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Semen Parameters Can Be Predicted from Environmental Factors and Lifestyle Using Artificial Intelligence Methods[1]

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ABSTRACT

Fertility rates have dramatically decreased in the last two decades, especially in men. It has been described that environmental factors as well as life habits may affect semen quality. In this paper we use artificial intelligence techniques in order to predict semen characteristics resulting from environmental factors, life habits, and health status, with these techniques constituting a possible decision support system that can help in the study of male fertility potential. A total of 123 young, healthy volunteers provided a semen sample that was analyzed according to the World Health Organization 2010 criteria. They also were asked to complete a validated questionnaire about life habits and health status. Sperm concentration and percentage of motile sperm were related to sociodemographic data, environmental factors, health status, and life habits in order to determine the predictive accuracy of a multilayer perceptron network, a type of artificial neural network. In conclusion, we have developed an artificial neural network that can predict the results of the semen analysis based on the data collected by the questionnaire. The semen parameter that is best predicted using this methodology is the sperm concentration. Although the accuracy for motility is slightly lower than that for concentration, it is possible to predict it with a significant degree of accuracy. This methodology can be a useful tool in early diagnosis of patients with seminal disorders or in the selection of candidates to become semen donors.

artificial neural network, decision support system, life habits, semen quality, supervised learning

INTRODUCTION

In the last two decades there has been a notable decline in fertility rates [1–3]. It was considered that this decline has been due to changes in behavior related to economic aspects, such as the incorporation of women into the labor force and the consequent delay in the age at which one decides to have offspring, as well as the widespread use of contraceptives [4–6]. Although it is clear that social aspects have contributed significantly to this global decline in fertility, some authors suggest that they occurred synchronously with the deterioration of reproductive health caused by adverse biological factors [7].

Demand for assisted reproduction treatment has shown an increase in situations where the male factor is altered [8, 9]. In the decades since the publication of a meta-analysis directed by Elisabeth Carlsen et al. [10], there has been a debate about the possibility of a decline in seminal quality. Numerous studies show a decrease in semen parameters among men [11–14], although there are studies that found no evidence of such a decline [15, 16]. Regarding the causes of this possible decline in semen quality affecting male fertility, several factors have been considered, including an increase in the incidence of male reproductive diseases [17, 18], environmental or occupational factors [19, 20], or a certain lifestyle [21, 22].

Semen analysis is the cornerstone of the male study [23]. Although semen analysis alone cannot determine whether a male can have offspring, it is a good predictor of male fertility potential [24–27]. Semen analysis is also necessary to evaluate candidates to become semen donors [28–31].

In this paper, we study male fertility, approaching the problem from the perspective of the possible influence of environmental factors and life habits on semen quality. To this end we used artificial intelligence (AI) techniques to produce a decision support system (DSS) that can help in the prediction of semen parameters (Fig. 1).

In the last two decades, the use of AI has also become widely accepted in medical applications. Many of those applications have advanced to the materialization of expert systems and DSSs in several different areas. In andrology there have been only a few approximations [32–36]. Although these works show the potential of artificial neural networks (ANNs), we believe that they have not been developed enough. Therefore, we found it necessary to evaluate this methodology as applied to this field.

Applications built with ANN architecture have several advantages, such as generalization, facility in optimization (which makes them more flexible for nonlinear modeling of large data sets), and accuracy for predictive inference with potential to DSS (the reason for using this architecture). Moreover, these models can make knowledge dissemination easier by providing explanations [37]. Artificial neural networks have been used to improve classification tasks because of a property they have called black-box learning, which is the most popular method for classification problems [38, 39] and has shown better performance than other methods [40, 41].

Artificial intelligence methods have been commonly used to improve accuracy. This also is probably one of most popular examples of AI use. However, these architectures are also very suitable in dealing with big data, as well as heterogeneous information.

