Available online at www.sciencedirect.com
ScienceDirect
Applied Mathematics and Computation 203 (2008) 482–492
APPLIED MATHEMATICS AND COMPUTATION
www.elsevier.com/locate/amc

Artificial neural networks based modeling for pharmacoeconomics application

Sebastian Polak [a,*], Agnieszka Skowron [a], Jerzy Brandys [a], Aleksander Mendyk [b]

[a] *Department of Pharmacoeconomics and Pharmacoepidemiology, Faculty of Pharmacy, Medical College, Jagiellonian University, Medyczna 9 Street, 30-688 Kraków, Poland*
[b] *Department of Pharmaceutical Technology and Biopharmaceutics, Faculty of Pharmacy, Medical College, Jagiellonian University, Medyczna 9 Street, 30-688 Kraków, Poland*

Abstract

Palliative chemotherapy is one of the major parts among costs of cancer. An aging population, introduction of new technologies and increased patients' healthcare expectations made the pharmacoeconomics analyses one of the mostly used tools in the decision making process. One of the main problems existing in pharmacoeconomics studies is the estimation of the effect. The aim of the study was to develop and validate on a real data artificial neural networks based systems for medical effect prediction and use them as a tool for modeling effect in pharmacoenomics analyses. Analysis was conducted on retrospective data from clinical records of non-small cell lung cancer in IIIB or IV (inoperative) stage patients treated with various therapy schemes. Logistic regression was used as the validation method. Based on the analysis of mean life duration (survival median) the output value in the database was transformed into a binary form. The threshold obtained after scientific, medical literature analysis was set at 35 weeks. Total classification rate as well as classification rate of both classes and AUROC value were used as a determinants of ANN's effectiveness. Best obtained neural model results was 84% of correctly classified records with 76% and 89% of class 1 (survival >35 weeks) and class 0 (survival <35 weeks). The AUROC value was 0.82. After training with using whole dataset, numerical experiments were conducted. Tests with *in silico* chemotherapeutics replacement was done. The results confirms effectiveness of artificial neural networks based pharmacoeconomics models.

Keywords: Artificial neural networks; Clinical effect modeling; Pharmacoeconomic analysis

1. Introduction

Palliative chemotherapy is one of the major parts among costs of cancer. An aging population, introduction of new technologies and increased patients' healthcare expectations made the pharmacoeconomics analyses one of the mostly used tools in the decision making process. In cancer the process of resource allocation is particularly difficult due to the size of patients' population and the ethical aspects of therapy. The main aim of pharmacoeconomics analysis remains the comparing between costs and effects of two or more alterna-

* Corresponding author.
E-mail address: polak@farmacja.cm-uj.krakow.pl (S. Polak).

0096-3003/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.amc.2007.10.043

tive treatment and presenting the results as the cost-effectiveness ratio. It lets the physicians, pharmacists and other health specialists involved in patient's care process make the decision.

One of the main problems existing in pharmacoeconomics studies is the estimation of the effect. However, the randomized clinical trials are the most popular and most often used in effectiveness estimation, they are also quite expensive and the obtained results could not be easily generalized to the population due to its specific, artificial and far from real life conditions. Furthermore ethical circumstances connected with experiments on humans are also important limitations. Above mentioned, these are the reasons for growing importance and practical use of computer modeling and so-called *in silico* studies.

1.1. Non-small cell lung cancer

Non-small-cell tumors account for approximately 80% of all lung cancers and almost 87% of lung cancer cases are related to cigarette smoking [1]. One-third of the patients are women [1,2]. NSCLC is a heterogeneous aggregate of distinct histological types of lung cancer (squamous cell carcinoma, adenocarcinoma, large cell carcinoma and rarely adenosquamous cell carcinoma, mucoepidermoid carcinoma, adenoid cystic carcinoma). NSCLC tends to be extremely lethal and respond poorly to chemotherapy [2–4]. A standard regimen for advanced disease has not been yet defined [2]. The recommendations are to be platinum based and combined with one of the newer agents – gemcitabine, vinorelbine, irinotecan and others. The most important prognostic factor in lung cancer is the stage of the disease. The staging is conducted in a detailed manner and often with the TNM staging system [5] and parallel stage grouping system [5]. The median survival time of NSCLC patients in stage IIIB and IV is ca. 35 weeks [6].

