

## Drug Design with Artificial Neural Networks

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### 17 Glossary

18 **Artificial neuron** An artificial neuron is a mathematical  
19 function that simulates in a simplified form the func-  
20 tions of biological neurons. Usually, an artificial neu-  
21 ron has four computational functions, namely receives  
22 signals through input connections from other neurons  
23 or from the environment, sums the input signals, ap-  
24 plies a nonlinear functions (transfer function or activa-  
25 tion function) to the sum, and sends the result to other  
26 neurons or as output from the neural network.

27 **Counterpropagation neural network** The counterprop-  
28 agation neural network is a hybrid network that con-  
29 sists of a self-organizing map as the hidden layer and  
30 an output layer that has as output a computed value for  
31 the modeled property. The network implements a su-  
32 pervised learning algorithm that converges to a unique  
33 solution.

#### 34 Multilayer feedforward artificial neural network

35 A multilayer feedforward (MLF) artificial neural net-  
36 work consists of artificial neurons organized in layers.  
37 The MLF network has an input layer that receives the  
38 structural descriptors for each molecule, an output  
39 layer that provides one or more computed properties,  
40 and one or more hidden layers situated between the  
41 input and the output layers. Each neuron in a hidden  
42 layer receives signals from neurons in the preceding  
43 layer and sends signals to the neurons in the next layer.

**Perceptron** A perceptron is a linear classifier that consists  
of a layer of input neurons and an output neuron. Each  
connection between an input neuron and the output  
neuron has a weight. Depending on the sum of the sig-  
nals received by the output neuron, its output is +1 or  
−1.

### Quantitative structure-activity relationships

Quantitative structure-activity relationships (QSAR)  
represent regression models that define quantita-  
tive correlations between the chemical structure of  
molecules and their physical properties (boiling point,  
melting point, aqueous solubility), chemical properties  
and reactivities (chromatographic retention, reaction  
rate), or biological activities (cell growth inhibition,  
enzyme inhibition, lethal dose). The fundamental  
hypotheses of QSAR is that similar chemicals have  
similar properties, and small structural changes result  
in small changes in property values. The general form  
of a QSAR equation is  $P(i) = f(\mathbf{SD}_i)$ , where  $P(i)$  is  
a physical, chemical, or biological property of com-  
pound  $i$ ,  $\mathbf{SD}_i$  is a vector of structural descriptors of  $i$ ,  
and  $f$  is a mathematical function such as linear regres-  
sion, partial least squares, artificial neural networks, or  
support vector machines. A QSAR model for a prop-  
erty  $P$  is based on a dataset of chemical compounds  
with known values for the property  $P$ , and a matrix of  
structural descriptors computed for all chemicals. The  
learning (training) of the QSAR model is the process  
of determining the optimum parameters of the re-  
gression function  $f$ . After the training phase, a QSAR  
model may be used to predict the property  $P$  for novel  
compounds that are not present in the learning set of  
molecules.

**Radial basis function network** The radial basis function  
(RBF) neural network has three layers, namely an in-  
put layer, a hidden layer with a non-linear RBF activa-  
tion function and a linear output layer.

**Self-organizing map** A self-organizing map (SOM) is an  
artificial neural network that uses an unsupervised  
learning algorithm to project a high dimensional input  
space into a two dimensional space called a map. The  
topology of the input space is preserved in SOM, and  
points that are close to each other in the SOM grid cor-  
respond to input vectors that are close to each other in  
the input space. A SOM consists of neurons arranged  
usually in a rectangular or hexagonal grid. Each neu-  
ron has a position on the map and a weight vector of  
the same dimension as the input vectors.

**Structural descriptor** A structural descriptor (SD) is  
a numerical value computed from the chemical struc-  
ture of a molecule, which is invariant to the number-

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ing of the atoms in the molecule. Structural descriptors may be classified as constitutional (counts of molecular fragments, such as rings, functional groups, or atom pairs), topological indices (computed from the molecular graph), geometrical (volume, surface, charged-surface), quantum (atomic charges, energies of molecular orbitals), and molecular field (such as those used in CoMFA, CoMSIA, or CoRSA).

**Structure–activity relationships** Structure–activity relationships (SAR) represent classification models that can discriminate between sets of chemicals that belong to different classes of biological activities, usually active/inactive towards a certain biological receptor. The general form of a SAR equation is  $C(i) = f(\mathbf{SD}_i)$ , where  $C(i)$  is the activity class of compound  $i$  (active/inactive, inhibitor/non-inhibitor, ligand/non-ligand),  $\mathbf{SD}_i$  is a vector of structural descriptors of  $i$ , and  $f$  is a classification function such as  $k$ -nearest neighbors, linear discriminant analysis, random trees, random forests, Bayesian networks, artificial neural networks, or support vector machines.

### Definition of the Subject

The fundamental hypothesis of the structure-property models is that the structural features of molecules determine the physical, chemical and biological properties of chemical compounds. The first studies that use structure-activity relationships to explain the biological properties of sets of compounds were published by Kopp [74], Crum-Brown and Frazer [18], Meyer [88], and Overton [97]. Modern structure-activity relationships (SAR) and quantitative structure-activity relationships (QSAR) models are based on the Hansch model that predicts a biological property as a statistical correlation with steric, electronic, and hydrophobic indices [27,35,36,37]. The Hansch model shaped the general scene of structure-activity correlations, and almost all subsequent SAR and QSAR models are variations that extend the Hansch model with novel classes of descriptors or with more powerful statistical models, such as partial least squares (PLS), artificial neural networks (ANN), support vector machines (SVM), or other machine learning algorithm. A structural descriptor is a numerical representation of some important molecular features, such as empirical indices (Hammett and Taft substituent constants), physical properties (octanol-water partition coefficient, dipole moment, aqueous solubility), counts of substructures or substituents, graph descriptors [13,54,125], topological indices [4,12,55], connectivity indices [65,66] electrotopological indices [67],

geometrical descriptors (molecular surface and volume), quantum indices (atomic charges, HOMO and LUMO energies) [60,124], and molecular fields (steric, electrostatic, and hydrophobic). SAR represent classification models that are used when the experimental property is a class label (+1/−1), such as substrate/non-substrate, inhibitor/non-inhibitor, ligand/non-ligand, toxic/non-toxic, or carcinogen/non-carcinogen. Classification models are used to screen chemical libraries and to identify compounds that have a desired biological activity, such as inhibitor for a particular enzyme. QSAR represent regression models that are used for experimental properties with continuous values, such as hydrophobicity, aqueous solubility, membrane penetration, lethal concentration, or inhibition constant for an enzyme.