In the evaluation of the infertility patient, it may be useful to apply AI methods, not only to improve accuracy but also to
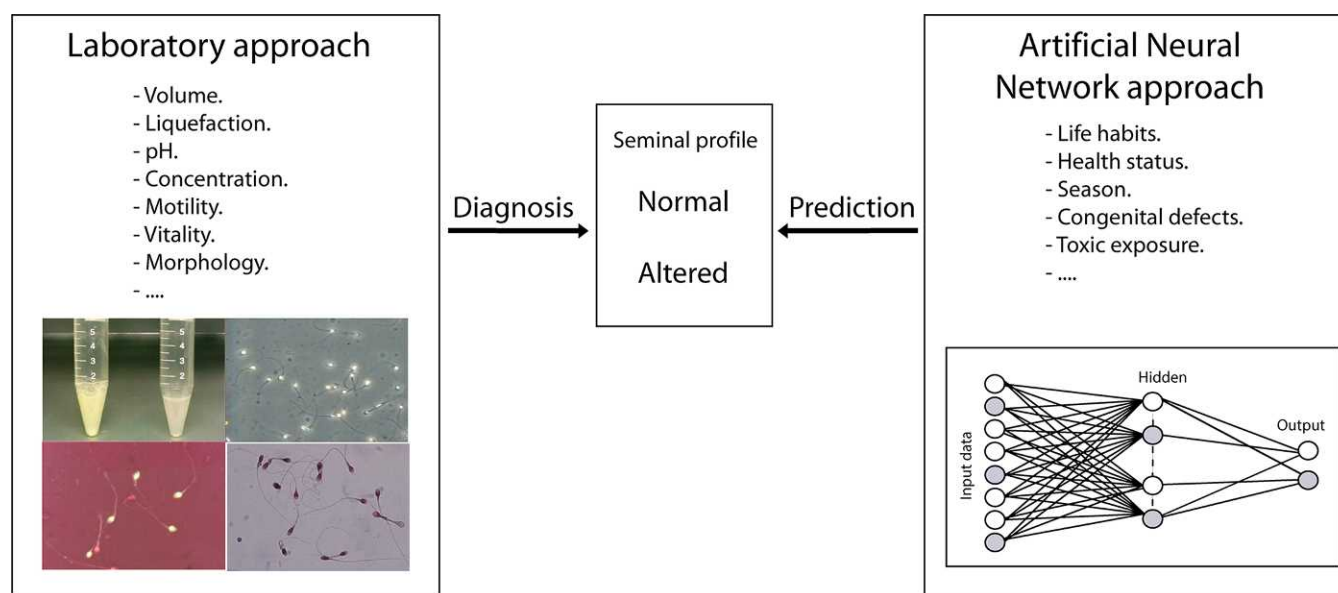
FIG. 1.   Diagram shows the proposed complementation of the laboratory and the AI approaches for the determination of the seminal profile.

select the best features, since the number of variables is huge, as is the amount of information used [42–46].

Knowledge discovery in databases, data mining, or extractions of patterns from large data sets (or recently summarized as big data) will be the natural next step in this research area.

The objective of this paper is to develop a DSS based on AI methods that can predict the results of a semen analysis from the answers of a questionnaire (see Supplemental Data, available online at www.biolreprod.org), and be a useful tool in the early diagnosis and cribbage of patients with seminal disorders or in the selection of candidates to become semen donors.

MATERIALS AND METHODS

Study Population

To perform the present study we recruited volunteers among the students of the University of Alicante as a population of young and healthy men. It has been previously established that the use of volunteers does not introduce selection bias into male fertility studies [47], and because we were interested in the impact of environmental factors and lifestyle on semen parameters we decided not to study individuals with known or suspected reproductive disorders (i.e., patients of a fertility clinic). Moreover, it is also important to highlight that the study population of this work presents characteristics close to those of regular candidates for semen donation (i.e., young, male, university students) [48]. A total of 123 volunteers between the ages of 18 and 36 yr participated in the study, but only data from 100 individuals were used because of incomplete information for some of the participants.

Semen Analysis

After being informed about the study, volunteers were asked to provide a semen sample after 3–6 days of sexual abstinence, and a semen analysis according to World Health Organization guidance was done [49]. All semen samples were processed by the same person with the same equipment, and analysis of motility and concentration was realized within the first 60 min after semen collection. All samples were obtained and processed with the approval of the Institutional Review Board of the University of Alicante.

In this study we used the seminal analysis results as a control to evaluate the accuracy in the prediction of the diagnosis for the ANN developed. These ANNs will only be based on the answers to the questionnaires of the individuals who participated.

Variables of the Questionnaire

On the day of the analysis, the volunteers were asked to fill out a questionnaire about life habits and health status. They were asked about 34 items (Table 1).