1.2. Artificial neural networks

Artificial neural networks systems belong to the general category of computational intelligence or artificial intelligence. They are defined as non-linear information processing systems designed as a reflection of biological neural structures, expressed in the structural and the functional composition of ANNs. The structure of ANNs, called the "architecture" is usually organized in layers consisting of units, which are sometimes called "nodes". Nodes are in fact artificial neurons responsible for information processing. Nodes from adjacent layers are usually fully interconnected through so-called "weights", representing synaptic connections between artificial neurons. Such connection-based approach has been proposed to simulate, in a very simple manner, the cognitive functions of biological neural systems.

One of the most important features of ANNs is their ability to detect complicated relationships, basing on empirical data. It is this feature that enables the use of the ANNs in pharmacoeconomics, where complicated and indirect relationships are to be identified and processed. The statistical approach is frequently tedious and ineffective due to the unknown *a priori* model structure. ANNs are capable of creating a model automatically, without any prior knowledge, basing only on empirical data, as stated before [5]. If the learning process is performed correctly, the neural model will be able to extrapolate its knowledge beyond the available database, which is called generalization ability. To achieve it, is the ultimate goal in the neural model preparation. Good generalization ability guarantees the reliability of the neural model, thus enabling potential use of ANNs in the prediction area. Application of well-trained and generalizing neural models in pharmacoeconomics would be considered mainly in scenario predictions. The scenarios might be recognized as consequences of particular therapeutic strategies, with respect to cost-effectiveness analysis or other pharmacoeconomic factors. The role of the ANN would be to provide answers describing the outcome of a hypothetical therapy. In this way, effect estimation in the cost-effectiveness ratio would be performed. Basing on the cost of scenarios calculation and the hypothetical outcomes predicted by the ANN model, the estimation of cost-effectiveness ratio and detailed pharmacoeconomic analysis could be easily performed.

1.3. Modeling in health care and pharmacoeconomics

Controlled trials in health care despite of fail results possibility are the most valuable sources of medical information to provide reliable data. Such opinion affect also the results of treatment with various drug

procedures even when the patient are part of a well-defined sample rather than in a real life settings. Politi et al. [7] proposed system based on the identification of complex relationships among such dimensions as clinician's reasoning, drug properties, and patient's condition. The authors tested the possibility of use the artificial neural networks in psychopharmacology and their ability to predict the patient's response to drug treatment. Dataset describing 82 patients with use of 12 parameters was used to model poor or good outcome of moclobemid based therapy (binary output). The ratio of positive answers was 84.1%.

The computational modeling techniques are also used to predict outcomes in other therapy methods like surgical therapy [8] or radiotherapy [9].

Despite of earlier controversies and objections of using mathematical models in economic analysis of healthcare they are being used more and more frequently [10]. Description of such phenomenon could be given follow Guidelines on Economic Modeling [11]: "Decision analytic modeling, undertaken for the purpose of economic evaluation of health technologies, involves the application of mathematical techniques to synthesize available information about healthcare processes and their implications." The same document presents assumptions of a good analytical model: transparency, internal consistency, reproducibility, interpretability, exploration of uncertainty, and others. Mentioned above demands are very strict but nevertheless scientists and practitioners implement various modeling techniques and use them in numerous healthcare and health economic fields [12–18].

2. Aim of the study

The aim of the study was to develop and validate on a real data artificial neural networks based systems for medical effect prediction and use them as a tool for modeling effect in pharmacoenomics analyses.

3. Materials and methods

3.1. Data

Analysis was conducted on retrospective data from clinical records of NSCLC patients treated with various therapy schemes. A database containing 100 records has been obtained from four Cancer Hospitals in Poland (Gdańsk, Poznań, Warszawa, Wrocław). The information therein was gathered from patient hospital documentation. The inclusion criteria were:

- IIIB or IV (inoperative) stage of non-small cell lung cancer (NSCLC).
- full schemes of anticancer therapy (adequate for every drug combination).

Every patient was described using 30 variables, as shown in Table 1.

The data contains basic demographic information, pharmacotherapy, laboratory tests, and radiotherapy information. Therapy dataset is divided into main disease therapy schemes and adverse drugs reactions (ADR's) preventing and treating.

Originally, the output value had a continuous character (number of survived weeks). Based on the analysis of mean life duration (survival median) the output value in the database was transformed into a binary form. The threshold obtained after scientific, medical literature analysis was set at 35 weeks [1,2,4,6]. A positive output value (coded as 1) meant that patient's survival time was equal to or longer than 35 weeks. A negative value (coded as 0) meant that the patient's survival time was shorter than 35 weeks.

Due to the small number of learning records a procedure based on adding random noise to the learning dataset was applied: "noisy" records were thus introduced, with the amplitude of the noise falling between 5% and 10% for each particular value (Table 2). The noise had random character with uniform ("flat") distribution.

