Prediction of Prostate Capsule Penetration using Neural Networks
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Abstract: - Prediction is a straightforward application of neural networks (NN). The problem of prostate cancer evolution prediction is approached in this paper using NN. The original database contained 650 records of patients, which underwent radical prostatectomy for prostate cancer. The NN variables were the parameters with the highest prognostic value selected and pre-processed from the original database. Different NN architectures and NN parameters have been tested. The NN performance has been compared with the most widely used prediction statistical method, the logistic regression. All NN models performed better than the logistic regression. The best obtained global prediction of 96.94% is better than the results of similar experiments available in literature. The NN prediction performance might be improved, because, in our opinion, its limit is given by the relatively small number of cases and the methods of collecting data.

Key Words: - neural networks, prediction, prostate cancer, capsule penetration

1 Introduction
Neural networks are nonlinear dynamical systems consisting of a large number of relative simple processing elements, named neurons that operate simultaneously, in parallel. The neurons interact through excitatory and inhibitory connections, which have associated weights, in a similar manner to the biological neurons. Learning is performed by weights changes conform to a learning rule. N.N. can learn from examples and deal with a great number of parameters, assessing non-linear relationships between any of the input to any of the desired output variable, with faster and better results, if compared with traditional statistical methods. NN are recommended especially in cases were a conventional process is not suitable, can’t be easy defined or cannot fully capture the data complexity and where stochastic behavior is important.

In this context, prediction, on the bases of examples defined as pairs of input model-output-model, is a straightforward application of NN.

In medicine, especially in oncology prediction is very important. For instance, in uro-oncology, treatment decision making is based on the ability to predict therapy outcome. New tools that could improve prediction are always welcome. These may assist the clinicians in the diagnosis process and in therapy decisions. Although the Tumor-Node-Metastasis (TNM) classification system is widely used, describing the anatomical level of lesion extent, it has some limitations, because it does not include the new tumor markers, or other pathological elements, which are necessary for a specific diagnosis, leading to the most appropriate therapy. Using new tools that can deal with a large amount of data and find relationships among them opens new perspectives.

Recent developments, as is the improved computational power and the advances in neural networks software encouraged us to investigate new potential applications, as the finding of correlations between different predicting factors, the prognosis prediction for different groups of patients, or as the risk group stratification. The largest number of experiments using the neural networks in urology was performed for prostate cancer, a domain full of uncertainties [1]. The necessity of early diagnosis, correct staging and of choosing the best therapy, eliminating the potential risk factors, could all benefit from neural networks. An explored application is the staging process, using the results of transrectal prostate biopsy, along other non-invasive parameters, in order to avoid radical therapy indications for advanced forms of cancer, which would not have significant benefits for the patients [2],[3].

Possible metastases prognosis was approached by Tewari et al with a NN [4] on a group of 1200 patients with prostate cancer using as input parameters age, race, tumor size, Gleason score, digital rectal examination and the number of positive biopsy cores. The results were promising at that time: the neural network had a specificity of over 72% and a sensitivity higher than 81%.

In 2001, Han et al has used the clinical stage, Gleason score, preoperative Prostate Specific Antigen (PSA) level and age as input parameters for a multilayer perceptron (MLP), trying to predict lymph node involvement. At a specificity of 90%, the neural network detected 34% of patients with localized prostate cancer and 59% of patients with lymph node involvement [5]. These predictions were much better than those obtained by using the Partin nomograms of that time [6].
In a paper published in 2001 [7], the performance of several types of neural networks with logistic regression in the prediction of organ confinement after radical prostatectomy was compared. The selected input parameters were: patients’ age, clinical stage, biopsy Gleason score and preoperative PSA. The results, obtained with the artificial neural networks simulation software available at that time, were not superior to logistic regression.

