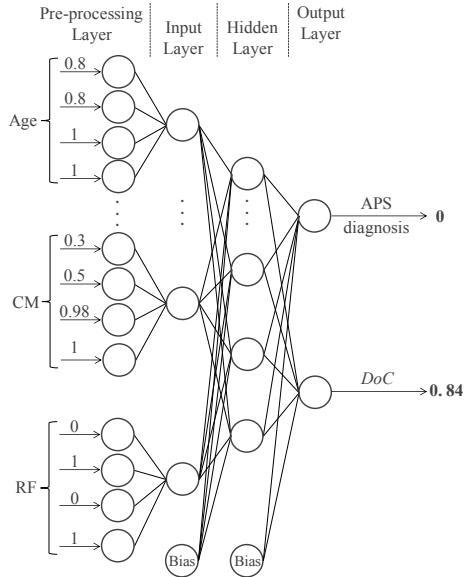


Fig. 2. The artificial neural network topology.

Table 1 shows that the model accuracy was 93.6% for the training set (219 correctly classified in 234) and 89.6% for test set (103 correctly classified in 115). Thus, the predictions made by the ANN model are satisfactory, attaining accuracies close to 90%. 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 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 92.0% to 92.3%, while the specificity ranges from 89.2% to 93.8%. PPV ranges from 52.2% to 63.9%, while NPV ranges from 98.9% to 99.0%.

Moreover, the Receiver Operating Characteristic (ROC) curves for the training and test sets are shown in Fig. 3. The areas under ROC curves are higher than 0.9 for both cases, denoting that the model exhibits a good performance in the diagnosis of APS.

Table 1. The coincidence matrix for ANN model.

Target	Predictive			
	Training set		Test set	
	True (1)	False (0)	True (1)	False (0)
True (1)	23	2	12	1
False (0)	13	196	11	91

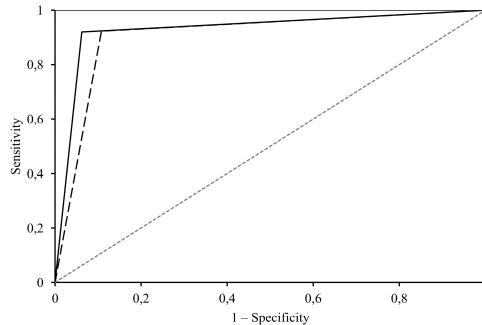


Fig. 3. The ROC curves for training set (—) and for test set (---).

The present model allows to integrate the results of the Sydney Clinical Criteria (SCC) and Sydney Laboratory Criteria (SLC) for the diagnosis of the APS with other factors such as, family story of patients of antiphospholipid syndrome and risk factors associated and integrate them with the main associated clinical manifestations, allowing to be assertive in the diagnosis of the APS. This model showed a high sensibility, enabling the diagnosis of APS comparing with the patients that really presented this pathology as well as classifying properly the absence of this autoimmune hypercoagulable state (i.e., specificity). Therefore it can be a major contribution to the early recognition and prevention of APS. Thus, it is our claim that the proposed model is able to diagnose the APS properly. The inclusion of the associated risk factors and associated clinical manifestations, such as systemic lupus erythmatosus, neurologic, cardiovascular, hepatic and gastrointestinal, pulmonary, renal, skin, and other organ manifestations, retinal and other coagulation, may be responsible for the good performance exhibited by the presented model.

5 Conclusions

Diagnosing antiphospholipid syndrome has shown to be a hard task, as the parameters that cause the disorder are not fully represented by objective data. The classification of APS syndrome and the risk stratification of this disease require the combination of at least one clinical and one laboratory criteria (persistent LA, IgG/IgM aCL or α 2GPI). Thus, it is difficult to assess to the APS diagnosis since it needs to consider different conditions with intricate relations among them, where the available data may be incomplete, contradictory, and even unknown. In this work the founding of a computational framework was presented. It uses powerful knowledge representation and reasoning techniques to set the structure of the information and the associate inference mechanisms (ANNs based). The ANNs were selected due to their proper dynamics, like adaptability, robustness, and flexibility. This approach not only allows to obtain the diagnosis of APS but it also permits the estimation of the Degree of Confidence (DoC) associated with the diagnosis. In fact, this is one of the added values of this approach that arises from the complementarily between Logic Programming (for knowledge representation and reasoning) and the computing process based on ANNs.

Future work may recommend that the same problem must be approached using others computational formalisms, namely Case Based Reasoning [28], Genetic Programming [16], or Particle Swarm [29], just to name a few.

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