ANNs were then trained for 2 million iterations (although other training periods were also tested).

3.2. Software

The process of ANN model development involves few stages, where data preprocessing and training process might be named as the most crucial and time consuming. ANN simulator called *Nets2004* was used

Table 1
Demographic data

No.	Variable	Description	Min	Max	Mean	SD
1.	SEX	Patient sex	.00	1.00	0.19	.39
2.	AGE	Patient age	41.00	77.00	62.09	8.98
3.	VINORELBINE	Summary dose of vinorelbine	.00	898.00	122.34	185.49
4.	ETOPOSIDE	Summary dose of etoposide	.00	4200.00	767.00	1222.89
5.	GEMCITABINE	Summary dose of gemcitabine	.00	100900.00	7182.10	14738.9
6.	CISPLATINE	Summary dose of cis-platine	.00	1380.00	571.87	355.54
7.	CARBOPLATINE	Summary dose of carboplatine	.00	3500.00	243.50	761.20
8.	ONDANSETRON	Summary dose of ondansetron	.00	368.00	46.50	58.50
9.	DEXAMETHASON	Summary dose of dexamethazon	.00	252.00	44.30	52.83
10.	TROPISETRON	Summary dose of tropisetron	.00	150.00	20.08	38.30
11.	FILGASTRIM300	Summary dose of filgastrim 300	.00	2400.00	39.00	251.02
12.	FILGASTRIM 480	Summary dose of filgastrim 480	.00	480.00	9.62	67.54
13.	METOCLOPRAMIDE	Summary dose of metoclopramid	.00	335.00	22.86	58.13
14.	AMBULATORY CARE	Total number of ambulatory visits	.00	27.00	8.72	7.17
15.	HOSPITALIZATION	Total number of hospitaliz. days	.00	129.00	34.22	30.08
16.	CHEST RTG	Total number of RTG	.00	13.00	3.35	2.65
17.	BONE RTG	Total number of bone RTG	.00	5.00	0.21	0.66
18.	MORPHOLOGY	Total number of morphology tests	3.00	35.00	13.10	7.72
19.	BIOCHEMISTRY	Total number of biochemical tests	1.00	19.00	6.38	3.00
20.	COAGULATION	Total number of coagulation tests	.00	12.00	1.47	2.56
21.	SCINTIGRAPHY	Total number of scintigraphy tests	.00	2.00	.20	.47
22.	EKG	Total number of EKG	.00	10.00	1.29	2.13
23.	TK CHEST	Total number of TK (chest)	.00	5.00	.74	1.06
24.	TK HEAD	Total number of TK (head)	.00	2.00	.23	.55
25.	USG	Total number of USG	.00	8.00	1.22	1.82
26.	URINE	Total number of urine tests	.00	7.00	1.62	2.23
27.	NMR	Total number of NMR	.00	2.00	.10	0.33
28.	HYDRATION	Total number of hydration	.00	18.00	4.70	3.13
29.	HOTEL	Total number hospital hotel days	.00	52.00	3.56	10.07
30.	RADIOTHERAPY	Total number radiotherapy units	.00	40.00	7.06	12.39
Out	SURVIVAL	Patients survival	.00	1.00	.48	.50

Table 2
Noise parameters

No.	Option	Multiplication coefficient	Noise amplitude (%)
1.	Noise, random	2	2
2.	Noise, random	2	5
3.	Noise, random	2	10
4.	Noise, random	5	5
5.	Noise, random	10	5

[13,19]. All computations necessary for ANN development were carried-out with use of three double Pentium Xeon and four double Pentium III workstations working under Linux environment. A special ported version of *Nets2004* simulator, *nets_x*, was used. Grid-like environment for management of computational tasks was developed and applied together with WWW control panel providing information about actual computational load on the whole network of available workstations.

3.3. Nets architecture

A sigmoid logistic transfer, hyperbolic tangent and fsr functions were tested. The learning rate was 0.6 and momentum 0.3 and a maximum length of learning was 2 000 000 iterations (epoch size set as 1). The "jog-of-weight" technique was used to avoid stopping in local minimum of target function [20]. ANN architecture was encoded in the same way (Fig. 1).