In 2003, Zlotta et al used the data from the European Prostate Cancer Detection Database to train a MLP, trying to predict the pathological stage for 200 patients with total PSA values lower than 10 ng/mL, before radical prostatectomy [8]. The NN input variables were: age, total serum PSA values, free/total PSA ratio, PSA velocity, PSA density, transition zone PSA, digital rectal examination and total Gleason score in trans-rectal prostate biopsy. The accuracy of the obtained prediction was of 92.7% in localized prostate cancer cases and of 84.2% in locally advanced prostate cases. These results were much better than those obtained using the logistic regression.

The prediction accuracy of the LR-based nomogram versus NN was studied considering age, digital rectal examination, PSA, percent-free PSA and prostate volume of 3980 patients, who underwent multicore systematic prostate biopsy [9]. The accuracy of the nomogram was 71%, versus 67% for the NN.

In paper [10] the probability of prostate cancer was studied based on initial biopsy results. The input variables were age, PSA, digital rectal examination (DRE) and prostate volume, available in 843 cases. The conclusion was that the predictive capacity of the NN was significantly improved in this case, if compared with the previous models, considering only PSA or prostate volume. The NN performance was similar to that of logistic regression.

The above papers and others [11], [12], show continuous interest for the use of NN in everyday practice prediction.

2 Problem Formulation
The single most important factor in the prognosis of prostate cancer is capsule penetration [1]. The performances obtained in uro-oncology by neural networks, comparably with those of traditional statistical methods encouraged us to study the problem of prediction of prostate capsule penetration using NN.

With the kind permission, we had access to the database records of the Department of Urology of the Radboud University, Nijmegen, the Netherlands. The original database contained 650 records of patients which underwent radical prostatectomy for prostate cancer between 1 January 1992 – 31 December 2005.

The parameters recorded were:
- Date of birth;
- Age at diagnosis;
- Height;
- Weight;
- Date of positive diagnosis;
- Total Gleason Score in initial specimen (from biopsy or TURP);
- Primary, secondary, tertiary and quaternary Gleason score;
- Preoperative total PSA;
- Preoperative TNM staging;
- Prostate volume;
- Date of prostatectomy;
- Capsule penetration;
- Seminal vesicles invasion;
- Positive margins;
- PSA recurrence;
- Time interval from prostatectomy to PSA recurrence.

As it is known, the success of a NN application depends significantly on the database [13]. In this designing phase expertise in the field of the problem to be solved, respectively in urology was absolutely necessary and invaluable. We selected the parameters with the highest prognostic value for prostate cancer diagnosis, excluded the cases with incomplete information and formed a new database of 548 cases, for our retrospective study.

The selected parameters were:
- Preoperative stage (according to the 2002 TNM classification): data from patients in stages T2a, T2b, T2c, T3a, T3b were included (T4 cases were excluded, because if the cancer is too advanced, radical prostatectomy alone has not curative intent);
- Age (42 – 73 years)
- Preoperative total PSA value (range: 0-84 ng/mL);
- Total Gleason Score in initial specimen (primary + secondary, range: 3-9);
- Capsule penetration (No / Yes).

As performance parameters the positive predictive value (PPV), negative predictive value (NPV) and global percentage of correct classification (GPCC) were considered relevant.

The positive predictive value represents the proportion of patients actually having the feature of interest among those classified as positive.

The negative predictive value means the proportion of patients not having the feature of interest among those classified as negative. Ideally one would like to have high values for both predictive values.

The global percentage of correct classification was calculated as the proportion of correctly classified patients (regardless of the positive or negative value), from the whole testing dataset.
3 Problem Solution

As NN application development environment we used Neurosolutions 5.0 for Excel. We have pre-processed data from the original SPSS format, a statistical analysis software program and exported them into the Microsoft Excel format, compatible with the Neurosolutions software. The cohort contained 365 cases with no prostate capsule penetration and 183 cases diagnosed after radical prostatectomy with positive capsule penetration.