After a preprocessing using decision trees, which are another AI method, we found that not all of the 34 questions developed in the questionnaire were relevant and necessary to the classification process [50]. Table 2 shows those questions that were found to be relevant for each of the seminal parameters studied. Only the age was present in both sets of questions. In this regard, the seminal alterations studied in this paper, which are sperm concentration and motility, are produced by different factors and in different moments. Sperm concentration is determined by the efficiency of the germinal epithelium, whereas motility reflects the maturation of the spermatozoa produced. Therefore, we decided to develop two specific neural networks, one of them to predict the sperm concentration (ANN1) and the other to predict the sperm motility (ANN2), in order to obtain the most accurate results.

Table 2 also shows descriptions and ranges of values for the variables used in the study, as well as the values normalized. We have converted the input data into a range of normalization according to the following rules:

a) Numerical variables, such as age, are normalized onto the interval (0–1).
b) The variables with only two independent attributes are prearranged with binary values (0, 1).
c) The variables with three independent attributes, such as ''Vaccines received,'' ''High fevers in the last year,'' and ''Smoking habit,'' are prearranged using the ternary values (−1, 0, 1).
d) The variables with four independent attributes, such as ''Season in which the analysis was performed'' or ''Marital status,'' are prearranged using the four different and equal distance values (−1, −0.33, 0.33, 1).

ANN Architecture

An ANN is a mathematical model inspired by biological neural networks. A neural network consists of an interconnected group of artificial neurons, and it processes information using a connectionist approach to computation. In this context, a neuron is the basic computation unit. In these units a series of mathematical operations are developed. Afterward they decide the next step in the computation pathway depending on the results obtained, which is called the activation function.

In this study we have used a multilayer perceptron (MLP) network [38, 51, 52], which as a special sort of ANN comprises an architecture of several layers of neurons (therefore keeping the resemblance with the biological brain, since it is a bioinspired method).

In our case, which is very common, we chose three layers (where each one is fully connected to the next one): an input layer that receives external inputs,

TABLE 1. Variables in the original questionnaire about life habits and health status.

Variable nonrelevant for prediction	Variable to predict sperm concentration (ANN1)	Variable to predict sperm motility (ANN2)
Children	Season in which the analysis was performed	Age at the time of analysis
Birth city (county)	Age at the time of analysis	Body mass index
City of the family home (county)	Childhood diseases (i.e., chickenpox, measles, mumps, polio)	Marital status
City of residence during the course (county)		Vaccines received
Birth defect, genetic disorder, or any hereditary disease	Surgical intervention	Number of siblings
Significant diseases	Accident or serious trauma	Allergy
Chemotherapy	High fevers in the last year	Time since radiation exposure
Radiations (i.e., x-rays)	Smoking habit	Warm baths
Number of exposures	Frequency of alcohol consumption	Average hours of sleep per day
Average number of cigarettes per day	Number of hours spent sitting per day	
Years of exposure to cigarettes		
Coffee consumption		
Alcohol consumption		
Drugs consumption		
Wearing tight clothes		
Average hours per week playing sports		
Average ejaculations per week		

one hidden layer, and an output layer, which normally, and as is also true in our case, generates the classification results (Fig. 2).

After the first level of neurons (in the input layer), the rest of the neurons form computational elements with a nonlinear activation function. In order to summarize the MLP functioning, the strategy of the network is that when data are presented in the input layer, the remainder neurons run calculations in the consecutive layers until an output value is achieved for the output neurons that will specify the correct class for the input data.

Figure 2 indicates how the hidden layers of neurons compute weighted sums of their inputs and add a threshold. The resulting sums are used to calculate the activity of the neurons by applying a sigmoid activation function.

This process is defined as follows:

$$v_j = \sum_{i=1}^{p} \omega_{ji} x_i + \theta_j, y_j = f_j(v_j), \qquad (1)$$

where v_j is the linear combination of inputs $x_1, x_2, \ldots, x_p$, and the threshold θ_j; ω_{ji} is the connection weight between the input x_i and the neuron j; f_j is the activation function of the j_{th} neuron; and y_j is the output. The sigmoid function

is a common choice of activation function. It is defined as:

$$f(t) = \frac{1}{1 + e^{-t}}. \qquad (2)$$

A single neuron in the MLP is able to linearly separate its input space into two subspaces by a hyperplane defined by the weights and the threshold. The weights define the direction of this hyperplane, whereas the threshold term θ_j offsets it from the origin.