The drug discovery and development process is lengthy, expensive, and has a high attrition rate. The duration of the drug development phases, namely pre-clinical (1 to 5 years), clinical (5 to 11 years), and approval (0.5 to 2 years) [9], puts at 18 years the upper limit for bringing a drug to market, without considering the duration of the drug discovery phase. For 168 drugs approved between 1992 and 2002, the median clinical trial and approval periods were 5.1 and 1.2 years, respectively, with no tendency of decreasing despite exceptional technological advances [63]. Cost data for 68 randomly selected drugs from 10 pharmaceutical companies show that better discovery and screening programs can reduce the total cost per approved drug by up to \$US 242 million [20]. A similar analysis shows that the average out-of-pocket cost per new drug is \$US 403 million (2000 dollars), which increases to \$US 802 after adding the opportunity cost (the cost of pursuing one choice instead of another) [21]. Depending on the therapy or the developing firm, the cost per new drug varies between \$US 500 million to \$US 2,000 million [1]. The attrition rate of the chemical compounds is also impressive, considering that the process starts with millions of compounds tested in high throughput screening and eventually ends with one successful drug on the market. From all compounds that enter the clinical trials, 30% fail due to lack of efficacy, 30% fail in toxicological and safety tests, and only 11% finish the trials [73]. A study considering all 548 new chemical entities approved between 1975 and 1999 found that 45 drugs (8.2%) received one or more black box warnings and 16 (2.9%) were withdrawn from the market [76]. Examples of drugs withdrawn from the market due to adverse reactions include troglitazone (Rezulin) in 2000 [25], cerivastatin (Baycol, Lipobay) in 2001 [28], nefazodone (Serzone) in 2003 [17], pemoline (Cylert) in 1999 (Canada) and 2005 (USA) [42], and rofecoxib (Vioxx) in 2004 [22]. For all difficulties, expenses,

194 and failures that are associated with the drug develop- 243  
195 ment process, the reward for a successful drug can be sub- 244  
196 stantial. The top 2006 best selling drugs (in \$US billions) 245  
197 are lipitor with 14.39 (Pfizer, cholesterol), advair with 246  
198 6.13 (GlaxoSmithKline, asthma), plavix with 6.06 (Bristol- 247  
199 Myers Squibb, vascular disease), nexium with 5.18 (As- 248  
200 traZeneca, acid reflux), norvasc with 4.87 (Pfizer, hyper- 249  
201 tension). 250

202 Computer-assisted drug design (CADD) uses compu- 251  
203 tational chemistry to increase the chances of finding valu- 252  
204 able drug candidates. Among the broad range of compu- 253  
205 tational tools used in CADD, artificial neural networks 254  
206 (ANN) have a special place due to their abilities to model 255  
207 with high accuracies the complex relationships between 256  
208 chemical structures and molecular properties. ANN can be 257  
209 used both for classification (SAR) and regression (QSAR), 258  
210 and they are essential tools in drug discovery cycles to 259  
211 identify active compounds in chemical libraries, and to 260  
212 optimize a wide range of physico-chemical and biologi- 261  
213 cal properties, such as enzyme inhibition, target selectiv- 262  
214 ity, or membrane transport. The SAR and QSAR models 263  
215 based on ANN may predict with high accuracy properties 264  
216 for novel chemicals, even before their chemical synthesis. 265  
217 CADD systems based on ANN may increasing the chances 266  
218 of bringing a drug to market, when they are integrated into 267  
219 the chemical, biological, pharmacological and clinical pro- 268  
220 cedures used by the pharmaceutical industry. 269

## 221 Introduction

222 The simulation of brain mechanisms with artificial neural 272  
223 networks was initiated by McCulloch and Pitts [84,101] 273  
224 and by [106]. Minsky and Papert investigated the math- 274  
225 ematical properties of these simple neural networks in 275  
226 their seminal book *Perceptrons* [92]. Although perceptrons 276  
227 are able to solve some problems, they fail to learn the 277  
228 XOR (exclusive-or) operation. As a result, the research in 278  
229 this field was limited until Hopfield demonstrated that by 279  
230 adding nonlinear functions to each artificial neuron the 280  
231 network could simulate complex behavior [43]. 281

232 Another milestone in ANN research was the discovery 282  
233 of the backpropagating algorithm for the training of mul- 283  
234 tilayer feedforward artificial neural networks [107,108]. 284  
235 Multilayer feedforward (MLF) networks consist of multi- 285  
236 ple layers of artificial neurons, all connected in a feedfor- 286  
237 ward way, from the input layer to the output layer. MLF 287  
238 networks have at least one hidden layer of neurons, and the 288  
239 neurons in the hidden and output layers have nonlinear 289  
240 activation functions. The hidden neurons and the nonlin- 290  
241 ear activation functions are essential in modeling nonlin- 291  
242 ear relationships between input variables and the output 292  
293

property. MLF networks represent the most widespread 243  
ANN type used to model physico-chemical, biological, and 244  
toxicological properties of chemical compounds. 245

246 In addition to MLF, other networks used in drug de- 247  
248 sign are radial basis function networks, self-organizing 248  
249 maps, counter-propagation networks, graph machine neu- 249  
250 ral networks, and probabilistic neural networks. Several 250  
251 reviews [49,52,144] and books are recommended for a de- 251  
252 tailed overview of neural networks and their applications: 252  
253 *Neural Computing* by Wasserman [134], *Neural Networks* 253  
254 *for Pattern Recognition* by Bishop [10], *Pattern Recogni-* 254  
255 *tion and Neural Networks* by Ripley [104], *Neural Net-* 255  
256 *works for Chemical Engineers* by Bulsari [15], and *Neu-* 256  
257 *ral Networks in Chemistry and Drug Design* by Zupan and 257  
Gasteiger [145]. 258

