DE GRUYTER OPEN

STUDIES IN LOGIC, GRAMMAR AND RHETORIC 47 (60) 2016
DOI: 10.1515/slgr-2016-0045

Application of Artificial Neural Networks and Principal Component Analysis to Predict Results of Infertility Treatment Using the IVF Method

Robert Milewski[1], Dorota Jankowska[1], Urszula Cwalina[1], Anna Justyna Milewska[1], Dorota Citko[1], Teresa Więsak[2], Allen Morgan[3], Sławomir Wołczyński[4]

[1] Department of Statistics and Medical Informatics, Medical University of Bialystok, Poland

[2] Department of Gamete and Embryo Biology, Institute of Animal Reproduction and Food Research, Polish Academy of Sciences, Olsztyn, Poland

[3] Shore Institute for Reproductive Medicine, Lakewood, USA

[4] Department of Reproduction and Gynecological Endocrinology, Medical University of Bialystok, Poland

Abstract. There are high hopes for using the artificial neural networks (ANN) technique to predict results of infertility treatment using the in vitro fertilization (IVF) method. Some reports show superiority of the ANN approach over conventional methods. However, fully satisfactory results have not yet been achieved. Hence, there is a need to continue searching for new data describing the treatment process, as well as for new methods of extracting information from these data. There are also some reports that the use of principal component analysis (PCA) before the process of training the neural network can further improve the efficiency of generated models. The aim of the study herein presented was to verify the thesis that the use of PCA increases the effectiveness of the prediction by ANN for the analysis of results of IVF treatment. Results for the PCA-ANN approach proved to be slightly better than the ANN approach, however the obtained differences were not statistically significant.

Introduction

Infertility is a phenomenon affecting both men and women, and the rate at which it affects couples in their reproductive years is increasing. The literature gives different values, but it is estimated that it affects 10 to 20 percent of couples trying to conceive (Case, 2003; Oakley et al., 2008; Radwan, 2011; Wilkes et al., 2009). The only effective method of treatment in this case is often in vitro fertilization (IVF). The development of knowledge,

ISBN 978–83–7431–508–1 ISSN 0860-150X

technology and experience have caused the efficacy of the IVF method in Poland to exceed 40% in recent years (Milewski et al., 2013a), while world literature reports the excess of 50% (Merchant et al., 2011).

A very important factor for increasing the effectiveness of the treatment is the ability to effectively predict the results of treatment based on data, including owned clinical and embryological data. Basic statistical methods predict the effectiveness of treatment only to a limited degree; hence the growing popularity of more advanced data-mining and artificial intelligence methods (Siristatidis et al., 2011). There are high hopes for the artificial neural networks (ANN) technique, which imitates the way the human brain functions. The literature presents works that describe artificial neural network models for predicting the efficacy of the IVF method (Milewski et al., 2009, 2013b).

A common feature of data on this subject is great correlation between independent variables, which can be an important problem when trying to simultaneously incorporate such variables into a created model. For example, in the case of the popular logistic regression method, this situation is a violation of the assumption of no correlation between independent variables. The solution here is to use principal component analysis (PCA), which creates a new set of variables that are uncorrelated with each other, saving the same information as the original features (Milewska et al., 2014). There are reports that the application of PCA may also improve the effectiveness of predictions made with ANN technology (Buciński et al., 2007; Ioele et al., 2011; Jilani et al., 2011). The aim of the study was to determine, through practice, whether the use of PCA improves the effectiveness of predictions made using ANN for the analysis of IVF treatment effects.

Materials and Methods

The data of 1,995 patients treated for infertility at the Shore Institute for Reproductive Medicine in Lakewood, NJ, USA, were analyzed. Each patient's age, number of cells and embryos at various developmental stages, and sperm characteristics were taken into account as numerical independent variables. The type of IVF method (classic IVF/ICSI), causes of infertility and type of applied ovulation stimulation (Antagon/Lupron) were used as the nominal variables. Table 1 presents a description of the considered variables. The dependent variable was clinical pregnancy, confirmed at an ultrasound scanning for gestational sacs. The efficacy of treatment as a percentage of obtained clinical pregnancy was 40.6% (810 out of 1,995 cycles).