This is essentially what makes MLP very suitable for the classification problems.

The MLP network uses the backpropagation algorithm [53], which is the most suitable algorithm for similar works [44, 50].

The different layers of the MLP architecture are assembled as follows:

a) Layer 1: This layer is built automatically from the input vector, which in our case consists of the answers of the questionnaire shown in Table 2.
b) Layer 2: To decide the number of hidden neurons for this layer is the hardest issue in the network's architecture. This number represents the equilibrium between good accuracy and the possibility of overfitting. As a matter of fact,

TABLE 2. Characteristics and normalization ranges of the input parameters used in the two neural networks developed, one of them to predict sperm concentration (ANN1) and the other to predict sperm motility (ANN2).

| Seminal parameter predicted	Variable description	Values (minimum-maximum)	Normalized
Sperm concentration (ANN1)	Season in which the analysis was performed	1) Winter, 2) Spring, 3) Summer, 4) Fall	(−1, −0.33, 0.33, 1)
	Age (yr) at the time of analysis	18–36	(0–1)
	Childhood diseases (i.e., chickenpox, measles, mumps, polio)	1) Yes, 2) No	(0, 1)
	Accident or serious trauma	1) Yes, 2) No	(0, 1)
	Surgical intervention	1) Yes, 2) No	(0, 1)
	High fevers in the last year	1) Less than 3 mo ago, 2) More than 3 mo ago, 3) No	(−1, 0, 1)
	Frequency of alcohol consumption	1) Several times a day, 2) Every day, 3) Several times a week, 4) Once a week, 5) Hardly ever or never	(0, 1)
	Smoking habit	1) Never, 2) Occasional, 3) Daily	(−1, 0, 1)
	Number of hours spent sitting per day	1–16	(0–1)
Sperm motility (ANN2)	Age (yr) at the time of analysis	18–36	(0–1)
	Body mass index	17–34	(0–1)
	Marital status	1) Unmarried and without a partner, 2) Unmarried with partner, 3) Married, 4) Other	(−1, −0.33, 0.33, 1)
	Number of siblings	0–6	(0–1)
	Vaccines received	1) Children calendar, 2) Children calendar and tetanus, 3) Only tetanus	(−1, 0, 1)
	Allergy	1) Yes, 2) No	(0, 1)
	Time since radiation exposure	1) Less than 3 mo, 2) More than 3 mo	(0, 1)
	Average hours of sleep per day	6–12	(0–1)
	Warm baths	1) Yes, 2) No	(0, 1)
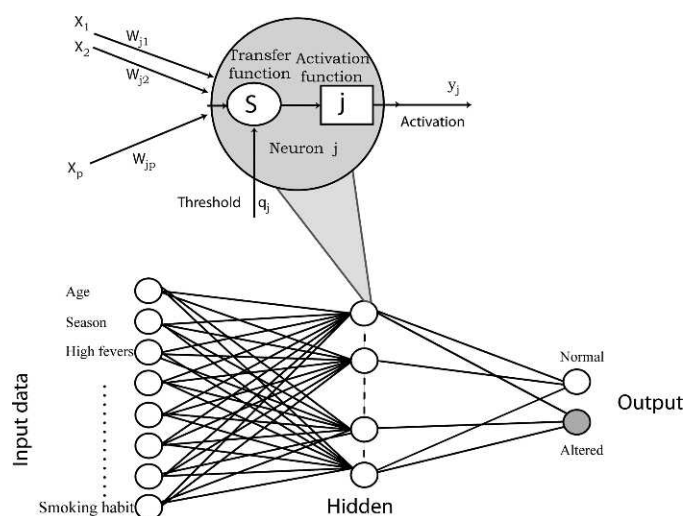
FIG. 2. The architecture of the MLP network (input layer, hidden layer, and output layer). For a single neuron in the hidden layer, the computation topology is shown (X_i is input value; ω_{ji} is the connection weight between the input X_i and the neuron j; θ_j is the threshold; f_j is the activation function; and y_j is the output).

the precise number of neurons in a hidden layer will notably improve the capacity of the network of generalization from new data [54].
c) Layer 3: This layer is the output (classification) layer. The output corresponds to the different problem classes. In our example there are two outputs: normal and altered.