259 The artificial neuron and the perceptron are de- 259  
260 scribed in Sect. “Perceptron”. MLF networks are used to 260  
261 model physico-chemical properties, such as melting tem- 261  
262 perature [75], boiling temperature [33], aqueous solubil- 262  
263 ity [46], and *n*-octanol/water partition coefficients [123]. 263  
264 Drug design applications of MLF networks include mod- 264  
265 els for enzyme inhibition [120], human intestinal absorp- 265  
266 tion [136], virtual screening of chemical libraries [102], 266  
267 and genotoxicity [127]. Another important application of 267  
268 MLF networks is in cancer diagnosis from gene expression 268  
269 data [70,119,135]. Section “Multilayer Feedforward Arti- 269  
270 ficial Neural Network” is an overview of the most important 270  
271 MLF network models in structure-property prediction and 271  
in drug design. 272

273 The radial basis function (RBF) neural network be- 273  
274 longs to the class of feedforward artificial neural network, 274  
275 and it has three layers, namely an input layer, a hidden 275  
276 layer with a non-linear RBF activation function and a lin- 276  
277 ear output layer [93]. RBF networks give predictive mod- 277  
278 els for various properties, such as boiling temperature [81], 278  
279 QSAR for enzyme inhibitors [99,100], ligand-target bind- 279  
280 ing affinity [142], and aquatic toxicity [87]. SAR and QSAR 280  
281 applications of the RBF network are presented in Sect. “Ra- 281  
dial Basis Function Network”. 282

283 The self-organizing map (SOM) was developed by Ko- 283  
284 honen as an unsupervised neural network that transforms 284  
285 a high dimensional input space into a two dimensional 285  
286 space [71,72]. SOM maps the objects by trying to preserve 286  
287 the topological properties of the input space. To predict 287  
288 the class of a new molecule, a vector of structural descrip- 288  
289 tors is sent as input for a trained SOM and projected onto 289  
290 a neuron from the map. The molecule is classified in the 290  
291 same class with the training molecules that are projected 291  
292 onto the same neuron. SOM networks cluster chemical 292  
293 compounds according to their similarity, and thus can be 293  
used to identify groups of molecules with similar proper-

ties [3]. Applications of SOM are found in virtual screening of chemical libraries [105], in modeling the aquatic toxicity of organic chemicals [98], or in structure-activity studies [11]. These and other SOM applications are examined in Sect. “Self-Organizing Map”.

The counterpropagation neural network (CPNN) was developed by Hecht-Nielsen by transforming a self-organizing map into a supervised learning neural network [39,40,41]. The input layer of neurons is connected to the hidden layer that is a self-organizing map, and the excited neuron from SOM sends a signal to the output layer. CPNN may be used for classification or for regression. SAR applications of CPNN include the mutagenicity prediction of aromatic amines [59], and the classification of organic compounds based on their mode of toxic action [117]. Applications of the counterpropagation neural network in SAR and QSAR are presented in Sect. “Counterpropagation Neural Network”.

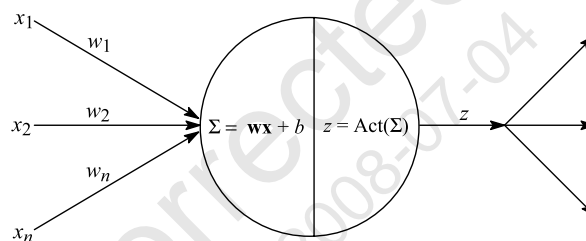
Graph machine neural networks learn SAR and QSAR models directly from the molecular graph [32], by translating the chemical structure into the network topology. For each chemical compound presented to the graph machine, the neural network adopts a structure derived from the molecular graph of the chemical. There are several graph machines used with success in SAR and QSAR, such as recursive neural networks [5,89], the Baskin–Palyulin–Zefirov (BPZ) neural device [7], ChemNet [69], and MolNet [47,50]. The BPZ neural device is constructed by analogy with a biological vision system and contains a sensor field, a set of eyes, and a brain. A chemical structure investigated with the BPZ neural device is represented as a molecular matrix that is superimposed over a sensor field that receives the network input. The information received by the sensor field is transmitted to a set of eyes that transforms it into several MLF networks, and sends signals to the next block, the brain. ChemNet encodes a molecular distance matrix between the input and hidden layers, and has as output an atomic property. In MolNet each atom in a molecule has a corresponding input and hidden neuron, and the connections between the input and hidden layers correspond to the weighted interactions between atoms. The output neuron offers the computed value for a molecular property. In Sect. “Graph Machine Neural Networks” we review structure-activity models computed with graph machine neural networks.

Other ANN used in drug design and molecular property modeling are the Bayesian regularized neural network [31,133], the probabilistic neural network [38,77], and the general regression neural network [141]. Their applications in SAR and QSAR are presented in Sect. “Other Neural Networks”.

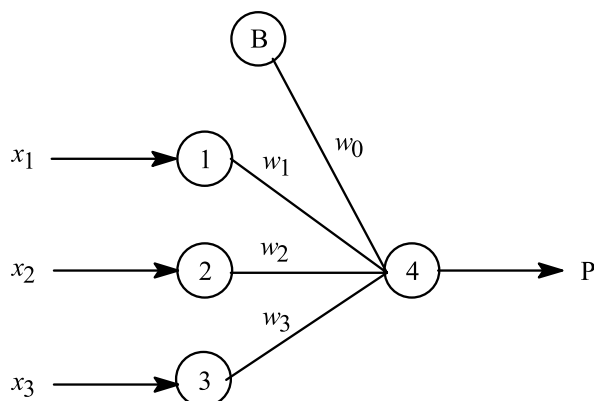
## Perceptron

An artificial neuron is a simple model of a biological neuron expressed as a mathematical function. Artificial neurons represent the basic computational units in an artificial neural network. Each artificial neuron has four basic functions (Fig. 1): (a) receives input signals through connections from the neurons in the previous layer or from the environment; (b) makes a summation of the inputs signals; (c) the result of summation is passed to the activation function and transformed with a mathematical function; (d) the result of the activation function is used by a transfer function to produce an output value that is sent to the neurons in the next layer of neurons. The artificial neuron depicted in Fig. 1 receives the input signals  $x_1, \dots, x_n$  through connections with the weights  $w_1, \dots, w_n$ . The summation of the input signal is computed as the dot product between  $\mathbf{w}$  and  $\mathbf{x}$  plus a bias parameter  $b$ . An activation function  $\text{Act}$  is applied to the sum  $\Sigma$  to give the output value  $z$ . The first artificial neuron was the threshold logic unit proposed by McCulloch and Pitts [84,101]. The activation function was a step function, which has the value is zero for negative argument and one for positive argument. Other important activation functions are: linear,  $\text{Act}(z) = z$ ; sigmoid,  $\text{Act}(z) = 1/(1 + e^{-z})$  [43]; hyperbolic tangent,  $\text{Act}(z) = \tanh(z)$ ; symmetric logarithm,  $\text{Act}(z) = \text{sign}(z) \ln(1 + |z|)$  [15].

A perceptron is the simplest type of ANN, consisting of a layer of input neurons and an output neuron (Fig. 2) [92,106]. The perceptron shown in Fig. 2 has three input neurons (1, 2, 3), a bias neuron B, and an output neuron 4. An input neuron receives an input signal, scales it and then sends it to the output neuron. A simple perceptron is a linear classifier, which cannot learn simple operations, such as the XOR (exclusive-or) operation. A major development was the introduction of nonlinear activation functions that allows ANN to simulate any nonlinear function [43].



Drug Design with Artificial Neural Networks, Figure 1  
Structure and functions of an artificial neuron



Drug Design with Artificial Neural Networks, Figure 2  
Perceptron structure and signal flow

### 382 Multilayer Feedforward Artificial Neural Network

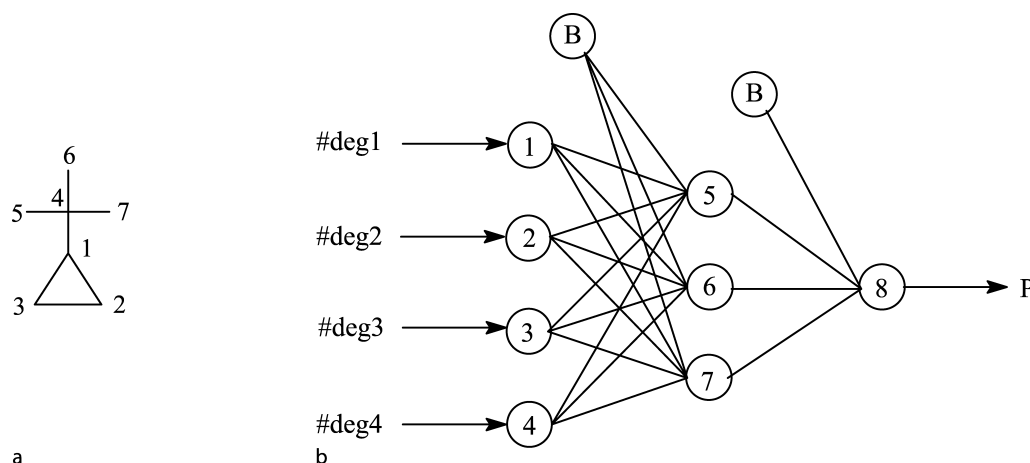
383 A multilayer feedforward artificial neural network, called  
384 also a multilayer perceptron (MLP) is a generalization of  
385 the simple perceptron obtained by inserting one or more  
386 hidden layer of neurons between the input layer and the  
387 output layer. Another important characteristic is the use  
388 of nonlinear activation functions in the hidden and output  
389 layers, although the output neurons can have also a linear  
390 activation function. MLF ANN are universal approxima-  
391 tors, namely they can approximate any function with arbi-  
392 trary precision provided that enough neurons are used in  
393 the hidden layer.

394 In SAR and QSAR applications the structural descrip-  
395 tors represent the input data received by the input neu-  
396 rons. As an example, we consider topological descrip-

397 tors computed from the molecular graph of *t*-butylcy-  
398 clopropane (Fig. 3a) that are used as input in an MLF  
399 ANN with one hidden layer (Fig. 3b). The input layer is  
400 formed by neurons 1–4, the hidden layer contains neurons  
401 5–7, and the output layer is represented by neuron 8. The  
402 bias neurons B send a signal with the value +1 through  
403 weighted connections, and have the role to fine-tune each  
404 neuron. The topological descriptors represent the counts  
405 of vertex degrees, namely  $\text{Deg} = \{3, 2, 1, 1\}$ , i. e., there  
406 are three atoms with degree 1, two atoms with degree 2,  
407 one atom with degree 3, and one atom with degree 4. These  
408 numbers are used as input to neurons 1–4, which perform  
409 a scaling and then send the values to each neuron from  
410 the hidden layer. The output neuron 8 offers the computed  
411 value of a property P for *t*-butylcyclopropane.

412 The MLF ANN application to property modeling con-  
413 sists of two phases, namely training and prediction. Dur-  
414 ing the training (learning) phase the weights of all con-  
415 nections are optimized (adjusted) in order to estimate  
416 with high precision the investigated molecular property.  
417 The most popular training method is the backpropagat-  
418 ing algorithm [107,108], a variant of the gradient algo-  
419 rithms. More efficient training algorithms are direction-  
420 set methods (Powell's method), methods that require the  
421 computation of the first derivatives such as conjugate gra-  
422 dient methods (Fletcher-Reeves or Polak-Ribiere), Lev-  
423 enberg-Marquardt, or quasi-Newton (variable metric)  
424 methods (Davidon-Fletcher-Powell or Broyden-Fletcher-  
425 Goldfarb-Shanno).

426 MLF ANN can be trained with artificial intelligence  
427 algorithms, such as particle swarm optimization, which  
was used in a QSAR study of inhibitors of platelet-derived



Drug Design with Artificial Neural Networks, Figure 3

ANN prediction of molecular properties from the molecular structure: topological descriptors computed from a the molecular graph of *t*-butylcyclopropane are used as input in b a multilayer feedforward neural network with one hidden layer

428 growth factor receptor phosphorylation [113]. Such algo-  
429 rithms can provide a complete optimization of an MLF  
430 ANN, namely they can optimize both the network topol-  
431 ogy and the connection weights. The network topology is  
432 defined by the number of hidden layers and by the num-  
433 ber of neurons in each hidden layer. The complete opti-  
434 mization of ANN with particle swarm optimization has  
435 fast convergence to the global minimum [85] and avoids  
436 the overfitting of the learning dataset of chemicals [112].  
437 The selection of the most important descriptors for the  
438 ANN input is an important step in obtaining predictive  
439 models. Several artificial intelligence algorithms can be  
440 used for an efficient feature selection, such as genetic algo-  
441 rithm [115,116], particle swarm optimization [2], and ant  
442 colony optimization [58].

443 Taskinen and Yliruusi reviewed the MLF ANN appli-  
444 cations in predicting several physico-chemical properties  
445 of interest in drug development, such as octanol-water  
446 partition coefficient, aqueous solubility, boiling tempera-  
447 ture, and vapor pressure [121]. The melting temperatures  
448 for sulfur-containing organic compounds were predicted  
449 from simple molecular graph indices [75]. The melting  
450 temperatures of 717 ionic liquids were modeled with MLF  
451 ANN, associative neural networks, support vector ma-  
452 chines,  $k$ -nearest neighbors, and multiple linear regres-  
453 sion [126]. The structural descriptors evaluated in these  
454 models were electrotopological indices [67] and Dragon  
455 descriptors [124]. The moderate accuracy of predictions  
456 obtained with all algorithms can be explained by the diffi-  
457 culty to encode the solid state characteristics of ionic liq-  
458 uids. Hall and Story used electrotopological indices and  
459 an MLF ANN to model the boiling temperatures of 298  
460 compounds and the critical temperatures of 165 com-  
461 pounds [33]. The best results for the boiling temperatures  
462 were obtained with a neural network with five hidden neu-  
463 rons with a mean absolute error of 3.93 K, whereas a net-  
464 work with four hidden neurons gave good predictions for  
465 the critical temperatures with a mean absolute error of  
466 4.52 K. In a similar study, atom type electrotopological  
467 state indices were used to model the boiling temperatures  
468 of alkanes, alcohols and chloroalkanes [34].

469 Huuskonen et al. developed MLF ANN models for the  
470 aqueous solubility of a diverse set of 734 organic com-  
471 pounds [46]. Atom type electrotopological state indices  
472 were used as input data in a neural network with five hid-  
473 den neurons. Good results were obtained both in train-  
474 ing ( $s = 0.52$ ) and prediction ( $s = 0.75$ ), showing that  
475 the aqueous solubility for a large and diverse set of or-  
476 ganic compounds can be predicted from topological in-  
477 dices. Tetko et al. developed a neural network model for  
478 the octanol-water partition coefficients of 12,908 organic

479 compounds [123]. The model consists of an ensemble of  
480 50 ANN, each ANN having 75 input neurons and 10 neu-  
481 rons in the hidden layer. The leave-one-out cross-valida-  
482 tion indicate that the model gives good predictions, with  
483  $r^2 = 0.95$ . The  $^{13}\text{C}$  NMR chemical shift can be predicted  
484 from simple topological parameters, as shown for a dataset  
485 of acyclic alkenes [56,57].

486 To compensate for the lack of toxicological data for  
487 aquatic organisms, a number of neural networks QSAR  
488 models were proposed for the toxicity of organic chemi-  
489 cals against fathead minnow, rainbow trout, bluegill sun-  
490 fish, *Daphnia magna*, *Tetrahymena pyriformis*, and *Vib-  
491 rio fischeri* [61]. These ANN models can be used to pre-  
492 dict the environmental impact of novel chemicals, and to  
493 prioritize their experimental evaluation in aquatic toxic-  
494 ity assays. Huuskonen tested multiple linear regression  
495 and artificial neural networks in QSAR models for toxic-  
496 ity of 140 organic chemicals against fathead minnow [45].  
497 A neural network trained with 14 electrotopological state  
498 indices provided a predictive model for the experimen-  
499 tal toxicity. Basak et al. modeled the toxic modes of  
500 action for 283 chemicals with ANN and topological in-  
501 dices [6]. The toxic compounds were classified as nar-  
502 cotics, electrophiles/proelectrophiles, uncouplers of oxida-  
503 tive phosphorylation, acetylcholinesterase inhibitors, and  
504 neurotoxicants. The modes of action SAR models provide  
505 reliable predictions, with rates of correct classification be-  
506 tween 65% and 95%. Lower predictions are obtained for  
507 classes with a low number of compounds.

508 Dopamine antagonists, serotonin antagonists, and  
509 serotonin-dopamine dual antagonists are used as anti-  
510 psychotics. Based on a training dataset consisting of  
511 1135 dopamine antagonists, 1251 serotonin antagonists,  
512 and 386 serotonin-dopamine dual antagonists, Kim et al.  
513 tested several machine learning algorithms, including  
514 ANN and recursive partitioning [68]. The average classi-  
515 fication rate in training was 73.6% and in prediction was  
516 69.8%, indicating that these models can be used in virtual  
517 screening to identify new active compounds. Siu and Che  
518 used multiple linear regression, partial least squares, and  
519 ANN to model the  $\alpha$ -amino acids affinities for  $\text{H}^+$  and for  
520 sodium, copper, and silver cations [114]. The cross-vali-  
521 dation tests indicate that the best predictions are obtained  
522 with the artificial neural network. These QSAR models are  
523 useful in elucidating the binding properties of the  $\alpha$ -amino  
524 acids.