Table 1. List of independent variables

Quantitative variables		Qualitative variables	
`Age`	Age of woman	`Insem_type`	ICSI/classical IVF
`Total_nr_eggs`	Number of retrieved eggs	`Tubal`	Tubal factor
`Nr_MII_eggs`	Number of mature eggs	`Endometr`	Endometriosis
`Nr_eggs_ins`	Number of inseminated eggs	`Ovulatory`	Ovulatory factor
`Nr_2pn`	Number of fertilized eggs	`MF`	Male factor
`Nr_cultured`	Number of cultured eggs	`AMA`	Advanced maternal age
`Nr_clvd`	Number of cleavage embryos	`PCOS`	Polycystic ovary syndrome
`Vol_prewash`	Volume of the semen	`DOR`	Diminish ovarian reserve
`Ct_prewash`	Sperm concentration	`Idiopathic`	Idiopathic factor
`Mot_prewash`	Sperm motility	`Stimulation`	Lupron/Antagon

Two popular data-mining methods were used in the study: artificial neural networks and principal component analysis.

Artificial Neural Networks

Artificial Neural Networks (ANN) are a method of data analysis, inspired by the structure of nerve cells and the nervous system (Rojas, 1996; Tadeusiewicz, 1993). The network scheme is reminiscent of the way neurons conduct nerve impulses. The obtained input signal is processed by the network, and is converted into the output signal. The input signal is a set of analyzed data (also called input vector). Classification of the case to a particular category can be treated as an output signal (Bottaci et al., 1997, Pouliakis et al., 2016).

ANN consist of a large number of elements called artificial neurons. They are interconnected by links assigning certain parameters (weights). The weight values change during a learning network process. Most of the presently used ANN have a stratified structure: the input, output and hidden strata located between them (one or more). The learning of such networks is proceeded by repeatedly putting the input data in the first stratum. Activated signals are then sent to the next network strata. Individual neurons convert the received information and learn simultaneously. The teaching process is that the weights of the connections are adjusted to match the network response with the result indicated by the investigator. After the completed learning process, the predictive effectiveness of the network is evaluated. The part of the analyzed data set that was not used in the construction of the network is a testing set. Network effectiveness can be determined by analyzing the frequency of correct responses obtained on the basis of the analysis of the testing set. The aim of this process is to create a network for which the response to the input vectors will be adjusted to the data as closely as possible.

Principal Component Analysis

The primary aim of principal component analysis (PCA) is to reduce the number of variables describing the studied phenomenon, and thus to reduce the dimensionality of the mentioned problem (Gonen, 2016; Jackson, 1991; Jolliffe, 2002). This method is used, for example, to classify cases in a multivariable database, or to reduce its dimension.

This method converts the analyzed set of characteristics into a completely new set of orthogonal variables. New variables, called principal components, represent a linear combination of the input correlated characteristics (Morajda, 2000). The components are arranged according to the decreasing amount of variance of the analyzed data they represent. As a result, they create a new space in which the first coordinates explain the largest part of the variation (Hillier et al., 2006). Principal components are determined by an axis rotation of the input coordinate system, so that the subsequent components, orthogonal to each other, present as much variability, not included by previous factors, as possible. Reduction of the base dimension, while minimizing the loss of information, can be made by rejecting the last components having the smallest variance.

The analyzed data can be projected onto the space spanned by the selected principal components, with a much reduced dimension. Then it is possible to observe rules and relationships in the data that were previously invisible (Buciński et al., 2007; Massart et al., 2004a, 2004b). PCA is used when the planned analysis requires that included variables are uncorrelated.

Experiment Design

In the first step of the experiment, the estimation of differences in the distributions of all independent variables between the groups, defined in accordance with the result of treatment (clinical pregnancy / lack of clinical pregnancy), was conducted. For further analysis, the variables for which differences between analyzed groups were statistically significant were selected. These variables generally contain information that affects the accuracy of predicting infertility treatment results.

On the selected set of independent variables and for the dependent variable (clinical pregnancy), the neural network learning process was performed. To find the best possible network, the learning process was repeated 3,000 times with random startup parameters (type of network, activation functions, error function and an initial value of the generator) each time. Next, the correlation matrix for quantitative independent variables was calculated and a set of variables highly correlated with each other was selected. For this set, principal component analysis was performed, resulting in a set of uncorrelated principal components, saving the same information as the original set of correlated variables. For the created principal components, the differences in their distributions between the groups, defined in accordance with the result of treatment (clinical pregnancy / lack of clinical pregnancy), were estimated. The variables that showed statistically significant differences between the analyzed groups were selected for further analysis.

Selected in this way, the principal components replaced the correlated set of independent variables and the learning process of the neural network was performed again. After repeating an analogous process 3,000 times, the network that best predicted the occurrence of clinical pregnancy was chosen. Both networks were compared in terms of their effectiveness in predicting the results of treatment.

Statistical Analysis

For the statistical analysis, the Chi-square test of independence was used to check the association between the qualitative variables. Normality of distribution was tested using the Kolmogorov-Smirnov test with the Lilliefors correction and the Shapiro-Wilk test. The quantitative variables were not normally distributed. To compare the quantitative variables between groups, i.e. those exhibiting clinical pregnancy or lack of clinical pregnancy, the nonparametric U Mann-Whitney test was used. To analyze the strength of correlations between the quantitative variables, Spearman's rank correlation coefficients were calculated. The data were also analyzed using artificial neural networks and principal component analysis methods with application of the Statistica 12.0 software (StatSoft, Tulsa, OK, USA). To determine the quality of obtained predictors, the receiver operating characteristic (ROC) curves and area under the curve (AUC) were analyzed (Hanley et al., 1982). The results were considered statistically significant at the level of $p < 0.05$.

Results

The results of the comparison of independent variables (both quantitative and qualitative) between groups – those exhibiting clinical pregnancy and lack of clinical pregnancy – are presented in Table 2. Due to the lack of normal distribution of quantitative variables, they were characterized by

Table 2. Comparison of independent variables between pregnancy and non-pregnancy groups

Parameter	Clinical pregnancy Me (Q1; Q3) / N (%)	Lack of clinical pregnancy Me (Q1; Q3) / N (%)	p-value
Age	34 (31; 36)	35 (32; 38)	<0.0001
Total_nr_eggs	13 (9; 18)	11 (7; 16)	<0.0001
Nr_MII_eggs	10 (7; 14)	8 (5; 12)	<0.0001
Nr_eggs_ins	11 (7; 15)	9 (5; 13)	<0.0001
Nr_2pn	7 (5; 11)	6 (3; 9)	<0.0001
Nr_cultured	7 (5; 10)	6 (3; 9)	<0.0001
Nr_clvd	7 (5; 9)	5 (3; 8)	<0.0001
Vol_prewash	2.5 (2.0; 3.8)	2.5 (2.0; 3.5)	0.19
Ct_prewash	34.8 (14.7; 63.4)	36.3 (15.1; 67.3)	0.25
Mot_prewash	60.0 (39.0; 73.0)	61.0 (43.0; 73.3)	0.14
Insem_type ICSI IVF	 493 (60.86%) 317 (39.14%)	 775 (65.40%) 410 (34.60%)	0.04
Tubal	136 (16.79%)	224 (18.90%)	0.23
Endometr	169 (20.86%)	237 (20.00%)	0.64
Ovulatory	105 (12.96%)	141 (11.90%)	0.48
MF	346 (42.72%)	464 (39.16%)	0.11
AMA	60 (7.41%)	102 (8.61%)	0.34
PCOS	22 (2.72%)	22 (1.86%)	0.20
DOR	129 (15.93%)	229 (19.32%)	0.05
Idiopathic	25 (3.09%)	38 (3.21%)	0.88
Stimulation Lupron Antagon	 665 (82.10%) 145 (17.90%)	 921 (77.72%) 264 (22.28%)	0.02

the median and quartiles, while qualitative variables were presented as numbers and percentages.

Significant differences were found for women's age and all parameters related to the number of cells and embryos at various developmental stages, as well as for kind of insemination and type of ovulation stimulation. There were no statistically significant differences for the sperm quality parameters and causes of infertility. Therefore, these variables were excluded from further analysis.

Later on, we started to train the neural network predicting the occurrence of clinical pregnancy based on the independent variables with $p < 0.05$ (Table 2). The training network process was repeated 3,000 times. Based on the quality of training, testing and validation, the following network was chosen: three-layer perception with 11 neurons in the input layer, 5 neurons in the hidden layer and two neurons in the output layer (for 9 input variables and one output variable). Table 3 contains the parameters of the selected network.

Table 3. Characteristics of the selected artificial neural network

Network name	Quality (training)	Quality (validation)	Quality (testing)	Training algorithm	Error function	Activation (hidden)	Activation (output)
MLP 11-5-2	62.133	63.880	61.873	BFGS 37	Entropy	Tanh	Softmax

Based on the created network, the probability of achieving clinical pregnancy was calculated for each patient. This parameter was analyzed using the ROC curve, and the area under the curve was AUC = 0.663 with a 95% confidence interval (0.634; 0.691). Figure 1 shows the obtained ROC curve. Table 4 presents the predictive effectiveness of the created neural network model. Checking the model on a validation set produces very similar results (AUC = 0.662), which confirms the quality of the created network.

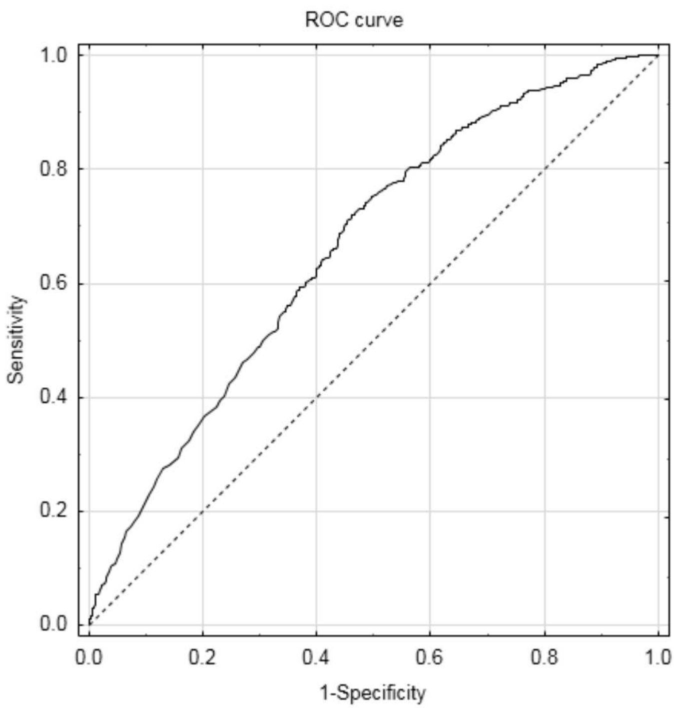

Figure 1. The ROC Curve for the created artificial neural network model

Table 4. The predictive effectiveness of the created neural network model

		The real IVF result	
		Clinical pregnancy	Lack of clinical pregnancy
Artificial neural network	Clinical pregnancy	244	221
	Lack of clinical pregnancy	308	624

Table 5 presents the correlations between quantitative independent variables. All variables except woman's age are strongly correlated with each other (the smallest correlation coefficient is R = 0.73). Woman's age is negatively and poorly correlated with other parameters (the strongest correlation is R = −0.21). Therefore, 6 independent variables describing the number of cells and embryos at various stages of development were selected for principal component analysis.

Table 5. Correlations between independent variables

	Total_nr_eggs	Nr_MII_eggs	Nr_eggs_ins	Nr_2pn	Nr_cultured	Nr_clvd
Age	−0.21	−0.20	−0.19	−0.18	−0.16	−0.16
Total_nr_eggs		0.89	0.88	0.77	0.74	0.73
Nr_MII_eggs			0.96	0.87	0.84	0.83
Nr_eggs_ins				0.86	0.83	0.81
Nr_2pn					0.97	0.96
Nr_cultured						0.99

As a result of the PCA method, 6 new f1–f6 variables (principal components) were created. These new components contained the same information as the input variables, but they were not correlated with each other. The matrix of coefficients of linear combinations for the principal components f1–f6 is presented in Table 6.

New f_1–f_6 variables were analyzed in order to estimate the differences in their distributions between the groups defined in accordance with the result of treatment (clinical pregnancy/lack of clinical pregnancy). Statistically

Table 6. Coefficients of the new variables obtained using the PCA method

	f_1	f_2	f_3	f_4	f_5	f_6
Total_nr_eggs	– 0.389358	– 0.512987	– 0.697632	0.295046	– 0.107177	0.003858
Nr_MII_eggs	– 0.418063	– 0.306760	0.306116	– 0.072491	0.795072	0.004595
Nr_eggs_ins	– 0.411222	– 0.356595	0.342444	– 0.547340	– 0.535496	– 0.011473
Nr_2pn	– 0.417464	0.180315	0.446618	0.726237	– 0.255494	– 0.032325
Nr_cultured	– 0.407594	0.483879	– 0.206953	– 0.184068	0.031095	0.722530
Nr_clvd	– 0.405106	0.498929	– 0.245025	– 0.216356	0.058091	– 0.690462

significant differences were obtained for all parameters except f_3 ($p = 0.22$). Therefore, this variable was excluded from further analysis. The other 5 variables were included in the set of independent variables in place of the parameters describing the number of cells and embryos at various stages of development. For the resulting set of independent variables, the ANN analysis was performed again (3,000 repetitions) and the neural network optimal for clinical pregnancy prediction was selected. Table 7 contains the parameters of the selected network.

Table 7. Characteristics of the selected artificial neural network (after PCA)

Network name	Quality (training)	Quality (validation)	Quality (testing)	Training algorithm	Error function	Activation (hidden)	Activation (output)
MLP 10-10-2	62.777	64.883	61.204	BFGS 41	SOS	Logistic	Logistic

Based on the created network, the probability of achieving clinical pregnancy was calculated for each patient. This parameter was analyzed using the ROC curve and the area under the curve was AUC = 0.666 with a 95% confidence interval (0.638; 0.694). Figure 2 shows the obtained ROC curve. The predictive effectiveness of the created neural network model is presented in Table 8. Checking the model on a validation set provided similar or even slightly higher results (AUC = 0.671), which confirms the quality of the created network.

The results of the neural network model for data after the applied PCA method are slightly better than without application of PCA: AUC = 0.666 vs. AUC = 0.663 (for validation set AUC = 0.671 vs. AUC = 0.662), however the differences are not statistically significant.

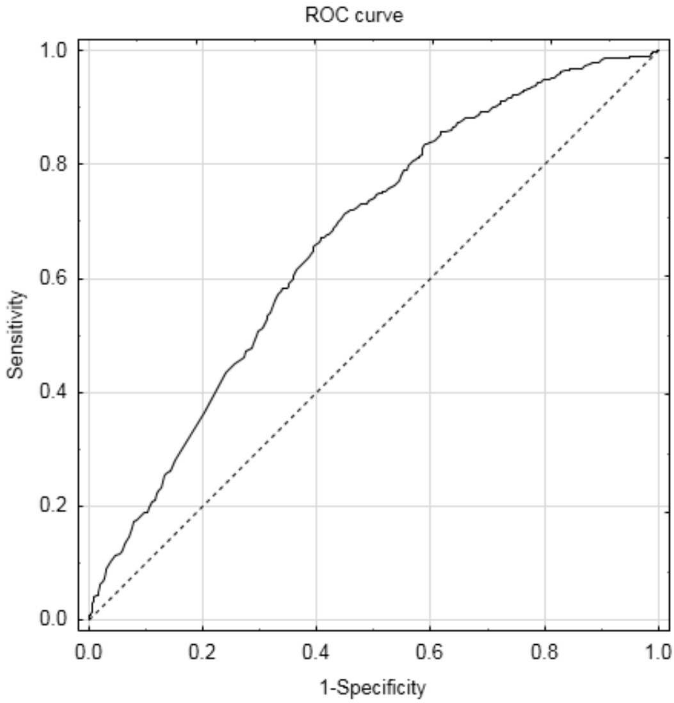

Figure 2. The ROC Curve for the created artificial neural network model (after PCA)

Table 8. The predictive effectiveness of the created neural network model (after PCA)