The weights and the threshold of the MLP are calculated during an adaptation process. In *Results*, the number of hidden neurons of the MLP will be established.

All of the computations of the neural network were developed using WEKA software [55]. WEKA includes most of the machine learning methods, and it is Open Source software developed by the University of Waikato in New Zealand.

ANN Experimentation

Because the amount of data needed to examine our system is normally not very big, a method called cross-validation is adapted. The idea is to divide the entire set of data into two subsets: namely, the training set and the test set. The training set is used to determine the system parameters (and also to configure the hidden layer explained in the subsection above). The test set is used to assess the prediction accuracy and the network generalization. This method has been used quite often to measure the generalization of neural networks.

The method is called n-fold cross-validation because this process is performed n times. For every test, the test subset is chosen randomly from the initial pull, and the remaining form the training data.

To evaluate the performance we obtained some measures as classification accuracy, sensitivity, specificity, positive predictive value, negative predictive value, and a confusion matrix. A confusion matrix [56] contains information about actual and predicted classifications done by a classification system.

RESULTS

Baseline Semen Characteristic and Laboratory Results

Table 3 shows the mean of the seminal parameters from the study population. Of all men surveyed, 38% had some alteration in sperm parameters. By studying in detail the individuals with altered parameters, the most frequently found seminal alteration was asthenozoospermia in 18% of cases, followed by oligozoospermia in 8%. The combined alterations of asthenoteratozoospermia and oligoasthenozoospermia showed a frequency of 4% in both cases. A total of 3% of individuals showed oligoasthenoteratozoospermia. Finally, the less frequent alteration was teratozoospermia without other alterations, present only in one individual.

TABLE 3. Characteristics of the study population.

Parameter	Mean ± SD	5th–95th percentile
Age (yr)	24.05 ± 4.38	18–33
Semen volume	3.85 ± 1.78	2–6.47
Sperm concentration	67.68 ± 44.23	11–150
Percentage of motile sperm	54.17 ± 18.47	14.52–76.97

ANN Performance

In order to keep a good generalization, and consequently a high accuracy, without getting overfitting, the experiments carried out show that a low number of neurons for layer 2 (the hidden layer) led to a poor performance for both the training and test sets. In the opposite edge, a high number of neurons performed very well for the training and test sets, although the risk of overfitting is high. The compromise between these two options leads us to find the optimal solution for this layer in six neurons for each of the neural networks developed.

The output (classification) layer has two classes for classification/prediction—normal and altered—based on World Health Organization reference values [49]. As we explained regarding Table 2, we decided to develop two neural networks—sperm concentration (ANN1) and motility (ANN2)—in order to analyze the measures of the seminal parameters studied, since both networks used different variables, except for age, which was used in common.

To assess the generalization of the network we applied a 10-fold cross-validation method for the performance assessment of every network. The data have been divided into 10 sets (S1, S2, … S10) in order to carry out 10 experiments. This validation was optimal and stabilized after the first 1000 epochs.

Table 4 shows the confusion matrix provided by our classifiers for each of the seminal parameters. With the results of confusion matrix the following parameters of ANN performance were acquired: classification accuracy, sensitivity, specificity, positive predictive value, and negative predictive value. Table 5 shows the values obtained for each seminal parameter.

Receiver-operator characteristic curves (Fig. 3) for each of the seminal parameters studied were made to show the accuracy in the prediction of the semen characteristic by the ANN using only the variables in the questionnaire as input. Sperm concentration is the seminal parameter that shows the highest prediction accuracy. Although the accuracy of motility is slightly lower than concentration, it is possible to predict it with a significant accuracy.

TABLE 4. Confusion matrix showing the results of the classification process.[a]

	Predicted	
	Normal	Altered
Sperm concentration (actual)		
Normal	TP = 84	FN = 4
Altered	FP = 6	TN = 6
Sperm motility (actual)		
Normal	TP = 75	FN = 9
Altered	FP = 9	TN = 7

[a] TP, true positive: seminal parameter was normal and was correctly classified; FP, false positive: seminal parameter was altered and was incorrectly classified; FN, false negative: seminal parameter was normal and was incorrectly classified; and TN, true negative: seminal parameter was altered and was correctly classified.