The input data were randomized and pre-processed as follows:

- Age, total Gleason Score and preoperative PSA were considered in absolute value;
- Preoperative TNM stages were assigned with the following values: $T_{2a} = 1; T_{2b} = 2; T_{2c} = 3; T_{3a} = 4; T_{3b} = 5$.

To the predicted output, the capsule penetration, values of 0 and 1 were assigned, for the cases without prostate capsule penetration, respectively for the cases with penetration.

The partition of the database into the training, validation and testing group has a major influence on the NN overall performance [13]. We used different partitions of our database according to some empirical common sense in order to improve the prediction accuracy. We have obtained the best results for the following data sets:

- 300 cases for training;
- 150 cases for cross-validation;
- 98 cases for testing.

A lot of models of prostate penetration prediction have been developed, using various NN architectures: MLP, radial basis function NN (RBF NN) [14] and recurrent NN (RNN) [13]. Different structures (different number of neurons on the hidden layers), different activation functions and different training algorithms were used, in order to obtain the best complexity/accuracy ratio.

The input data were pre-processed and weighted in different ways, trying to consider their prognosis significance.

The best results were obtained for the data inputs and corresponding range of values already mentioned above. The MLP NN with the best performance had a structure of 4 neurons on the first hidden layer, 8 neurons on the second one and 1 neuron as output. The Gaussian activation function and Euclidean distance were used for the RBF neurons and the hyperbolic tangent for the other ones. The competitive algorithm with conscience was used to obtain the RBF centres. The back-propagation algorithm with momentum (the chosen momentum was 0.7) was used to determine the MLP parameters.

Various RNN with different memory constants have been tested: partially RNN and fully RNN. The best one had a structure of 4 neurons on the first hidden layer, 8 neurons on the second one and 1 output neuron. The back-propagation through time algorithm with momentum (the chosen momentum was 0.7) was used to train the RNN parameters. The memory constant was 0.8.

Table 1 represents the NN performance in terms of positive predictive value, negative predictive value and global percentage of correct prediction. The PPV and NPV in our study were better than the results of similar experiments available in literature [4], [5], [7].

<table>
<thead>
<tr>
<th>Type of NN/Performance parameter</th>
<th>PPV[%]</th>
<th>NPV[%]</th>
<th>GPCC[%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLP (4-8-1)</td>
<td>96.88</td>
<td>95.45</td>
<td>95.92</td>
</tr>
<tr>
<td>RBF-MLP (4-8-1)</td>
<td>96.88</td>
<td>93.94</td>
<td>94.9</td>
</tr>
<tr>
<td>Partial RNN (4-8-1)</td>
<td>96.88</td>
<td>95.45</td>
<td>95.92</td>
</tr>
<tr>
<td>Fully RNN (4-8-1)</td>
<td>100</td>
<td>95.45</td>
<td>96.94</td>
</tr>
<tr>
<td>LR</td>
<td>-</td>
<td>-</td>
<td>94.89%</td>
</tr>
</tbody>
</table>

For comparison, the statistical logistic regression (LR) applied to the same database, in order to predict the prostate capsule penetration, was used. The percentage of correctly classified cases was 94.89%. It can be observed that all NN prediction models performed better than the statistical method. In the best case it can be noticed an improvement of 2.05%. This can be interpreted as quite an encouraging result.
4 Conclusion
The NN performance prediction in prostate cancer prediction was better than one obtained with the statistical logistic regression. The gain improvement by using NN is 2.05 %, quite a significant difference. In clinical terms this is beneficial, avoiding over treatment in the cases with prostate capsule penetration, when radical prostatectomy is not an option. This also has a beneficial psychological impact on the patient, by avoiding unnecessary surgery.

The performance limits of the neural network prediction, in our opinion, are given by the rather reduced dimension of the database and the modality of its collecting.

Taking account of more parameters, as for instance the third and fourth grade Gleason patterns might improve the overall NN prediction.

References:


