Design of Neural Network models for screening anticancer activities in Taxol analogues

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Bioinformatics at KUMC

Our mission is to advance the understanding of integrative functions in biological systems, including human, through the application of computational models and data analysis with focus on microarray analysis.

Research activities

- **Neural Network** (NN) prototypes to facilitate **q**uantitative **s**tructure-**a**ctivity **r**elationship (QSAR) research in drug design.

- **Fuzzy distributions** on neural network projects with highly disproportional data sets (drug libraries).

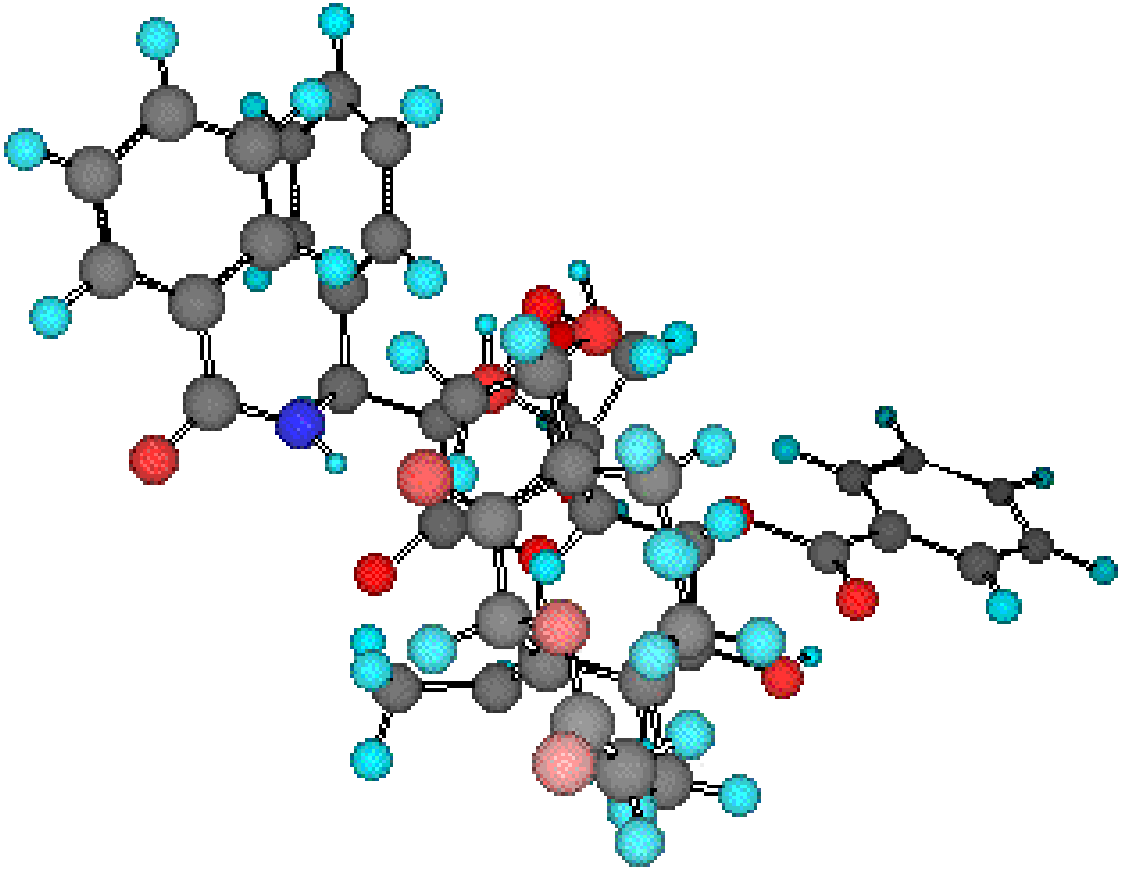
Experimental design

- **Goals**: To design neural network models to screen taxol analogues for anticancer activity (based on QSAR) with the prediction of potential pharmaceutical target compound.
- The application of neural network prototype for a sample of **50** taxol analogues (NCI data) with **known chemical structure and anticancer activity.**

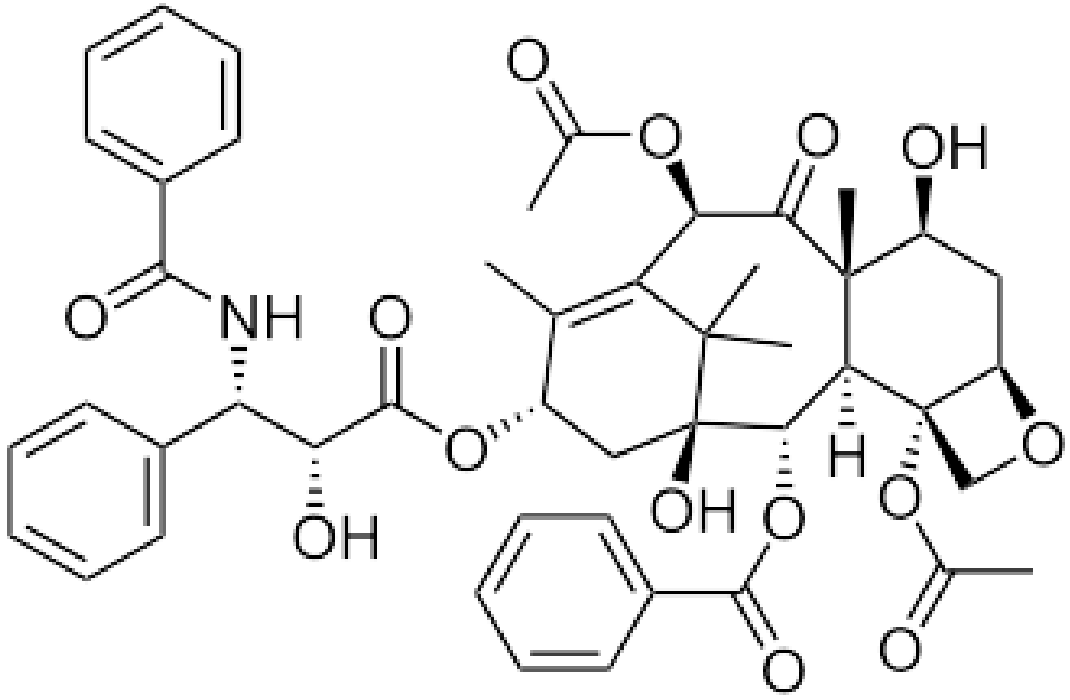
Experimental design

- **Hypothesis:** Is the antitumor activity of tested drug analogue against the particular cancer cell line higher or lower than taxol anticancer activity?

Taxol



Taxol

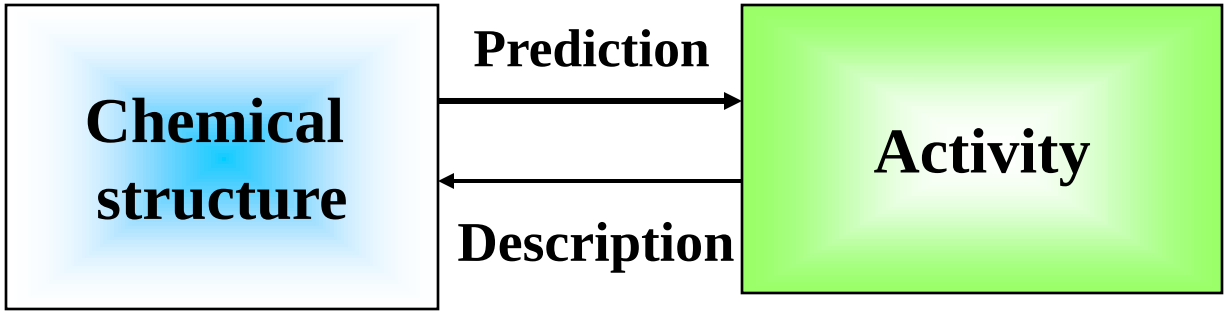


Computer-assisted molecular design

Quantitative structure-activity relationship is only based on one postulation:

Bioactivity = f {$\sum$(steric) + $\sum$(electronic) + $\sum$(hydrophobic)} interactions

QSAR



Properties:
steric
electronic
hydrophobic

Anticancer activity of 50 compounds *in vitro* screened against a panel of 20 human cancer cell lines (binary data in 0, 1 format)

Neural network

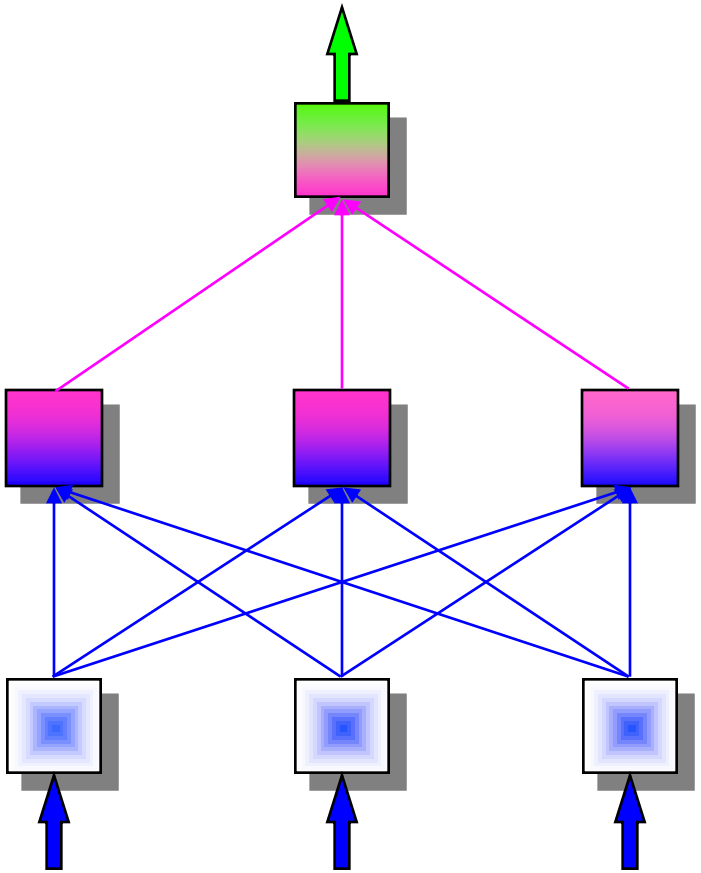
System composed of many simple elements operating in parallel whose function is determined by network design, connection weights (strengths), and supervised processing performed at computing elements (nodes).

Neural network

The intensity of signals produced by the neurons can differ depending on the intensity of their stimulus (inputs).

The fundamental assumption is that the transfer signals are not linearly dependent on the input values.

The system is based on one-layer hidden units, where all the neurons (nodes) have the same number of weights (synapses) and all receive the input signal simultaneously.



Output layer

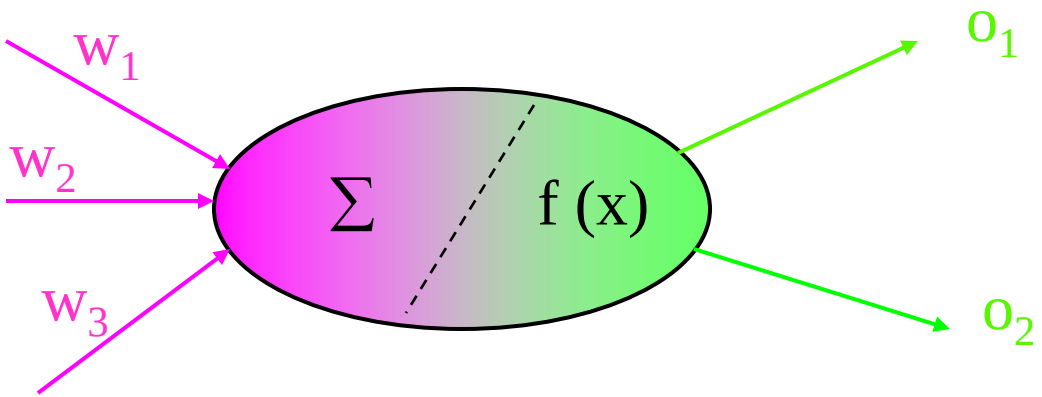
Hidden layer

Input layer

One-layer neural network

Back-propagation Neural Network (BPNN)

Formal neuron (node)

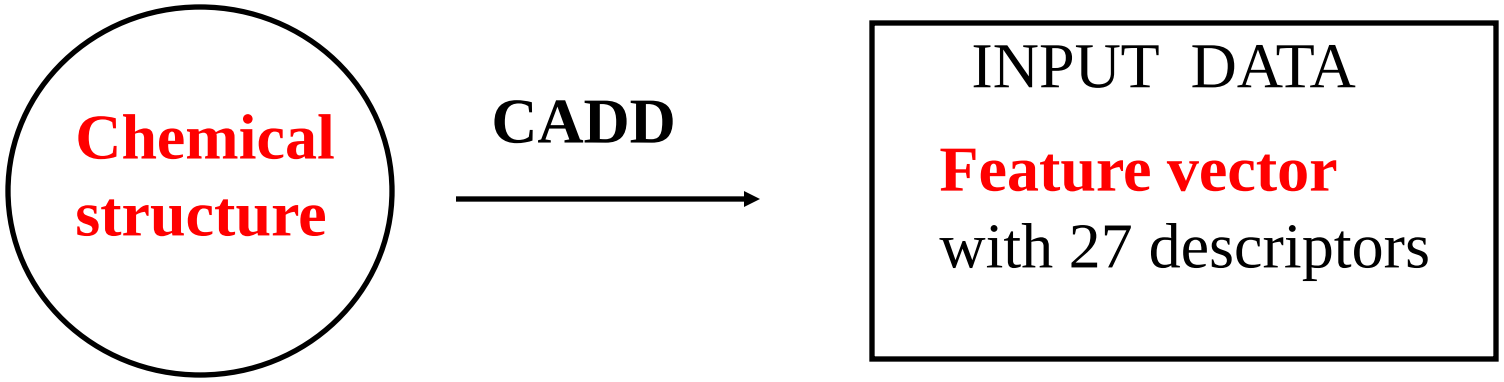


Action of formal neuron consists in summing weighted inputs and producing output signal(s) via the activation function. In BPNN it is the sigmoid function:

$$f(x) = 1/[1+\exp(-x)]$$

Computer Assisted Drug Design

Desktop software package (Oxford Molecular, CA) is used for a ‘structure description’. Based only on the chemical structure, the potential of the compound can be established **prior** to the synthesis.



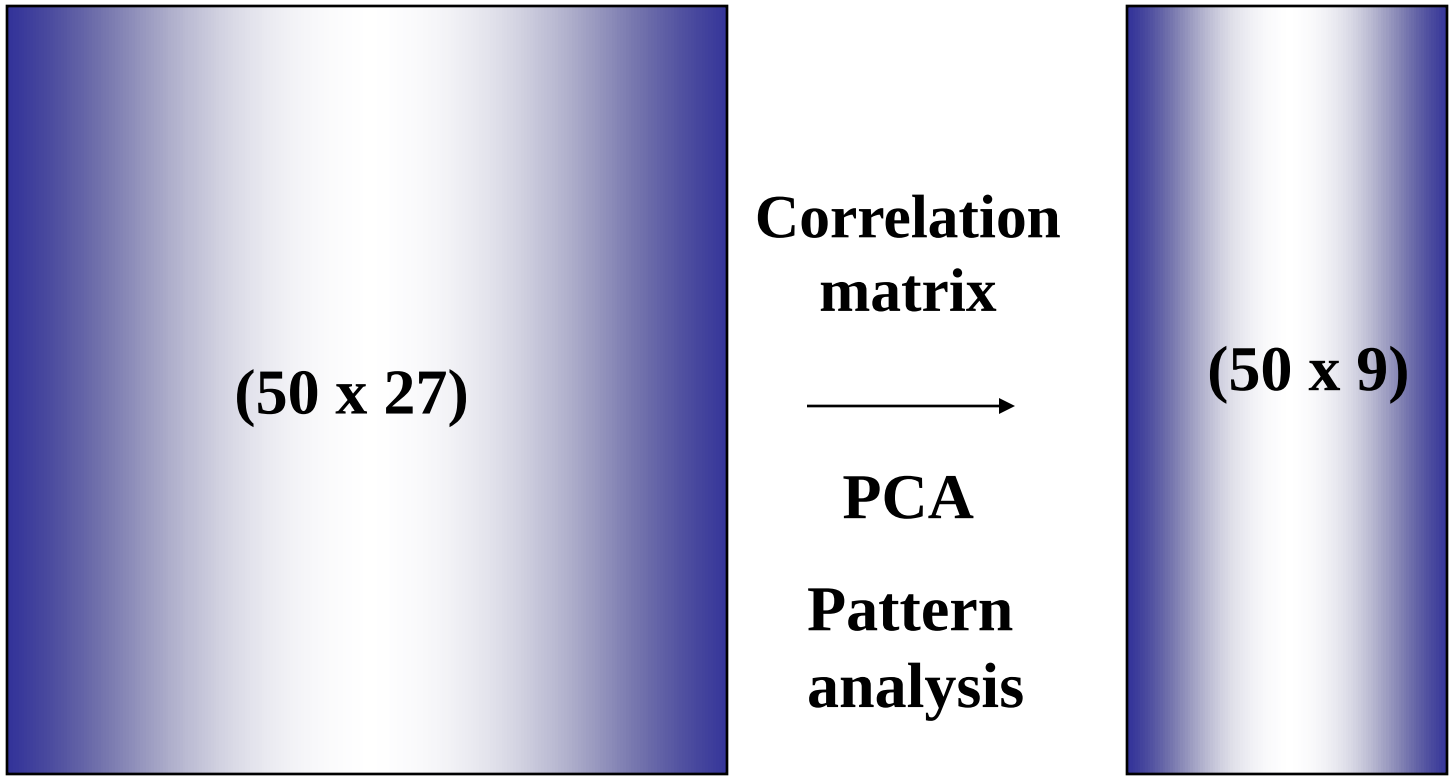
Input data

- We use : atom and bond count, MW, conf. min. E, connectivity index (0,1,2), steric E, LogP, dipole moment, heat of form., HOM E, LUM E, molar refractivity, molecular shape index order (1,2, and 3), and valence connectivity index (0,1, and 2).

Optimization procedures

- **Input data:** dimensionality reduction via: correlation matrix, principal component analysis, and pattern analysis to eliminate the variables without any serious loss of information.
- **NN design:** Selection of the NN parameters (learning rate, momentum, number of training epochs, and initial weights).

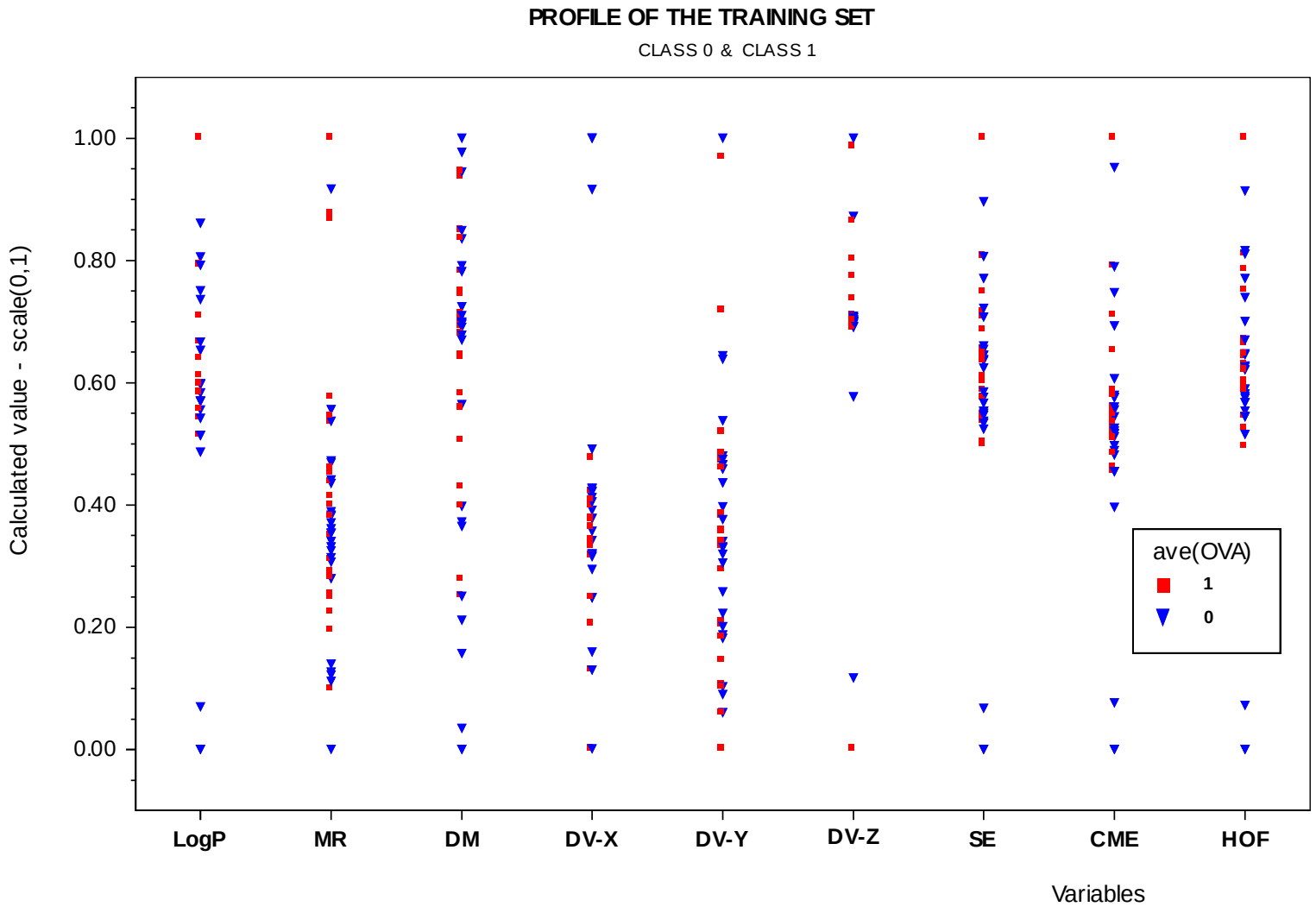
Input data analysis



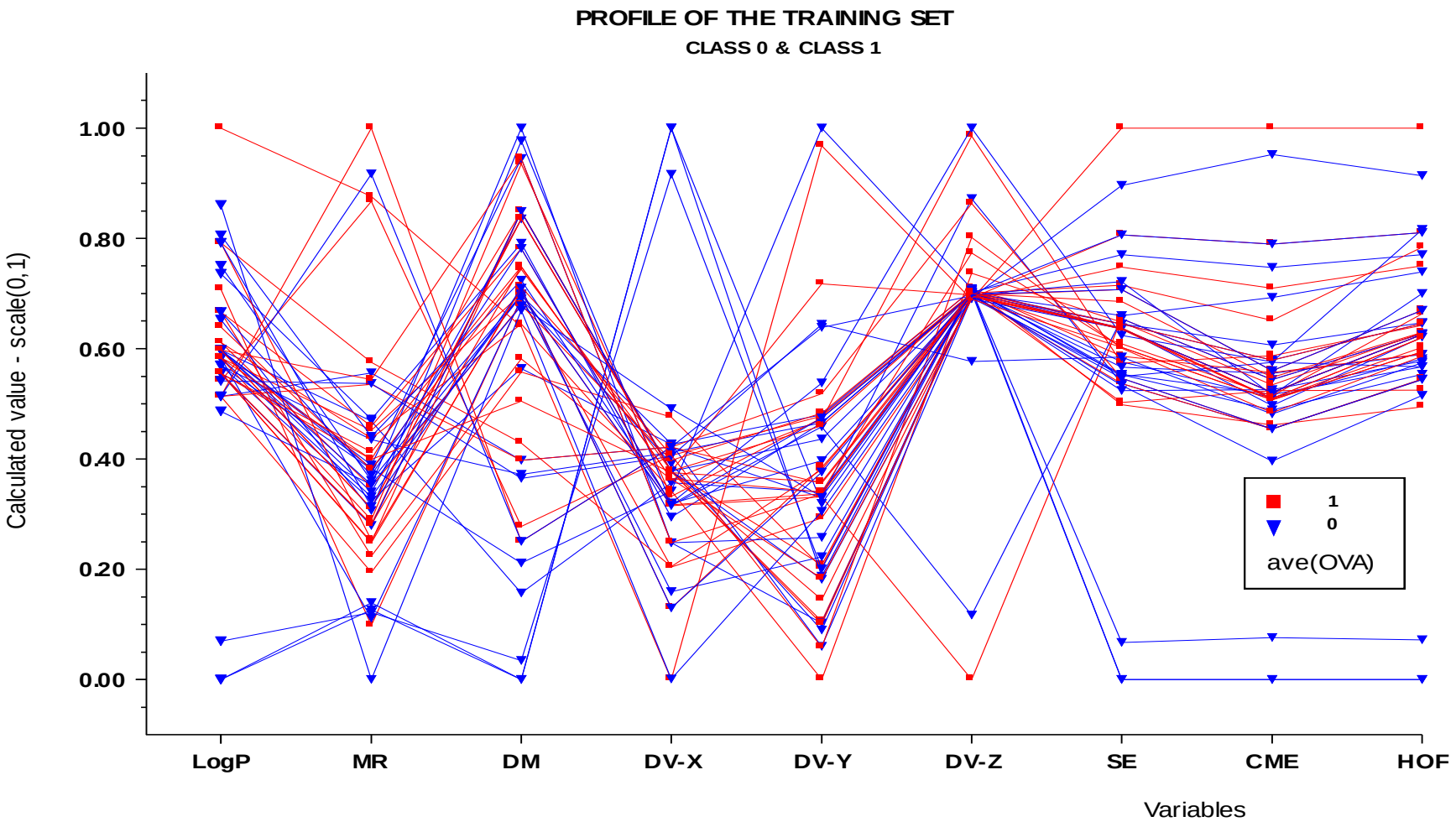
Optimization procedures

- Random selection of the training and validation set (40 + 10 feature vectors).
- Selection of the NN type and architecture (feed-forward back propagation by MATLAB software).
- Analysis of the prediction accuracy with error = $\Delta = \pm 0.1$

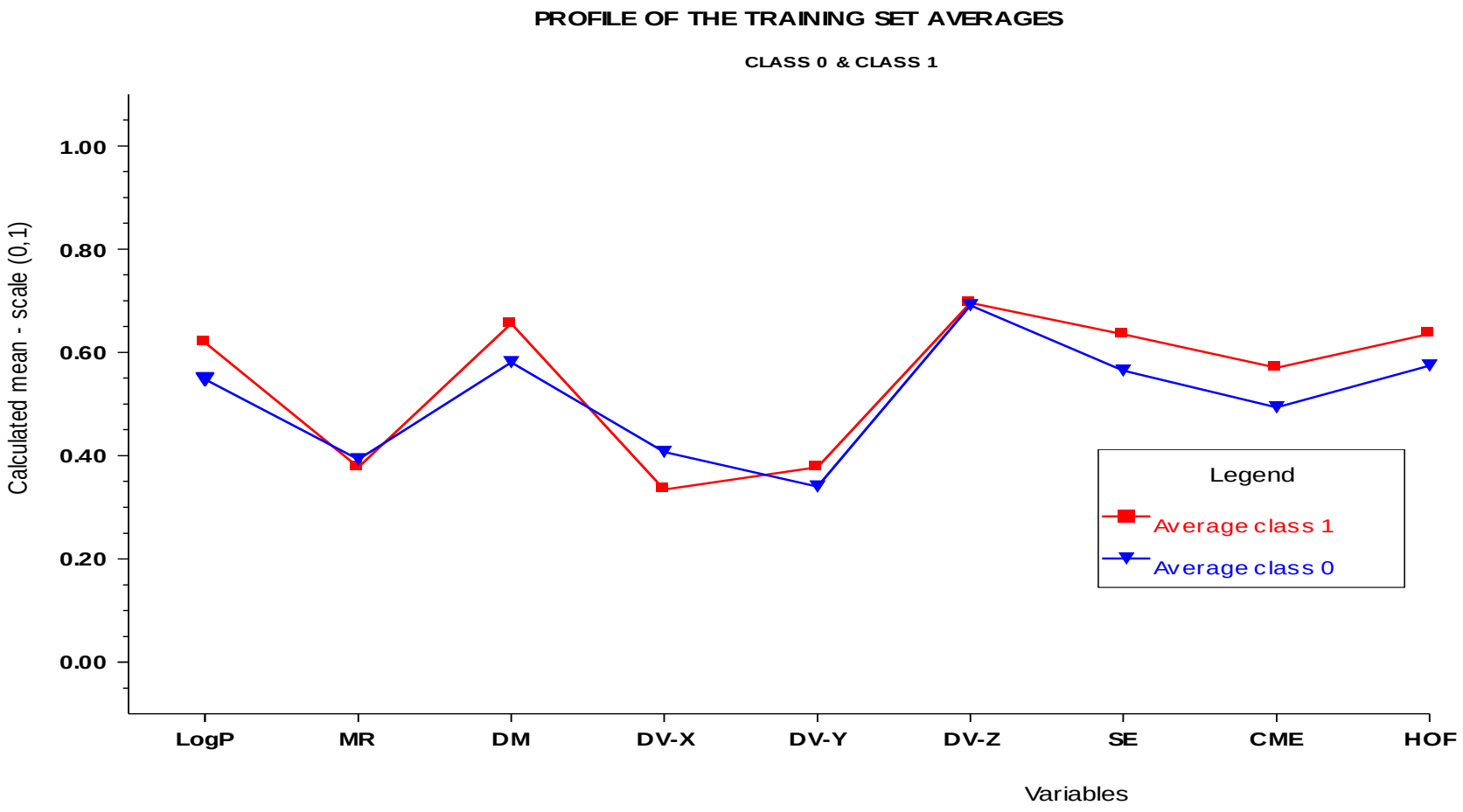
Profile of the training set



Profile of the training set



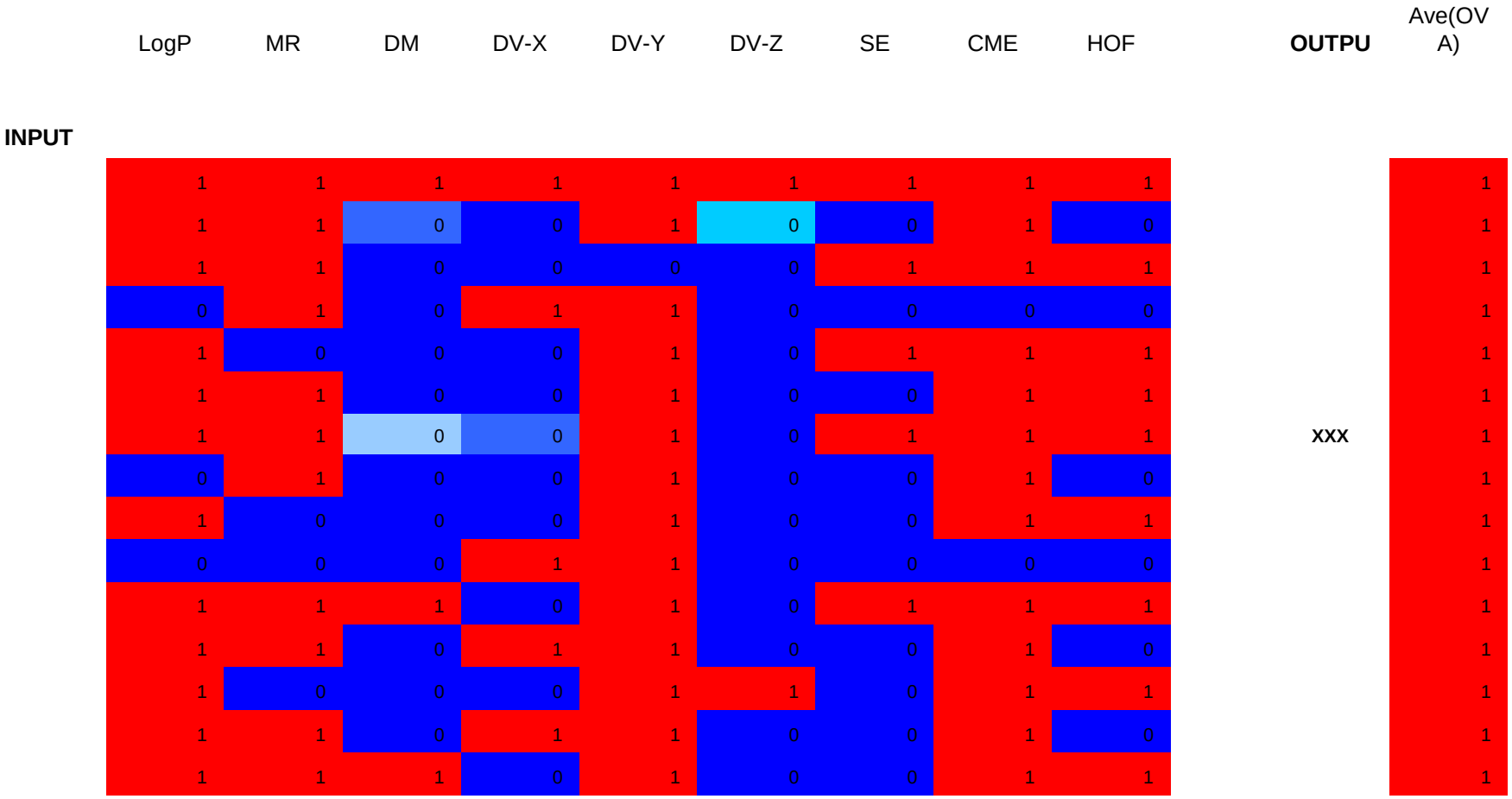
Profile of the training set averages



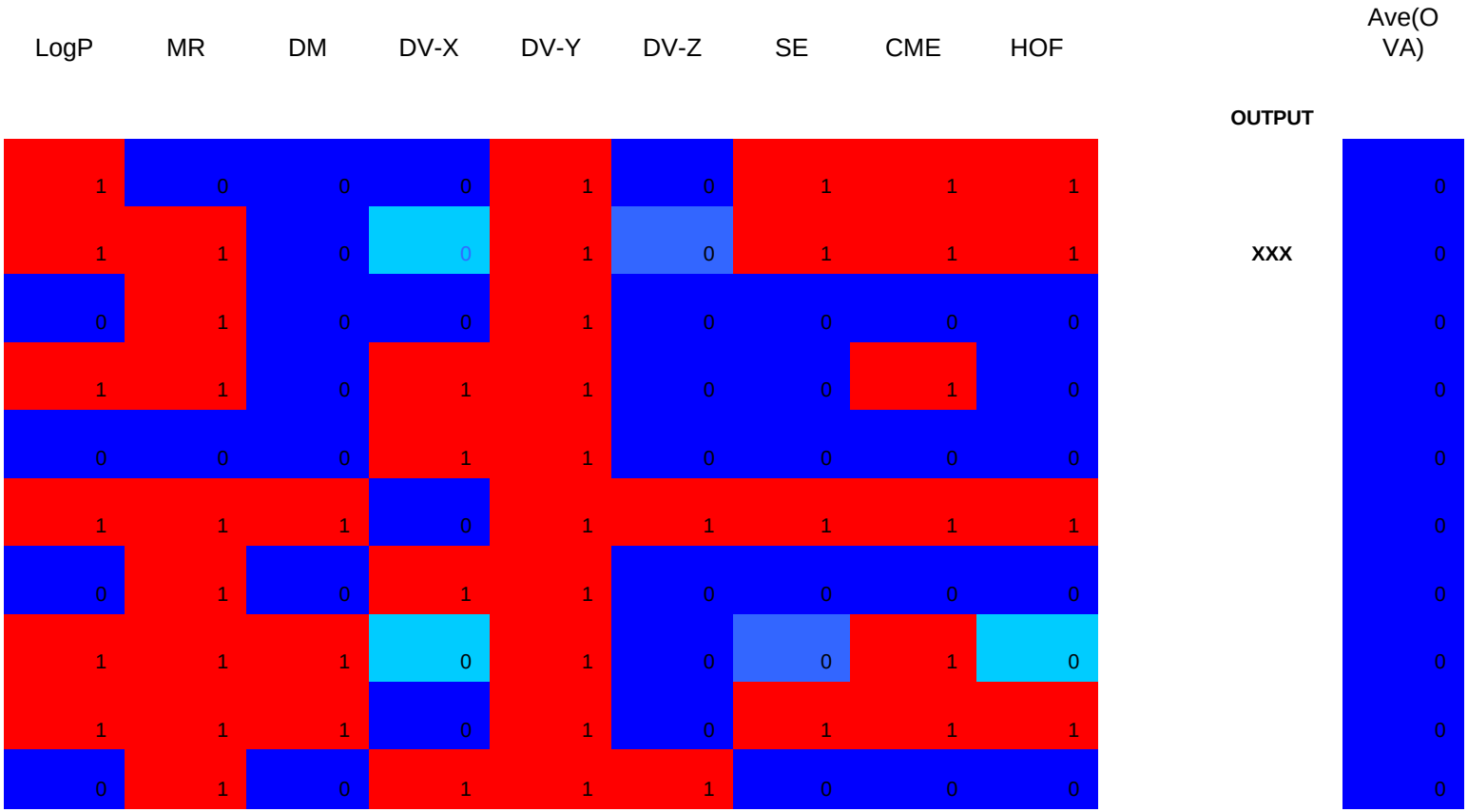
Results

- Feed-forward back-propagation NN system was used on MATLAB software for testing the anticancer activity of taxol analogues against a panel of 4 cell lines of breast/ovarian cancer.
- There are **2** errors (out of 10 compounds in validation set) in classification by neural network model while the discriminant analysis made **4** errors.

Pattern recognition of binary input data



Pattern recognition of binary input data



Results

Analogue		Measured activity
1.	10y110939	**1.7**
2.	10y110943	**2.3**
3.	10y110963	**12.7**
4.	10y110964	**7.7**
5.	10y110905	**0.8**
6.	10y110913	**1.9**
7.	10y110937	**1.1**
8.	07y001119	**1.8**
9.	10y001127	**1.4**
10.	10y110938	**2.0**

More information

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KUMC Bioinformatics Core:

http://www.kumc.edu/kinbre/bioinformatics.html

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