TABLE 5. Accuracy measures obtained by the MLP for each seminal parameter studied.

Parameter	Classification accuracy[a]	Sensitivity[b]	Specificity[c]	Positive predictive value[d]	Negative predictive value[e]
Sperm concentration	90%	95.45%	50%	93.33%	60%
Sperm motility	82%	89.29%	43.75%	89.29%	43.75%

[a] Calculated as $\frac{TP+TN}{TP+FP+FN+TN} \times 100$.

[b] Calculated as $\frac{TP}{TP+FN} \times 100$.

[c] Calculated as $\frac{TN}{FP+TN} \times 100$.

[d] Calculated as $\frac{TP}{TP+FP} \times 100$.

[e] Calculated as $\frac{TN}{FN+TN} \times 100$.

DISCUSSION

In this paper, we have presented the functioning of an ANN, specifically an MLP, as a new approach in the prediction of male fertility potential from life habits and environmental factors. The experiments have been carried out with the data obtained from 100 volunteers between the ages of 18 and 36 yr, and we show the relationship between those factors and semen parameters.

The experiments carried out have achieved very good accuracy parameters for MLP. Among them, classification accuracy, sensitivity, and negative predictive value obtain the highest precision values, whereas specificity and positive predictive value present lower percentages. This situation occurs even when the classification and the confusion matrix are good. We have to find the explanation for this in the input data, because the study population shows an imbalanced distribution [57]—there are more individuals with normal semen parameters than people with alterations. This is very common in AI applied to classification in general and in medicine in particular. The development of this system and its gradual incorporation into medical centers will improve those values.
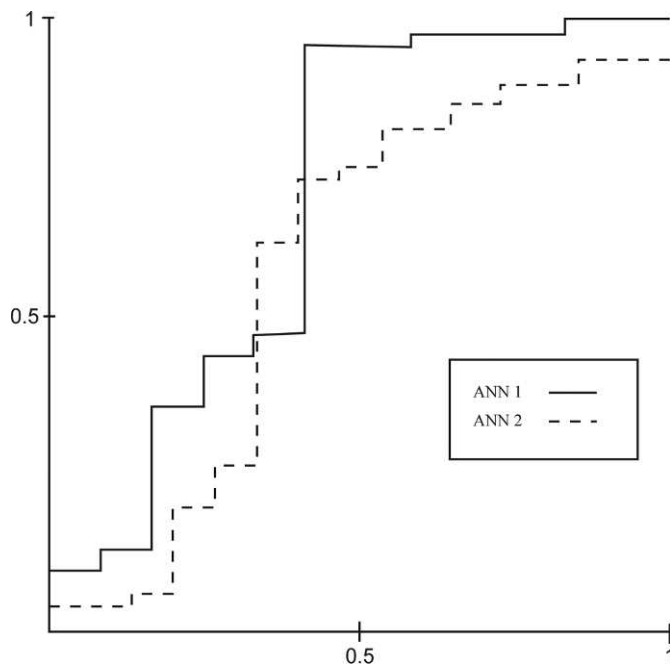
Although there are other good classifiers in the AI field, such as decision trees [43], support vector machines [58], or even hybrid methods that combine ANN and fuzzy neural network [59], the advantage of MLP is the power of its generalization and extrapolation to many different areas. This is especially interesting when one deals with a large and heterogeneous amount of information, and one must evaluate it in the most objective manner possible. In addition, MLP has been used in many other fields [39, 40] with a high accuracy.

Therefore, MLP shows a very interesting approach for the prediction of male fertility potential. In the field of reproductive biology, and particularly male factor studies, ANN has been used to predict the results of in vitro fertilization/intracyto-plasmic sperm injection [32, 33, 35], assess sperm morphology [60] and predict the presence of sperm in the testes of men with nonobstructive azoospermia [36, 61].

Neural network seems to be an alternative to more expensive laboratory tests, at least during the initial moment of the fertility study of the couple, as well as in the selection of semen donors. It is also important to highlight that the study population of this work presents characteristics close to those of regular candidates to become semen donors (i.e., young, male, university students) [48]. It can also help in the prioritization and selection of the next steps of infertility treatment, such as whether to focus on the male partner and potentially avoiding painful and expensive examinations on the female. The authors suggest incorporating this tool into the protocols of the diary of andrologic evaluation in order to obtain a first estimate of the seminal profile.

Other studies in different areas, especially in the field of medicine, have shown several deficiencies and limitations. Most of those problems are related to the complexity of the information treated because of its diversity and heterogeneous data types. In our opinion, the problem is that previous works [62] have approached the study of the relationship between environmental factors/lifestyle and seminal quality using linear statistical techniques. In this paper, we develop the use of nonlinear techniques that may allow a better approach to the complexity of the problem [63, 64].

Related to the different factors used to develop the two neural networks, only age was present in both of them, showing specificity between these particular variables and the semen parameters they affect. In ANN1, which predicts the sperm concentration, one of the factors used is the season in which the analysis was performed. This seems to be in accordance with previous studies that show differences in sperm concentration and total sperm count between seasons [65, 66]. Another factor present in this neural network is the presence of childhood diseases (i.e., mumps, chickenpox, polio). These diseases are usually accompanied by high fever, and in some cases, like mumps, are related to other reproductive problems, like orchitis, factors that are known to impair sperm production in the testis [19, 67]. In relation to this

FIG. 3. Receiver-operator characteristic curves showing the performance of the two neural networks developed (ANN1 and ANN2).

factor, febrile illness is present in this neural network, and other studies have shown a relationship between febrile illness and sperm concentration [68]. Another factor related to heat stress in the testis, that is present in this neural network, is time spent sitting, and sitting time has been previously reported to increase the risk of oligozoospermia [69]. Information on smoking habit and alcohol consumption is a factor used by the neural network in the classification process. The relationship between tobacco and sperm concentration has been shown in several studies [70, 71]. Meanwhile, it seems to be difficult to relate alcohol consumption with an impairment of sperm counts as a single factor [72]. There are two factors—history of surgical intervention and accident or serious traumas (but nontesticular trauma)—without previous studies on their impact in sperm production. Therefore, we suggest further research that can show the possible mechanism of their relationship with sperm concentration. In the second neural network, ANN2, which predicts sperm motility, we found body mass index as a first factor. Although previous studies show this relationship [73], there have been contradictory results, and further studies are needed to evaluate the impact of body mass index in semen quality [74, 75]. Another contradictory factor is marital status. Although it is present in most of the studies on environmental factors, there is no evidence of its influence on semen quality, and on sperm motility in particular [76]. Radiation exposure (i.e., medical x-ray) is known to have a potential detrimental effect on testis function [77] and is included as an input variable in this network. Experiencing an allergy is also included as a factor in the neural network. It has been suggested previously that this factor may affect male fertility potential, but the mechanism of action is not completely known. Another factor included, with contradictory results, is the use of hot baths [78]. For the other factors in this network there is no scientific evidence regarding their influence on semen quality, suggesting the necessity of further investigation. Among these factors are the number of siblings, the exposure to vaccines, and the average hours of sleep by day.

The direct application of AI techniques in previous studies by the authors [44–46, 50] has made it possible to adjust and configure the architecture of ANNs to satisfy the needs of the data analyzed in this study. To allow other investigators access to the ANNs developed, we offer an open access software implementation through the website http://dbt.ua.es/en/research/vida.html.

The next step is to solve the effect of imbalanced classes on classification performance. It has been pointed out that this is one of the drawbacks of the development of MLP, especially in the area of medicine [79]. Increases in data collection, repositories such as data warehouses, will lead to the use of *machine learning* methods, as well as *data mining*, which may provide a more precise correlation between seminal data and information collected by means of questionnaires. In accordance with this, we have donated the whole database from this study to the most important repository of databases used for machine learning tasks, the UCI Machine Learning Repository (http://archive.ics.uci.edu/ml/), at the University of California, Irvine. The purpose of it is to allow other researchers to access this information without limitations.

In conclusion, to our knowledge this is the first time that MLP has been used to evaluate the relationship between life habits and semen quality. The neural networks developed in this study show very high prediction accuracies, being slightly superior in the case of sperm concentration prediction. The construction of two different architectures for the prediction of the two seminal parameters studied, sperm concentration and motility, has helped us to identify those factors that specifically affect each of the two seminal parameters. In this regard, further studies should be carried out in order to propose additional recommendations to improve male fertility potential.

ACKNOWLEDGMENT

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