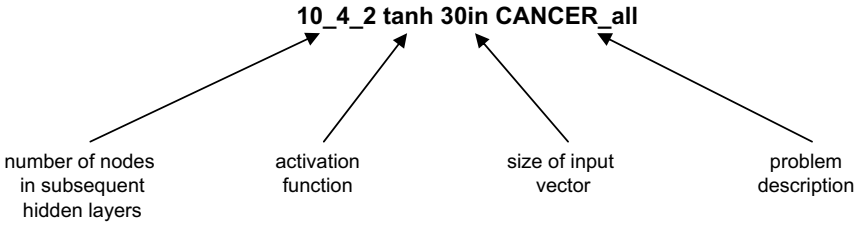


Fig. 1. ANN architecture encoding system.

3.4. Validation method

Neural networks were researched to find optimal architecture. Search was performed with use of 10-fold cross-validation scheme. It means that the randomly chosen 90% of the data were used for training and then obtained models were tested on the remaining 10% of data. This procedure was repeated 10 times but each time different part of training dataset was excluded. The estimated error rate was the average classification error rate from 10 sub-samples. It was the main criterion for optimal model selection. Receiver–operator curve was computed and area under it (AUROC) was also used as the criterion of models comparison [21,22].

3.5. Logistic regression

Logistic regression is a widely used statistical modeling technique in which the probability of an outcome is related to the predictor variables. It is the standard procedure in a situation when the output has a dichotomous characteristics. Such modeling technique is commonly used in biological area [23–25].

4. Results

4.1. Neural and statistical modeling

During the research more than 300 architectures were tested. Parameters undergoing research were: net architecture, learning coefficients, activation functions, and added to native data noise parameters. Tables 3 and 4 presents results and receiver–operator curves of best obtained neural models and with use of native data.

Tables 5 and 6 presents results and receiver operator curves of best obtained neural models and with use of noised datasets.

In this study logistic regression analysis was used to predict survival time on the basis of 30 chosen inputs and all data sets used for ANNs training with use for 10-fold cross-validation scheme (Table 7). The dependent and independent variables entered into the analysis were the same as for the ANN modeling.

4.2. Cost estimation

The cost of treatment was based on the 2003 hospital price in Poland [23].

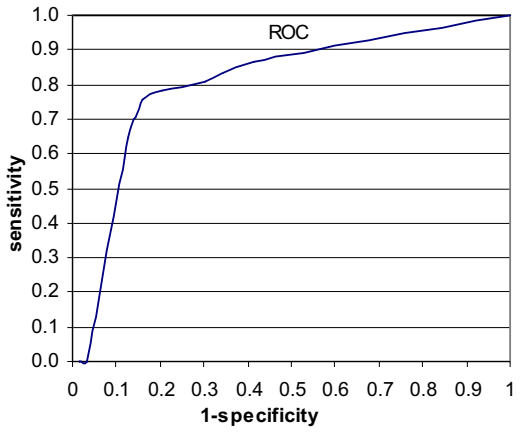
Table 3
Results of best obtained architectures (binary data, threshold – 35 weeks, data without noise)

No.	Architektura sieci	GLOBAL (%)	1 (%)	0 (%)	AUROC
1.	20_10_2hid fsr_30in_all	81	76	84	0.81
2.	60_20hid sigma_30in_all	81	70	87	0.83
3.	20_16_8_4hid sigma_30in_all	80	70	86	0.77
4.	20_18_10hid sigma_30in_all	80	73	84	0.80

Notation: GLOBAL (%) – total classification rate; 1 (%) – classification rate of records with 1 value; 0 (%) – classification rate of records with 0 value.

Table 4
Results of best obtained architectures – ROC (binary data, threshold – 35 weeks, unnoised data)

Net architecture	AUROC	Net architecture	AUROC
20_10_2hid fsr_30in_all	0.81	60_20hid sigma_30in_all	0.83



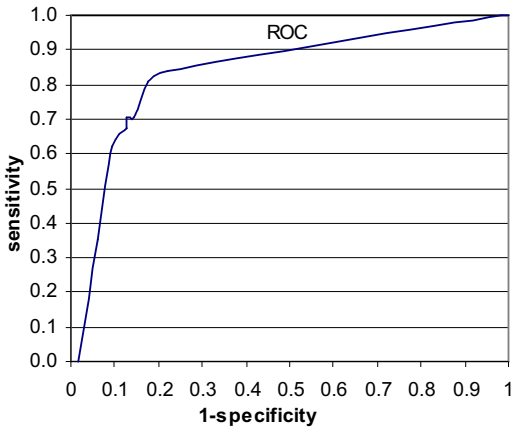


Table 5
Results of best obtained architectures (binary data, threshold −35 weeks, noise parameters – 5 × 5%)

No.	Architektura sieci	GLOBAL (%)	1 (%)	0 (%)	AUROC
1.	**15_5hid sigma_30in_all**	**84**	**76**	**89**	**0.82**
2.	20_18_10hid sigma_30in_all	80	73	84	0.82
3.	7_5_3hid sigma_30in_all	80	70	86	0.80
4.	60_20hid sigma_30in_all	79	68	86	0.79

Notation: GLOBAL (%) – total classification rate; 1 (%) – classification rate of records with 1 value; 0 (%) – classification rate of records with 0 value.

