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# Application of neuron networks in the diagnostics of endometrial pathologies

## Zastosowanie sieci neuronowych w diagnostyce patologii *endometrium*

Kotarska Maria[1], Smoleń Agata[2], Stachowicz Norbert[3], Kotarski Jan[3]

[1] University of Nevada, Las Vegas, USA
[2] Department of Mathematics and Biostatistics, Medical University of Lublin, Poland
[3] Ist Department of Oncological Gynecology and Gynecology, Medical University of Lublin, Poland

**Abstract**

***Aim:*** *The aim of the study was to construct neuron networks utilizing selected risk factors and ultrasonographic (USG) examination parameters in a two-dimensional (2D) and three-dimensional (3D) presentation in relation to endometrial pathologies.*

***Materials and methods:*** *The following risk factors were statistically analyzed: age and menopausal status, parity, using hormonal replacement therapy (HRT), BMI, 2D USG of the endometrium (thickness, uterine artery blood flow indices) and 3D USG (volume, vascularization indices) in relation to the result of histopathological examination of the endometrial tissue in 421 women, aged 22-87 years, with abnormal bleeding from the uterus. The changes of the sensitivity and specificity in the applied models corresponding to changes of the limit value, were presented in the form of receiver operating characteristic curves (ROC) and the comparison of the values of the area under the curve (AUC). The threshold value for the obtained models was established and models of artificial neuron networks (ANN) were constructed on the basis of the ROC.*

***Conclusion:*** *Application of artificial neural networks in medicine has been developing rapidly. They have been applied in pre-surgical differentiation of ovarian tumors and other neoplasms. In case of endometrial carcinoma the degree of clinical usage of artificial neural networks has been limited, despite the fact that, from the mathematical point of view, the differentiation using neural networks would be much more precise than the one that could be obtained by chance.*

Key words: **neural networks** / **uterine bleeding** / **endometrial diseases** / / **sonography** /

**Corresponding author:**
Jan Kotarski
1st Department of Oncological Gynecology and Gyecology, Medical University of Lublin, Poland
Poland, 20-081 Lublin, Staszica 16
tel./fax: +48 81 53 27 847
e-mail: j.kotarski@am.lublin.pl

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## Streszczenie

***Cel pracy:*** *Celem pracy było skonstruowanie sztucznych sieci neuronowych wykorzystujących wybrane czynniki ryzyka oraz parametry oceny ultrasonograficznej (USG) w prezentacji dwuwymiarowej (2D) i trójwymiarowej (3D) w odniesieniu do patologii endometrium.*

***Materiał i metody:*** *Analizie statystycznej poddano czynniki ryzyka: wiek oraz status menopauzalny, rodność, stosowanie hormonalnej terapii zastęczej, BMI, 2D USG endometrium (grubość, indeksy przepływu krwi w t. macicznej) i 3D (objętość, wskaźniki naczyniowe) w odniesieniu do wyniku badania histopatologicznego z endometrium u 421 kobiet z nieprawidłowym krwawieniem z macicy w wieku 22-87 lat. Zmiany czułości i specyficzności przy przesuwaniu wartości granicznej, dla zastosowanych modeli przedstawiono w formie krzywych ROC (Receiver Operating Characteristic Curves) oraz porównania wartości pola pod badanymi krzywymi AUC (Area Under the Curve). Na podstawie krzywych ROC stwierdzono wartość progową dla uzyskanych modeli oraz skonstruowano modele sztucznych sieci neuronowych (ANN).*

***Wnioski:*** *Wykorzystanie sztucznych sieci neuronowych w medycynie rozwija się dynamicznie. Znalazły one zastosowanie w przedoperacyjnym różnicowaniu guzów jajnika oraz innych nowotworów. W odniesieniu do raka endometrium pomimo tego, że z punktu widzenia matematycznego różnicowanie jest znacznie lepsze niż można by otrzymać przez przypadek, to jednak z punktu widzenia klinicznego w chwili obecnej zastosowanie ich jest ograniczone.*


Słowa kluczowe: **sieci neuronowe** / **krwawienia maciczne** / **choroby *endometrium*** / / **sonografia** /

## Introduction

Many complex biological functions are not characterized via linear relationships and cannot be described using simple statistical methods. Advanced statistical models enable us to describe difficult to discover relationships within biological functions [1, 2, 3, 4, 5]. Neural networks as advanced statistical models are capable of describing non-linear and complex relationships, even in multidimensional problems with a large number of variables.

Neural networks are most commonly used to solve regression type problems, related to classification of data and prediction of trends. In classification type problems neural networks assign the given date to appropriate categories. Specific values of each variable are represented as a series of input values into each artificial neuron. The main task of each artificial neuron is to transform the input data into the output values. Each input value is assigned a given weight: w1, w2...wn. Series of input signals are summed up with their appropriate weights, and fed into the activation function, which can be represented mathematically in several ways, depending on the nature of the studied problem.

Interconnections between neurons and the direction of the signal flow determines the type of the neural network. Networks also differ in the methods in which input values are assigned weights and the training algorithms used. Generally, neural networks have layered architecture, where we can distinguish input, hidden, and output layers. The number of studied parameters, which we can use to represent input variables for the desired model, controls the number of input neurons. Neurons of the input layer introduce the input data into the hidden layer of the neural network, where the given data is processed in order to obtain the solution to the given problem in the output layer, which is the answer to the studied question.

An important factor in construction of a neural network is the choice of the appropriate learning algorithm. During training the neural network 'learns' to minimize error and match the output values with the desired target values.

The assigned weights are modified accordingly in order to minimize error. The most common learning mechanisms involve supervised and unsupervised algorithms, where the given model is trained with or without target values provided, accordingly.

Currently in medicine there are no specific diagnostic methods which can be applied in screening exams for endometrial cancer. Risk factors, for which pathological relationship with endometrial cancer is well documented, show a large variability within populations and do not allow for a successful selection of the group of patients with a high risk of endometrial cancer [6].

USG exam provides physicians with important information regarding the morphology of endometrium, however USG parameters do not have sufficient specificity and sensitivity. Today only a microscopic study of endometrial tissue can confirm the presence of endometrial cancer; it is therefore necessary to aim for the development of noninvasive diagnostic methods.

The aim of the study was to develop a neural networks model, based on chosen risk factors, as well as 2D and 3D USG parameters with respect to pathology of the endometrium.

In efforts to decrease mortality rates due to endometrial cancer, there are many extensive research studies that aim to identify specific markers for this neoplasm. Presently, there is no successful screening method. Currently available diagnostic tools involve microscopic evaluation of endometrial tissue after a D&C or a hysteroscopy. We suspect that the analysis combining endometrial cancer risk factors with 2D and 3D USG parameters, based on advanced statistical methods, will allow for the construction of a predictive model for non-invasive differentiation of endometrial cancer and other endometrial pathologies.

The aim of the study was to differentiate between:

a. Normal and pathological endometrium,
b. Non-neoplastic endometrium and EC.

## Material & Methods

The study analyzed data from 421 women with uterine bleeding from The 1st Department of Oncological Gynecology and Gynecology Medical University in Lublin. Patient age ranged from 22 to 67 years. The main criterion for D&C and histological verification of endometrium in all patients was abnormal uterine bleeding. Patients with bleeding during pregnancy, uterine fibrioids, and adenomyosis were excluded from our analysis.

Based on medical documentation, selected risk factors were identified for all patients and included: age, menopause, parity, use of Hormonal Replacement Therapy (HRT), body mass index, as well as 2D ultrasound parameters (endometrial thickness, flow parameters for uterine arteries: SD, PI, RI, and PSV, EDV, MnV), and 3D parameters (volume, vascularization indices: Vascular index-VI, Flow index-FI, Vascular Flow Index – VFI, and MG).

**Definitions**

With regard to patient age, the studied group was arbitrarily divided into patients below and above 50 years of age. Menopause was defined according to WHO as last menstrual bleeding within 12 months. Weight was expressed in kilograms and patients were analyzed in groups of below and above 75 kg in weight. BMI was calculated and the norm was defined as 18.5-24.5, overweight as 25-29.5, and obesity as BMI over 30.

The results were presented in relation to the histology of endometrium for each patient. Normal endometrium was defined as proliferative, secretive, and atrophic. All types of hyperplasia were analyzed together. Clinical data was analyzed in two groups:

I. Patients with normal versus pathological endometrium (hyperplasic and EC)
II. Patients with non-neoplastic (normal plus hyperplasia) versus EC

**Endometrium was evaluated using 2D and 3D ultrasound**

Data was collected using Kretz Voluson V730 and GE Voluson E8 machine with transvaginal 5-9MHz probe, and transabdominal 3.5-5 MHz probe with the color and "power" angio Doppler capabilities. Volume and flow parameters were measured using post processing VOCAL tm software ("Virtual Organ computer-aided Analysis"). Patients were instructed to rest in supine position for 20 min prior to measurements being taken. One physician collected all data (NS).

**Statistical Analysis**

Statistical analysis was performed on selected risk factors and the 2D and 3D ultrasound parameters. Diagnostic accuracy was assed by the comparison between the given test result and the histopathology results obtained surgically. Sensitivity and specificity was calculated for each parameter. Changes in sensitivity and specificity for different threshold values for the constructed models were presented on ROC (Receiver Operating Characteristic Curve) and by comparison of the AUCs (Area Under the Curve) for the obtained graphs. Optimal cut off and threshold values for each constructed model were determined based on ROC analysis. ROC curves were constructed using GraphROC software for Windows (Graph ROC Software, Finland).

**Artificial Neural Networks (ANN)**

The constructed models utilized linear neural networks, multilayer perceptrons, radial basis function, and probabilistic neural networks. Database was randomly divided into three sets training, testing and validating.

Multilayer perceptrons were trained using the back propagation algorithm of supervised learning. Nonlinear function was used as an activation function. Using the data to adjust the network's weights and thresholds minimized errors in perditions for the training set. All studied parameters were appropriately scaled and used as input data. All nominal-valued parameters were represented numerically, and all numerical parameters were assigned a linear value between 0-1. Numerical output values for each variable were in the range (0,1).

Confidence levels with accept and reject threshold levels, which must be exceeded before the unit is deemed to make the decision, were adopted. Variables with output values above the accept threshold level were classified into the groups of patients with normal or non-neoplastic endometrium, respectively per the given analysis. Neural networks were constructed with STATISTICA DATA MINER 8.0 software (Statsoft, Poland).

## Results

**data analysis based on constructed Artificial Neural Networks.**

Classification of patients with normal and pathological endometrium, based on three layer neural network (ANN1).

The constructed model consisted of six input neurons and three neurons in the hidden layer. The structure of ANN1 neural network is displayed in Figure 1.

Model was built using statistically significant input parameters: age, menopause, hormonal replacement therapy, as well as the following ultrasound parameters: endometrial thickness, VI, and MG. (Table I).

With the accepted threshold level for the probability of endometrial pathology above 50%, in the training set the sensitivity of the model was 65%, and specificity 45%. In the testing set the model has sensitivity of 51%, and specificity of 42%, while in validation set the obtained values were 56% and 40%, respectively. (Table II).

Diagnostic accuracy of the constructed model was described with the following ROC graph. The area under the curve for the given ANN1 model was 0,8799. (Figure 2).

Classification of patients with non-neoplastic endometrium and EC was based on a three layer neural network (ANN2). Constructed model consisted of seven input neurons and four neurons in the hidden layer. (Figure 2).

Constructed neural network (ANN2) chose the following input parameters as statistically significant: age, hormonal replacement therapy, endometrial thickness, VI, VFI, PSV, and MG. (Table III).

With the accepted threshold level for the probability of endometrial cancer above 50%, in the training set the sensitivity of the model was 27%, and specificity 82%. In the testing set the model has sensitivity of 1%, and specificity of 71%, while in validation set the obtained values were 30% and 77% respectively. (Table IV). Diagnostic accuracy of the constructed model was described with the following ROC graph. The area under the curve for the given ANN2 model was 0,8213. (Figure 4).

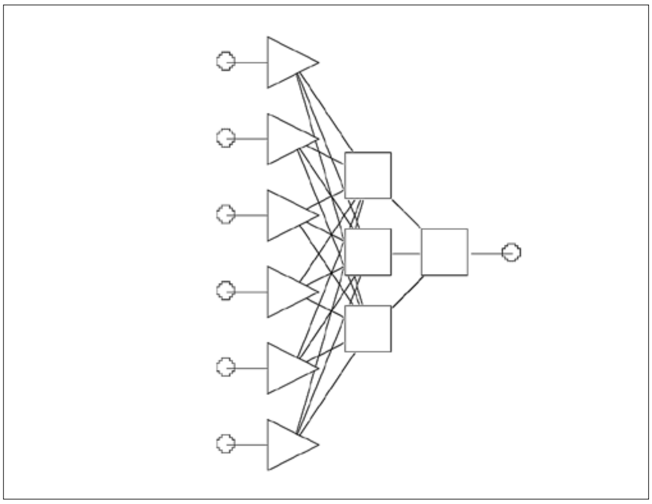

**Figure 1.** Constructed neural network model (ANN1) classifying between normal and pathological endometrium.

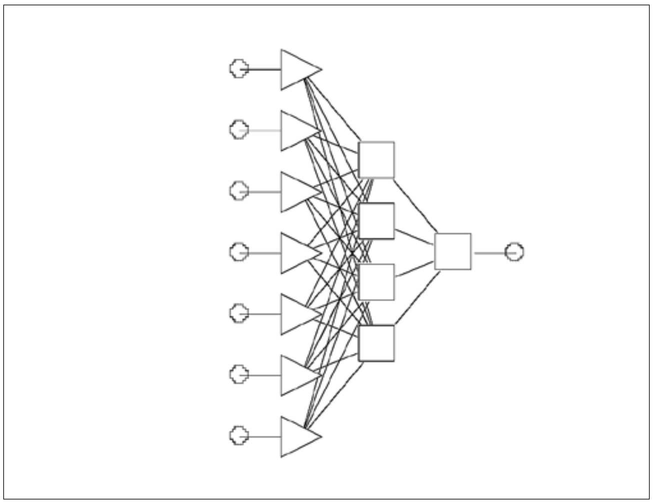

**Figure 3.** Constructed neural network model (ANN2) classifying between patients with non-neoplasm endometrium and endometrial cancer.

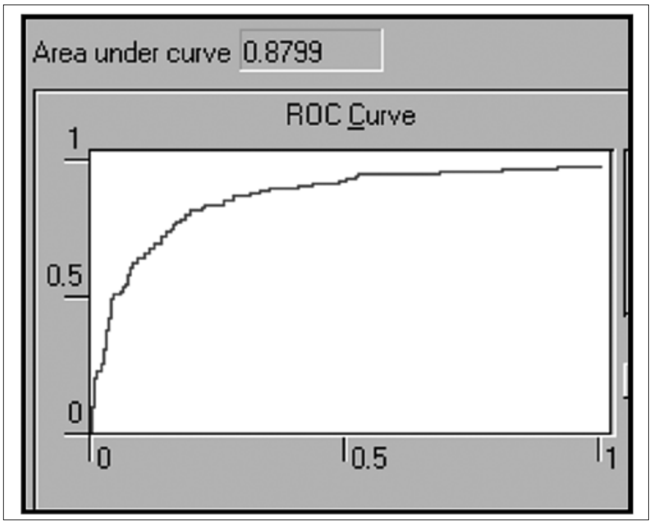


**Figure 2.** ROC curve for the ANN1 model classifying patients with normal vs. pathological endometrium.

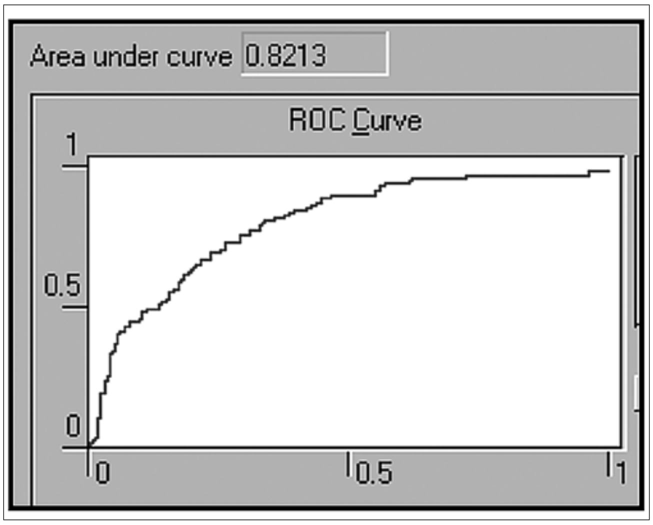


**Figure 4.** ROC curve for the ANN2 model classifying between patients with non-neoplastic endometrium and endometrial cancer.

## Discussion

Cancer sickness and death rates are continually increasing. Current predictions show that by 2020 the number of deaths due to cancer will be significantly higher in comparison with hearth disease.

Detection of pre-cancer stages, as well as early detection of cancer, has a significant effect on patient potential to survive in oncology. In developed countries cervical cancer screening programs have reduced the incidence of invasive cervical cancer by 50% or more. They show high diagnostic accuracy in detection of hyperplastic endometrium and early carcinoma. Unfortunately, in relation to endometrial cancer, no screening methods have been developed to make population screening exams.

For many years epidemiological studies have attempted to identify risk factors for endometrial cancer. However, despite strong pathogenetic correlation between the risk factors and oncogenesis, in practice it is not possible to use these relationships to identify a group of patients who require special oncologic care. Probably, due to the fact that in endometrial tumors we can favor different pathogenetic tumors, hormonal-dependent or hormonal-independent.

2D and 3D ultrasound is a noninvasive method commonly used to evaluate endometrium. Advancing technology allows physicians to evaluate more advanced morphology (thickness, volume), as well as more complex flow parameters, which provide characteristics for the perfusion of the organ [7].

Even though the new indices which can characterize endometrial vascularization and blood circulation were introduced to supply us with new information on the endometrial findings, their value is still lower than recognized factors like endometrial thickness or volume.

**Table I.** Input parameters for the ANN1 model.

| | WIEK | MNP | GRUB_END | VI | MG | HTZ |
|---|---|---|---|---|---|---|
| Rank | 1 | 3 | 4 | 2 | 5 | 6 |
| Error | 0.3926312 | 0.3874132 | 0.3836114 | 0.3875929 | 0.3833666 | 0.3674682 |
| Ratio | 1.089122 | 1.074648 | 1.064102 | 1.075146 | 1.063423 | 1.019322 |
| Rank | 4 | 5 | 3 | 1 | 6 | 2 |
| Error | 0.4165883 | 0.4111054 | 0.4167805 | 0.4205755 | 0.3899118 | 0.4199094 |
| Ratio | 1.08059 | 1.066367 | 1.081088 | 1.090932 | 1.011393 | 1.089204 |

**Table II.** Classification results for the constructed ANN1 model. Black, red and blue colors represent training, validating, and testing sets respectively .

| | n | r | n | r | n | r |
|---|---|---|---|---|---|---|
| Total | 131 | 80 | 57 | 48 | 57 | 48 |
| Correct | 85 | 36 | 32 | 19 | 29 | 20 |
| Wrong | 6 | 5 | 1 | 5 | 2 | 3 |
| Unknown | 40 | 39 | 24 | 24 | 26 | 25 |
| n | 85 | 5 | 32 | 5 | 29 | 3 |
| r | 6 | 36 | 1 | 19 | 2 | 20 |

**Table III.** Input parameters for the neural network (ANN2) classifying between patients with non-neoplasm endometrium and endometrial cancer.

| | WIEK | GRUB_END | VI | VFI | MG | PSV | HTZ |
|---|---|---|---|---|---|---|---|
| Rank | 5 | 3 | 6 | 7 | 4 | 2 | 1 |
| Error | 0.3608622 | 0.3912089 | 0.3413104 | 0.3361915 | 0.3742468 | 0.3939316 | 0.4542749 |
| Ratio | 1.084925 | 1.176162 | 1.026143 | 1.010753 | 1.125166 | 1.184348 | 1.365769 |
| Rank | 5 | 2 | 6 | 7 | 3 | 4 | 1 |
| Error | 0.3859819 | 0.4209792 | 0.377683 | 0.3719336 | 0.4080745 | 0.3923217 | 0.4875368 |
| Ratio | 1.052203 | 1.147607 | 1.02958 | 1.013907 | 1.112428 | 1.069486 | 1.329046 |

**Table IV.** Classification results for the model ANN2.

| | r | n | r | n | r | n |
|---|---|---|---|---|---|---|
| Total | 160 | 51 | 75 | 30 | 82 | 23 |
| Correct | 123 | 14 | 58 | 9 | 58 | 1 |
| Wrong | 2 | 11 | 1 | 7 | 7 | 12 |
| Unknown | 35 | 26 | 16 | 14 | 17 | 10 |
| r | 123 | 11 | 58 | 7 | 58 | 12 |
| n | 2 | 14 | 1 | 9 | 7 | 1 |

The above reasons provide basis for the studies that aim to utilize advanced mathematical models based on selected risk factors and ultrasound parameters characterizing endometrium, especially since the effects of even well documented risk factors vary greatly, depending on the source.

The results of studies analyzing the risk factors are difficult to interpret directly, because publications concerned with the Polish population of women significantly differ in their methods.

The publication by Brinton et al. [6] published in 2007, which studied 2476 women, including 551 with endometrial cancer, seems to be the most relevant. In comparison to our study, there might be some discrepancy in results due to the fact that Brinton's study analyzed patients from large and industrialized cities, while population of our study included women from a typical farming region.

Statistical analysis was designed based on the assumption that the studied patients represent a pre-selected population.

Selection for the study was based on two criteria: pathological symptoms – bleeding, and elimination of organic causes of bleeding designated as the exclusion from the study. Despite the fact that chosen selection criteria significantly limited the population available for the study, the chosen system maximized the probability that within the selected patient the bleeding was caused by the pathology of endometrium. In order to minimize differences in risk factors due to demographics, data was analyzed not only for all of the studied patients, but also within specific subdivisions. Ultrasound parameters were divided into 2D and 3D data sets and all statistical analysis was done with that distinction.

Currently, ultrasound has become one of the most commonly performed tests to evaluate female reproductive organs, due to physician recommendations as well as patient requests, which makes the 2D and 3D parameters very important factors in our analysis. Despite the fact that there have been many publications devoted to the evaluation of endometrium with 2D and 3D ultrasound parameters, agreement is yet to be been reached as to which parameters can help differentiate between benign or malicious tumors or other reasons of uterine bleeding [8, 9, 10, 11, 12].

The theory of artificial neural networks has been developing dynamically within the last decade. Neural networks have been successfully implemented within many areas of life including medicine [13, 14, 15]. It is one of few methods capable of performing advanced mathematical operations at a very low cost of implementation.

The study performed statistical analysis of the selected risk factors, we well as 2D and 3D ultrasound parameters in differentiation between: I endometrial pathology, II endometrial cancer.

Three layer neural network models were designed in order to perform the desired classification within the studied groups. For the differentiation between normal and pathological endometrium the constructed model chose the following parameters as significant: age, menopause, HRT, as well ultrasound parameters: endometrial thickness, FI and MG. The model (ANN1) showed the highest diagnostic accuracy, and obtained area under the curve 0,8799 in the ROC analysis, which is constant with findings by Stachowicz et al., [16]. The constructed network was trained via supervised learning and the training set consisted of 211 patients. In this set, the network correctly classified 20 out of 48 women with endometrial pathology, and 29 out of 57 women with normal endometrium.

The next neural network was constructed in order to differentiate between non-neoplastic endometrium and endometrial cancer. The model chose the following parameters as statistically significant: age, HRT, and ultrasound parameters: endometrial thickness, VI, VFI, PSV, and MG. The diagnostic accuracy of the model was assessed via ROC analysis and the model obtained the area under the curve of 0,8213. In the testing set, the model correctly classified only 1 out of 23 patients with endometrial cancer and 58 out of 82 women with non-neoplastic endometrium. Smaller diagnostic accuracy of this model is surprising, especially considering the fact that the model used higher number of parameters to solve the classification problem in comparison with the neural network differentiating between normal and pathological endometrium.

One of the most important factors when constructing a neural network is the number of hidden layers, which directly influences the effectiveness of the training process. In case of applying too few hidden layers, the training process could be hindered, or even become impossible. On the other hand, too many hidden layers can cause the model to lose the ability to generalize and produce output values.

In our studies we attempted to construct four-layer neural network models, with two hidden layers and more input parameters. However, the constructed model was not able to successfully complete its training and generate output values for the given classification problems.

## Conclusion

There is dynamic increase in the application of neural networks in medicine. Neural networks have been successfully implemented and applied in pre-surgical classification of endometrial benign or malicious tumors. In relation to endometrial cancer, despite the fact that from mathematical point of view the classification is much better than at random, from a clinical perspective the diagnostic accuracy of neural networks continuous to be limited.

## References:


1. Adlassnig K, Scheithauer W. Performance evaluation of medical expert system using ROC curves. *Comput Biomed Res.* 1989, 22, 297-313.
2. Altman D, Royson P. What do we mean by validating a prognostic model? *Stat Med.* 2000, 453-457.
3. Revett K, Gurunescu F, El-Darzi E, [et al.]. A breast cancer diagnosis system: A combined approach using rough sites and probabilistic neural networks. *Eurocon.* 2005, 1124-1127.
4. Sokołowski A. Metody stosowane w data mining. W: Data mining-metody i przykłady. *Statsoft Polska.* 2002, 5-12.
5. Timmerman D, Van Calster B, Jurcovic D, [et al.]. Inclusion of Ca 125 does not improve mathematical models developed to distinguish between benign and malignant adnexal tumors. *J Clin Oncol.* 2007, 25, 4194-4200.
6. Brinton L, Sakoda L, Lissowska J, [et al.]. Reproductive risk factors for endometrial cancer among Polish women. *Br J Cancer,* 2007, 96, 1450-1456.
7. Stachowicz N, Czekierdowski A, Daniłoś J, Kotarski J. Sonoangiografia dopochwowa w diagnostyce patologii endometrium. *Ginekologia Po Dyplomie.* 2003, 26, 27-35.
8. Aleem F, Predanic M, Calame R, [et al.]. Transvaginal color and pulsed Doppler sonography of the endometrium: a possible role in reducing the number of dilatation and curettage procedures. *J Ultrasound Med.* 1995, 14,139–145.
9. Kaaks R, Riboli E. Epidemiologic studies of nutrition and cancer: let us not throw out the baby with the bath water. *Int J Cancer.* 2005, 116, 662-664.
10. Kotarski J. Stężenie estronu w tkance raka trzonu macicy w odniesieniu do masy ciała kobiet. *Ginekol Pol.* 1994, 64, 65-69.
11. Kotarski J, Wertek I, Smoleń A, Kotarska M. Małoinwazyjne metody leczenia objawowych mięśniaków macicy. *Med Prakt. - Ginekologia i Położnictwo.* 2008, 1, 16-23.
12. Vittinghoff E, Gliden D, Shiboski S, [et al.]. Regression methods in biostatistcs. Linear, logistic, survival and repeated measures models. New York: *Springer Verlag,* 2001.
13. Markowska J. Rak błony śluzowej trzonu macicy. W: Onkologia ginekologiczna. Red. Markowska J. Warszawa: *Springer PWN.* 1998.
14. Swets J. Measuring the accuracy of diagnostic system. *Science.* 1988, 240, 1285-1293.
15. Tadeusiewicz R. Neurokompuetry – wczora,j dziś i jutro. *Wiedza i życie.* 1990, 7, 19-26.
16. Stachowicz N, Smoleń A, Daniłoś J, [et al.]. The Use of ROC curves in diagnostic usefulness of transvaginal sonography in normal and pathological endometrium. *Polish Journal of Environmental Studies.* 2007, 16, 6D, 342-345.
17. Stachowicz N, Czekierdowski A, Daniłoś J, Kotarski J. Zastosowanie trójwymiarowej ultrasonografii w ocenie objętości błony śluzowej macicy u kobiet z krwawieniami z jamy macicy. *Ginekol Pol.* 2002, 76, 970-975.
18. Stachowicz N, Smoleń A, Czekierdowski A, Kotarski J. Wykorzystanie modelu logistycznego w prognozowaniu istnienia raka endometrium na podstawie badania indeksów unaczynienia i przepływu w trójwymiarowej sonoangiografii dopplerowskiej. *Ginekol Pol.* 2003, 74, 872-877.