		The real IVF result	
		Clinical pregnancy	Lack of clinical pregnancy
Artificial neural network	Clinical pregnancy	252	220
	Lack of clinical pregnancy	300	625

Discussion and Conclusions

Many different factors affect the results of infertility treatment using the IVF method (factors that are often unrecorded during treatment or even impossible to measure), hence predictive effectiveness of success is limited. The application of classical statistical methods gives unsatisfactory results; therefore, there is a need to use complex methods (data mining, artificial intelligence) to extract maximum information from the data. There are high hopes for the artificial neural networks (ANN) technique, for which effectiveness of pregnancy prediction has already been confirmed (Milewski et al., 2009, 2013b). Neural networks-based models give better results than classical statistical models but the level of prediction quality is not fully satisfactory yet, hence there is a need for continued research into finding more effective solutions.

Several applications indicate that the combination of advanced mathematical or statistical methods provides more accurate results than those obtained by the application of single classical techniques (Dinç et al., 2007). Reports have appeared in the literature that have indicated that preceding the neural network training process with use of the PCA method for inputting data can increase the predictive power of obtained models. In recent years, e.g., in Chemistry, combined methods based on artificial neural networks and principal component analysis have been proposed for the analysis of mixtures when spectral data were complex or when noise interference, nonlinear, and interaction interferences were present (Jin-Mei et al., 2007). Ioele et al. (2011) suggest that the combined use of PCA and ANN usually improves the training speed and enhances the robustness and quality of created models. They compare both approaches, ANN vs. PCA-ANN, highlighting the superiority of the second approach. The authors illustrated that both of the ANN models were reliable, but that the PCA-ANN model demonstrated a better prediction quality, showing lower residual errors. Morajda (2000) claims that PCA is a tool commonly used to perform decorrelation of the input data, for example, before applying ANN technology.

Besides orthogonalization of the initial space, this method also allows for the reduction of dimensionality. It is particularly useful if data contains a lot of correlated input variables. Elrharras et al. (2015) present design and implementation on an FPGA device of a new method of spectrum sensing based on PCA and ANN. They argue that PCA is used to reduce the ANN complexity. Chen et al. (2009) introduce the qualitative identification of different wine through use of an electronic nose. They adopt principal component analysis and artificial neural networks technology to investigate this issue. They prove that the combination of PCA and ANN is a valid method to use in classification and pattern recognition problems.

The PCA-ANN approach also has many applications in medicine. Buciński et al. (2007) show the application of PCA and ANN for breast cancer recurrence prediction using the original data set analysis based on uniform long-term records. They prove that PCA and ANN analyses allow for a practically unlimited number of either mutually related or unrelated factors to be tested. Jilani et al. (2011) use PCA-ANN technology for classification of hepatitis-C patients. The accuracy obtained from their applied process is impressive: 99.1% for training data and 100% for testing data.

In the current study, evaluation of whether the transformation of input data using the PCA method affects the quality of obtained neural networks has been attempted. The results of such analysis can only be approximate, because the neural network training process depends on many parameters, which are usually randomly determined, and the process of training the network is often repeated many thousands of times. Thus, the objection that the differences, or lack thereof, obtained in the two approaches can be caused by a random factor that led to a more favorable selection of the parameters to train the network in one approach, and was passed on in the second approach, is valid. However, an attempt was made to practically verify the effectiveness of the two approaches, repeating the training procedure 3,000 times in each case. The set of six variables highly correlated with each other, describing the number of cells and embryos at various stages of development, were analyzed using the PCA method. These variables were replaced with uncorrelated principal components when the PCA-ANN approach was used. In both approaches, the network with the best prediction parameters was selected. We found that the network has a slightly better predictive effectiveness for the PCA-ANN approach (AUC = 0.666 vs. AUC = 0.663 for the training set and AUC = 0.671 vs. AUC = 0.662 for the validation set), but the differences were not statistically significant. Thus, this study failed to indicate a situation where the use of the PCA method significantly improves the quality of prediction. However, as mentioned above, this is not proof of the lack of positive effect of this method on the obtained results. There can be many reasons for this; perhaps the specifics of the collected data influenced the reduction of the effect, but the results presented in the literature are enough to encourage further development of combined PCA-ANN technology.

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