4.3. Scenarios testing – cost-effectiveness ratios comparison

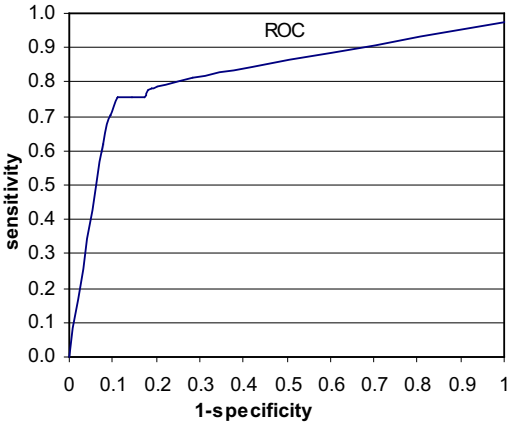
The best neural model obtained during prior investigations was used in the next stage of research. After training with using whole dataset, numerical experiments were conducted. Using clinical and – further – cost data it was possible to predict average expected results and to calculate costs. The most commonly used pharmacoeconomic factor – cost-effectiveness ratio (CER) was used due to the methodological and practical reasons. The numerical experiments could be divided into two main groups – simple with only one variable being changed and complex with two or more variables being changed. Best neural model (15_5hid sigma – noised learning dataset) was used in this task.

The simulation was projected as follows:

(1) all cases in the dataset were used to train best ANN architecture,
(2) mean survival time was computed basing on the all available data,
(3) test dataset was prepared, where the records describing native treatment were replaced with information about modeled treatment,
(4) the test dataset was presented to the ANN model and mean survival time was computed,
(5) both mean survival times from original and altered datasets were compared to reveal impact of therapy replacement on the survival time,

Table 6
Results of best obtained architectures – ROC (binary data, threshold – 35 weeks, noise parameters – 5 × 5%)

Net architecture	AUROC	Net architecture	AUROC
15_5hid sigma_30in_all	0.82	20_18_10hid sigma_30in_all	0.82



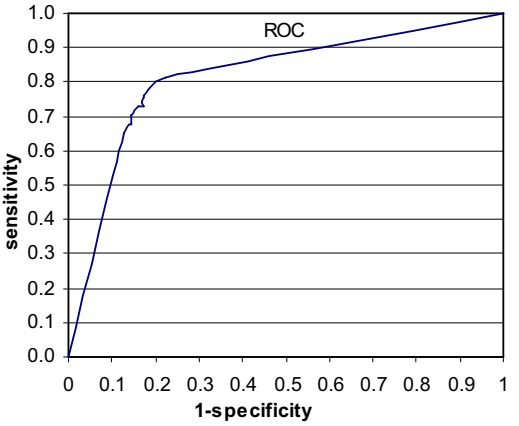


Table 7
Results of best obtained architectures in comparison with logistic regression based models

No.	Data set	Modeling tool	ALL (%)	1 (%)	0 (%)	AUROC
1.	Native	20_10hid sigma_30in	82	76	86	0.80
		Logistic regression	74	73	75	0.70
2.	Noised – 2 × 10%	20_10_2hid sigma_30in	80	70	86	0.77
		Logistic regression	70	74	63	0.75
3.	Noised – 2 × 10%_500 000 iter	5_3hid tanh_30in	79	68	86	0.77
		Logistic regression	73	74	70	0.70
4.	Noised – 2 × 5%	7_5_3hid tanh_30in	81	73	86	0.78
		Logistic regression	70	71	68	0.66
5.	Noised – 5 × 5%	15_5hid sigma_30in	84	76	89	0.82
		Logistic regression	73	74	70	0.70

Notation: GLOBAL (%) – total classification rate; 1 (%) – classification rate of records with 1 value; 0 (%) – classification rate of records with 0 value.

(6) for each therapy prices of drugs, medical procedures, etc. were collected,
(7) for each therapy cost and CER were computed.

In NSCLC the most commonly used chemotherapeutic agent is cis-platin in combinations as follows: vinorelbine – cis-platine, etoposide – cis-platine or gemcitabine – cis-platine. Another anticancer platine derivative is carboplatine, with significantly better pharmacological characteristic (lower side effects) but considerably higher price. It would be valuable to know, whether the use of carboplatine instead of cis-platine would be beneficial in such extent, that it would justify costs of pharmacotherapy carried-out with it. It is a matter of quantified approach to assess the impact of carboplatine use on the patients' survival time and, in the consequence, to compute CER of this procedure. However, such experiment carried-out with biological subjects (patients) would be unacceptable under ethical point of view, therefore one is limited only to the data collected from clinical cases. Original dataset was not constructed to prove or falsify hypothesis about profits

of treatment with carboplatine – it was the result of accidental data acquisition, not statistically planned experiment (randomized, controlled trial). ANN model is the solution of this limitation.

Model reaction on the replacement of cis-platine with carboplatine in particular patients was tested. It is worthy to mention here, that sensitivity analysis [20] of ANN model revealed that one of the most important factor for the survival time was the amount of cis-platine. Therefore, any change in cis-platine use was suspected to be crucial to the patients' survival time.

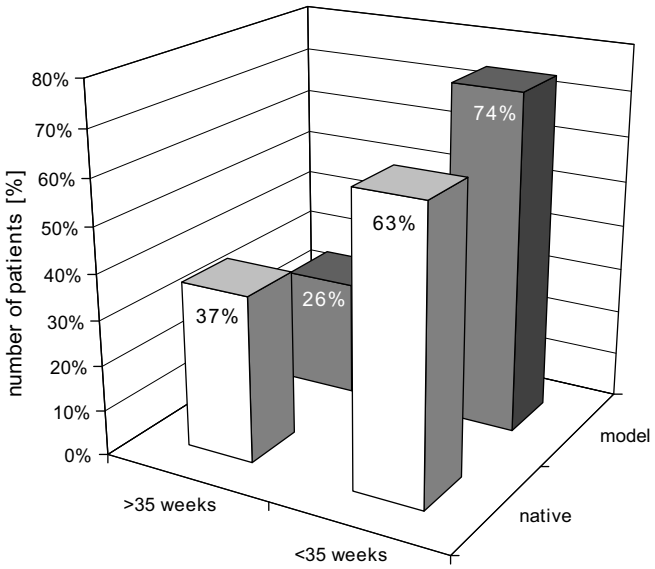


Fig. 2. Effect of cis-platine based therapy replacement with carboplatine.

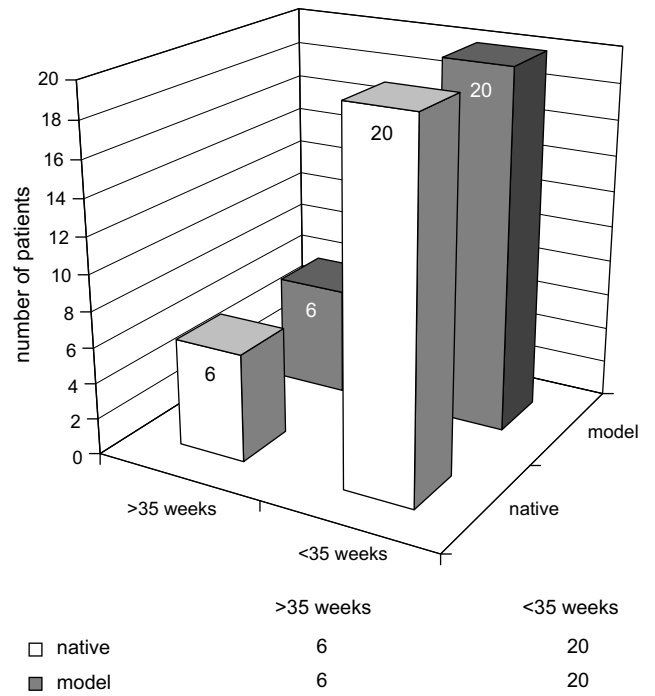


Fig. 3. Effect of gemcitabine based therapy replacement with vinorelbine.

The effect implied as a proportion of patients with 35 and more weeks of survival time to patients with less than 35 weeks of survival time is worse for modeled carboplatine scheme. It is revealed in Fig. 2, where bars with "native" etiquette represent original data and bars with "model" etiquette represent altered test data. Bars representing survival time over 35 weeks are higher for native, what means that more patients have benefited from cis-platine treatment than from carboplatine. ANN model indicates that carboplatine therapy should not have better outcome than cis-platine.

The CER was not computed due to the coexistence of two factors – higher cost and lower effect of switched therapy scheme.

Another tested scenario assumption was gemcitabine to vinorelbine *in silico* conversion. The modeled results of such therapy replacement is presented in Fig. 3. System shows that combination with vinorelbine is as effective as the gemcitabine based scheme. To validate the neural networks based tool the contrary experiment was conducted. The vinorelbine was replaced by gemcitabine (Fig. 4).

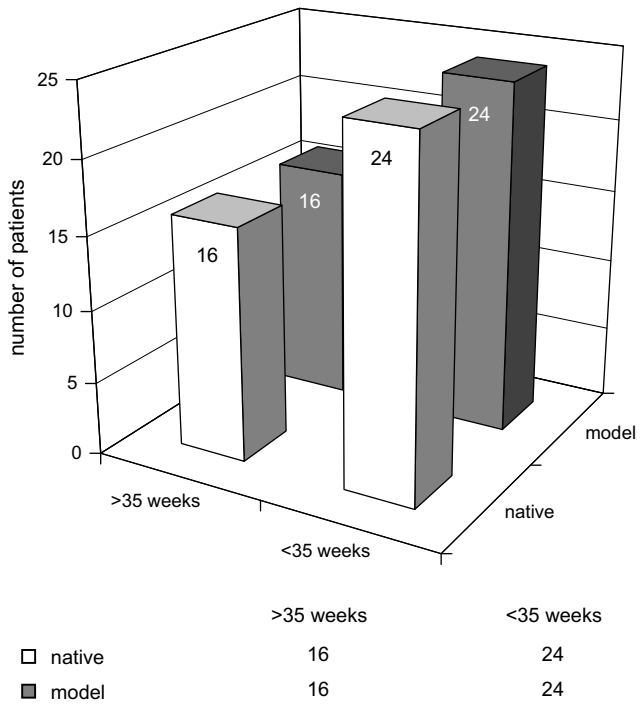


Fig. 4. Effect of vinorelbine based therapy replacement with gemcitabine.

Table 8
Cost comparison of two schemes

Costs	Scheme	
	Cis-platine vinorelbine	Cis-platine gemcitabine
Per patient		
Ambulatory	3043 (±2384)	12472 (±7287)
Hospital	9678 (±4383)	16919 (±8778)
Per cycle		
Ambulatory	864 (±471)	8084 (±3305)
Hospital	3755 (±2310)	3224 (±1794)

Due to lack of differences between effectiveness of two described therapy schemes the cost-minimalisation analysis was conducted. The assumption of equal effect of the tested schemes permits to use mentioned above type of pharmacoeconomics analysis. The comparative analysis is limited to cost comparison only (Table 8).

Lower therapy costs of cis-platine and vinorelbine based scheme set together with modeled equal effectivenss proves that such therapy is more cost-effective than gemcitabine based.

5. Conclusions

Specificity of daily clinical activity and medical doctors attitude cause that application of computational and mathematical models in the real life is limited. In the same time the huge and still growing amount of the medical data which should be analyzed cause that importance of such tools – sooner or later – will increase. The FDA has begun use of the data mining technologies in their adverse drug reactions database [27]. The largest international database of case reports of spontaneous reporting of adverse drug reactions – the WHO Uppsala Monitoring Centre use in a daily practice data mining technology based on Bayesian neural networks [28].

Despite of medical environment mistrust manifest for computational methods as valuable tools and advisors for decision makers, the artificial intelligence based models have some advantages in comparison with widely used classical models. One of the main which could be provided, is the possibility to obtain results of "what if" analysis for every single patients not only for specific group of patients.

As it was described above, during modeling procedure for pharmacoeconomic needs it is expected to point out the analytical character of developed model. Obtained in this research results prove that the quality of models developed with use of "black-box" modeling tools, when the analytical character of model is hard to be revealed, could be equal or even better than classical. From that point of view such systems could be for example comparative models for other techniques used during pharmacoeconomic analysis.

References

[1] Cancer management: a multidisciplinary approach, in: R. Pazdur, L.R. Cois, W.J. Hoskins, L.D. Wagman (Eds.), Medical, Surgical & Radiation Oncology, ninth ed., CMP Media, Lawrence, 2005–2006.
[2] S. Sörenson, B. Glimelius, P. Nygren, A systematic overview of chemotherapy effects in non-small cell lung cancer, Acta Oncol. 40 (2001) 327–339.
[3] M.L.G. Janssen-Heijnen, J.-W.W. Coebergh, Trends in incidence and prognosis of the histological subtypes of lung cancer in North America, Australia, New Zealand and Europe, Lung Cancer 31 (2001) 123–137.
[4] Chemotherapy and non-small-cell lung cancer, Drug Ther. Bull. 40 (2) (2002) 9–11.
[5] C.F. Mountain, Revisions in the international system for staging lung cancer, Chest 111 (1997) 1710–1717.
[6] J. Klastersky, M. Paesmans, Response to chemotherapy, quality of life benefits and survival in advanced non-small cell lung cancer: review of literature results, Lung Cancer 34 (2001) S95–S101.
[7] E. Politi, C. Balduzzi, R. Bussi, L. Bellodi, Artificial neural networks: a study in clinical psychopharmacology, Psychiatry Res. 87 (1999) 203–215.
[8] M.F. Jefferson et al., Comparison of a genetic algorithm neural network with logistic regression for predicting outcome after surgery for patients with non-small cell lung carcinoma, Cancer 79 (7) (1997) 1338–1342.
[9] S. Gulliford, Predicting post-radiotherapy outcomes for prostate patients using artificial neural networks, in: 44th AAPM Annual Meeting, Montreal, 2002.
[10] D. Coyle, K.M. Lee, B.J. O'Brien, The role of models within economic analysis. Focus on type 2 diabetes mellitus, Pharmacoeconomics 20 (Suppl. 1) (2002) 11–19.
[11] Decision analytic modelling in the economic evaluation of health technologies a consensus statement, Pharmacoeconomics 17 (5) (2000) 443–444.
[12] S. Walczak, W.E. Pofahl, R.J. Scorpio, A decision support tool for allocating hospital bed resources and determining required acuity of care, Decision Support Syst. 34 (2002) 445–456.
[13] S. Polak, A. Mendyk, Artificial intelligence technology as a tool for initial GDM screening, Expert Syst. Appl. 26 (2004) 455–460.
[14] R. Davies, P. Roderick, J. Raftery, The evaluation of disease prevention and treatment using simulation models, Eur. J. Operat. Res. 150 (2003) 53–66.
[15] A.L. Byers, H. Allore, T.M. Gill, P.N. Peduzzi, Application of negative binomial modeling for discrete outcomes. A case study in aging research, J. Clin. Epidemiol. 56 (2003) 559–564.
[16] C. Martin, M. Vanderpump, J. French, Description and validation of a Markov model of survival for individuals free of cardiovascular disease that uses Framingham risk factors, BMC Med. Inform. Decision Making 4 (6) (2004) 1–15.

[17] S.M. Shechter, A.J. Schaefer, R.S. Braithwaite, M.S. Roberts, Modeling the progression and treatment of HIV, in: R.G. Ingalls, M.D. Rossetti, J.S. Smith, B.A. Peters (Eds.), Proceedings of the 2004 Winter Simulation Conference, December 5–8, 2004, Washington, DC.
[18] S. Walczak, J.E. Scharf, Reducing surgical patient costs through use of an artificial neural network to predict transfusion requirements, Decision Support Syst. 30 (2000) 125–138.
[19] A. Mendyk, R. Jachowicz, Neural network as a decision support system in the development of pharmaceutical formulation – focus on solid dispersions, Expert Syst. Appl. 28 (2005) 285–294.
[20] A. Osowski, Neural Networks in the Algorithmic Approach, WNT, Warsaw, 1996 (in polish).
[21] K.H. Zou et al., Statistical validation based on parametric receiver operating characteristic analysis of continuous classification data, Acad Radiol. 10 (2003) 1359–1368.
[22] A.P. Bradley, The use of the area under the ROC curve in the evaluation of machine learning algorithms, Pattern Recognition 30 (7) (1997) 1145–1159.
[23] L. Ohno-Machado, Modeling medical prognosis: survival analysis techniques, J. Biomed. Inform. 34 (2001) 428–439.
[24] S. Dreiseitl, L. Ohno-Machado, Logistic regression and artificial neural network classification models: a methodology review, J. Biomed. Inform. 35 (2002) 352–359.
[25] A.B. Cantor, Understanding logistic regression, Evidence-based Oncol. 3 (2002) 52–53.
[27] J.K. Jones, The role of data mining technology in the identification of signals of possible adverse drug reactions: value and limitations, Curr. Therap. Res. 62 (9) (2001) 664–672.
[28] A. Bate, M. Lindquist, I.R. Edwards, S. Olsson, R. Orre, A. Lansner, R.M.D. Freitas, A Bayesian neural network method for adverse drug reaction signal generation, Eur. J. Clin. Pharmacol. 54 (1998) 315–321.