525 Votano et al. used ANN,  $k$ -nearest neighbors, and  
526 decision forest to model the mutagenicity of 3363 di-  
527 verse compounds tested for their Ames genotoxicity [127].  
528 The dataset was split into 2963 training compounds and  
529 400 prediction compounds, and the SAR models

were developed with 148 topological indices that included electrotopological state indices and molecular connectivity indices. All three classifiers gave good predictions, with a slight advantage for the neural network, as indicated by the area under the receiver operator characteristic (AUROC) curve, namely AUROC = 0.93 for ANN, AUROC = 0.92 for  $k$ -nearest neighbors, and AUROC = 0.91 for decision forest.

A good intestinal absorption is desirable property for drugs, but its experimental determination is costly and time-consuming. Wessel et al. used ANN to estimate the percent human intestinal absorption (% HIA) of 86 drugs [136]. A neural network optimized with a genetic algorithm provided the best results, with an error of 9.4% HIA units for training, 19.7% HIA units the cross-validation, and 16.0% HIA units for an external prediction set.

Sutherland et al. evaluated ANN, PLS, genetic function approximation, and genetic PLS in QSAR models for inhibitors of angiotensin converting enzyme, acetylcholinesterase, benzodiazepine receptor, cyclooxygenase-2, dihydrofolate reductase, glycogen phosphorylase B, thermolysin, and thrombin [120]. ANN gave the best predictions for QSAR models obtained with graph indices and geometrical descriptors. Another large scale evaluation of structure-activity models was made for chemicals that target HIV-reverse transcriptase, COX2, dihydrofolate reductase, estrogen receptor, and thrombin [102]. A comparison of several nonlinear modeling algorithms shows that ANN are successful in identifying active compounds from chemical libraries and can be used in virtual screening. Pharmaceutical companies constantly enrich their collections of chemical compounds by acquisitions that increase the structural diversity of molecules available for high throughput screening. Muresan and Sadowski proposed an ANN system to compute an “in-house likeness” score for compound acquisition [94]. The analysis of several datasets show that a set of atom-type counts used as input to the ANN models represents an efficient way of identifying structural patterns that are missing from an in-house collection.

Votano et al. compared multiple linear regression, ANN,  $k$ -nearest neighbors, and support vector machines in QSAR models for the human serum protein binding of 1008 chemicals (808 for training and 200 for prediction) [128]. The best predictions ( $r^2 = 0.7$ ) were obtained with ANN models, indicating that these QSAR can assist the drug design process. Katritzky et al. evaluated ANN and multiple linear regression in QSAR models for 277 inhibitors of glycogen synthase kinase-3 [62]. The descriptors were selected from a pool consisting of subgraph counts, topological indices, geometrical parameters and

quantum indices. The QSAR models highlight the structural factors that influence the inhibition of glycogen synthase kinase-3. Inhibitors of the hERG (human ether-á-go-go-related gene) potassium channel can lead to a prolongation of the QT interval that can trigger torsade de pointes, an atypical ventricular tachycardia. Seierstad and Agrafiotis used ANN to model the nonlinear structure-activity relationship for hERG channel inhibitors [110]. The QSAR models with best predictive power are obtained with a feature selection to prevent over-fitting and by aggregation several ANN into an ensemble model to minimize the instability in predicting novel chemicals. The time- and dose-dependent anti-inflammatory in vivo activity of substituted imidazo[1,2-*a*]pyridines was modeled with artificial neural networks [109]. This study shows that ANN have unique properties to study pharmacodynamic and pharmacokinetic properties of drugs and drug-like compounds. Peptides that have a good binding affinity for major histocompatibility complex (MHC) class I molecules are candidates in the development of new vaccines against cancer and viral infections. Filter et al. modeled the peptide binding to MHC class I allele HLA-A\*0201 with artificial neural networks [26]. The ANN system can identify peptides that do not correspond to the usual recognition motifs, as shown for several new melanoma-associated peptides.

Artificial neural networks represent the method of choice is cancer prediction and prognosis [19]. Their use improves the accuracy of predicting cancer susceptibility, recurrence and mortality. Molecular data, such as protein biomarkers and microarrays, together with ANN models can improve the understanding of cancer development and progression. The mechanism of action of drugs against 60 malignant cell lines in the National Cancer Institute drug screening program was investigated with ANN [135]. Out of the 141 drugs, the ANN gives incorrect predictions for only 12 of them, showing that the model can be used to guide the screening program. Khan et al. used ANN and gene expression data to identify the class of small, round blue-cell tumors [64]. Although the classification of these tumors difficult in clinical practice, the neural networks identified the relevant genes and correctly classified all samples. ANN trained with gene microarray data can identify with success several types of cancers, such as colon cancer [111] and esophageal cancer [138].

### Radial Basis Function Network

An RBF neural network is a feedforward network with three layers, in which the neurons in the hidden layer have a RBF activation function [93]. RBF neural networks are

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universal approximators, that can approximate any continuous function with arbitrary precision if enough neurons are allowed in the hidden layer. An early application of the RBF network in structure-property studies was reported by Lohninger for the boiling temperatures of organic compounds [81]. The training process of a radial basis function artificial neural network (RBF ANN) consists of selecting the network topology, finding the centers and widths of the RBF neurons, and computing the connection weights between the hidden and output layers. Zhou et al. showed that the particle swarm optimization is very efficient in training an RBF neural network [143]. The procedure was tested with a dataset of 40 inhibitors of murine P388 leukemia cells and 70 structural descriptors, and the results indicate that the swarm optimization converges fast to a global optimum. Wan and Harrington compared two algorithms for RBF ANN training, namely K-means clustering and linear averaging [131]. The results obtained for two datasets (polychlorobiphenyl mass spectra and Italian olive oil classification) indicate that the linear averaging method gives better predictions.

QSAR models for glycine/NMDA receptor antagonists, which may treat stroke or seizure, were computed for a dataset consisting of 109 compounds [99]. The set of structural descriptors included topological indices, geometric descriptors, quantum indices, and polar surface parameters. The optimum set of descriptors was selected with a genetic algorithm and an RBF network. SAR models for inhibitors of protein tyrosine phosphatase 1B, which are potential agents for the treatment for type 2 diabetes and obesity, were computed for 128 compounds [100]. The classification models were obtained with RBF networks, linear discriminant analysis, and  $k$ -nearest neighbors. A correct classification rate of 85.7% was obtained for an external prediction set, indicating that the SAR model can be used to find inhibitors in virtual libraries. Neuraminidase is a key target treating infections with the influenza virus, and many classes of inhibitors are tested for this enzyme. In order to identify the structural features that influence the inhibition of this enzyme, Lü et al. evaluated RBF networks in QSAR models for 46 neuraminidase inhibitors [82]. Five important descriptors were found with a heuristic search among several hundred indices. Prediction tests show that the RBF network results are comparable with those obtained with a multiple linear model, indicating a possible absence of nonlinear structure-activity relationships for these inhibitors.

Zheng et al. compared RBF networks, support vector machines, and partial least square in QSAR models for the Ah receptor binding affinities of polychlorinated, polybrominated, and polychlorinated-brominated

dibenzo-p-dioxins [142]. The best leave-one-out cross-validation predictions are obtained by the RBF network, with  $q^2 = 0.88$ . Melagraki et al. used RBF networks to model the toxicity of 39 organic compounds against *Vibrio fischeri* [87]. The descriptors used in the simulation include topological indices, electronegativity parameters, and lipophilicity. The good QSAR predictions indicate that the model can be used to evaluate the toxicity of diverse chemicals. QSAR models based on RBF networks were developed for the toxicity of 221 phenols against *Tetrahymena pyriformis* [86]. Prediction tests performed with cross-validation and with an external set show that the RBF network gives more accurate predictions than multiple linear regression.

### Self-Organizing Map

A self-organizing map is an artificial neural network that projects a high-dimensional input space into a low-dimensional (usually two dimensional) output space [71,72]. A SOM is trained with unsupervised learning, meaning that the training molecules do not need a class label or property value. The input vectors are mapped in a two dimensional space by preserving the topological properties of the input space. The output layer in a SOM is a matrix of neurons, with the property that an input vector is projected into a single output neuron. Several similar input vectors may be project into the same output neuron, or into adjacent output neurons that form clusters of similar objects. This SOM property is used to discover clusters in collections of chemical compounds. The chemical similarity of large chemical libraries is easily evaluated by projecting the molecules onto a SOM that auto-organizes similar compounds by preserving their similarity relationships in the descriptor space. SOM are used to screen libraries to identify clusters of structurally similar compounds that may have similar biological properties.

SOM may be used also for classification by assigning class labels to a trained network (Fig. 4). This example shows an  $8 \times 8$  SOM with labels attached to the output neurons. The class labels are attached after training and represent the majority class for objects projected onto a particular output neuron. The objects are organized in four clusters, two for class 1, one for class 2, and one for class 3. The SOM predictions are straightforward, namely a new object is projected onto an output neuron and takes the label of the output neuron as its predicted class. Single molecules may be mapped onto a SOM network by projecting the points situated on the molecular surface [3]. The Cartesian coordinates of each surface point are used as input for the SOM network that provides a two-dimen-



2	2	2		1	1	1	1
2	2				1	1	1
2	2			1	1	1	1
3	3	3					
3	3		1		1		
3	3	3	1	1	1	1	
			1	1	1		

**Drug Design with Artificial Neural Networks, Figure 4**  
A self-organizing map with three classes

sional display of the molecular surface. To add more structural information on the map, output neurons are colored according to the molecular electrostatic potential of the surface points projected onto them.

SOM networks are very efficient in discovering activity clusters in chemical libraries that contain active compounds for several targets. Terfloth and Gasteiger clustered with SOM a number of 299 compounds representing four activity classes, namely 75 5-hydroxytryptamine 5-HT<sub>1a</sub>-receptor agonists, 75 histamine H<sub>2</sub>-receptor antagonists, 74 monoamine oxidase MAOA inhibitors, and 75 thrombin inhibitors [122]. All classes are generally clustered in distinct regions, but a small number of neurons represent chemicals from different classes. Such degenerate mapping may be solved by increasing the size of the map or by testing other structural descriptors that may discriminate better these activity classes. Drug candidates are routinely screen to determine if they are hERG channel blockers, because such chemicals can cause sudden cardiac death. Roche et al. examined the hERG activity of a chemical library with SOM, PLS, MLF ANN, principal component analysis, and substructure analysis [105]. These classification models offer good predictions for a validation set, with 71% success rate for active compounds and 93% for inactive compounds.

*Trypanosoma cruzi* is deposited on the skin surface by bugs from the Reduviidae family, and then it infects the human host by penetrating through insect bites, thus causing trypanosomiasis, or Chagas disease. The chronic form of the disease may develop more than 10 years after the infection, and may be fatal. Boiani et al. developed several computational models to evaluate the anti-*Trypanosoma cruzi* activity of *N*-oxide containing heterocycles [11]. A SOM was applied to separate between activity classes and to select an optimum set of descrip-

tors. Other models tested with success for this dataset are *k*-nearest neighbors and decision tree.

QSAR models have limitations for the domain of chemical structures and biological activities for which they give reliable predictions. For example, interpolation gives better predictions than extrapolation, and extrapolations far away from the training structural space or activity space are not reliable. Also, all compounds used to train a QSAR should have the same mechanism of interaction with the biological target. A SOM can easily identify if a prediction compound is similar or not with the training set of chemicals. If the prediction compound is mapped in the SOM regions occupied by the training compounds, then the QSAR prediction has a high confidence level. SOM is also used to select from a large dataset only those chemicals that act through a common mechanism or form a cluster of compounds with similar structures. Gini et al. applied such an approach to separate molecules into homogeneous groups of chemicals with similar biological and structural properties [30]. These groups were then used to compute local QSAR models for the aquatic toxicity of chemicals against *Pimephales promelas* and *Tetrahy-mena pyriformis*. A proper validation of a QSAR model gives vital information regarding its prediction error and validity domain. SOM is a good choice to split a dataset into a training set and a validation (prediction) set. Papa et al. applied this method to develop QSAR models for the toxicity of organic chemicals against *Pimephales promelas* [98].

SOM networks are flexible tools to cluster and visualize large chemical libraries. von Korff and Hilpert applied SOM to cluster a library containing 3000 G-protein-coupled receptor (GPCR) ligands for about 130 receptors and 3000 non-GPCR ligands [147]. The chemical structure was described with fingerprints and topological pharmacophores. Cross-validation tests indicate that SOM can separate GPCR ligands from non-GPCR ligands. A possible application of the SAR model is in the design and identification of focused libraries that target a specific GPCR receptor. The supervised self-organizing map (sSOM) is a SOM variant that uses property labels during the training phase. Xiao et al. compared sSOM with *k*-nearest neighbors, PLS and other linear methods in their ability to model a set of 256 inhibitors of dihydrofolate reductase [137]. The predictions tests show that sSOM is insensitive to noise and provides more accurate predictions than linear QSAR methods.

The experimental data obtained in the National Cancer Institute antitumor drug screening program were investigated with SOM to identify clusters of chemicals having the same biological action [103]. SOM clusters high-

816 light four classes of mechanism of action of drugs, namely  
817 mitosis, nucleic acid synthesis, membrane transport and  
818 integrity, and phosphatase- and kinase-mediated cell cy-  
819 cle regulation. SOM and fuzzy C-means clustering were  
820 used by Wang et al. to identify marker genes and to classify  
821 tumors based on DNA microarray data [132]. The meth-  
822 ods were tested with good results for four datasets, namely  
823 leukemia, colon cancer, brain tumors, and National Can-  
824 cer Institute cancer cell lines. For each dataset the algo-  
825 rithm identifies sets of marker genes with predictive power  
826 for tumor classification.

### 827 Counterpropagation Neural Network

828 Hecht-Nielsen developed the counter-propagation neural  
829 network (CPNN) as a supervised learning network that  
830 combines a self-organizing map that sends signals to an  
831 output layer of neurons [39,40,41]. CPNN applications in  
832 chemistry and in structure-activity are reviewed by Zupan  
833 et al. [146] and by Vracko [129]. Recent CPNN studies  
834 in molecular modeling and structure-activity relationships  
835 are reviewed in this section.

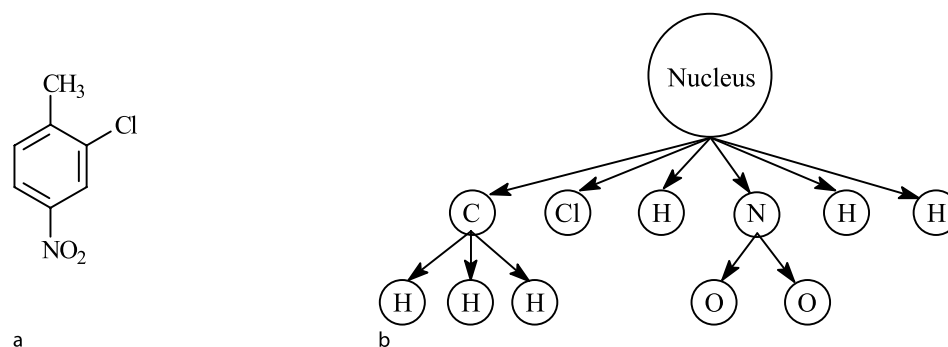
836 Jezierska et al. used CPNN to select an optimum group  
837 of descriptors for mutagenicity QSAR models obtained  
838 for 95 aromatic and heteroaromatic amines [59]. Start-  
839 ing from 275 descriptors, CPNN selected six topologi-  
840 cal indices and the LUMO energy as the best combina-  
841 tion of input parameters. The reduced set of descriptors  
842 give good predictions, with  $R_{cv} = 0.85$  obtained in leave-  
843 one-out cross-validation. Numerous organic chemicals are  
844 environmental pollutants, and a considerable number of  
845 studies are dedicated to the computational prediction of  
846 their mechanism of aquatic toxicity (MOA). The reli-  
847 able prediction of MOA has major applications in se-  
848 lecting the appropriate QSAR model, to identify chemi-  
849 cals with similar toxicity mechanism, and in extrapolat-  
850 ing toxic effects between different species and exposure  
851 regimens [53]. Spycher et al. developed MOA classifiers  
852 for 115 compounds comprising nine MOA classes and 24  
853 descriptors [117]. The four classifiers evaluated, namely  
854 CPNN, PLS, logistic regression, and linear discriminant  
855 analysis, had an overall correct classification between 52%  
856 and 59%, as determined by five-fold cross-validation. Sev-  
857 eral MOA classes contain a small number of compounds,  
858 which might explain the low prediction rate. In a related  
859 study, CPNN and logistic regression classifiers were com-  
860 puted for a dataset of 220 phenols with four MOA [118].  
861 The rate of correct predictions in five-fold cross-valida-  
862 tion was 92%, much higher than in the previous study  
863 that considered nine MOA classes. The higher prediction  
864 rate may be a result of a larger number of compounds in

865 each MOA class and of a more homogeneous set of chem-  
866 icals.

867 CPNN and support vector machines (SVM) were com-  
868 pared in a QSAR study for the estrogen receptor binding  
869 affinity of 131 compounds [29]. Several methods of feature  
870 selection were tested, and the predictions obtained with  
871 CPNN and SVM vary significantly with the different sets  
872 of selected descriptors. Mazurek et al. investigated CPNN  
873 structure-selectivity models for a set of artificial metalloen-  
874 zymes [83]. These catalysts perform the enantioselective  
875 hydrogenation acetamidoacrylic acid with a high enan-  
876 tiomeric excess (%ee). The structural descriptors are com-  
877 puted from the geometry of the complexes ligand-metal-  
878 loenzyme, and the CPNN is trained to predict the %ee. The  
879 predictions obtained for an external test set ( $R = 0.953$   
880 and  $RMS = 16.8\%$ ee) provide convincing evidence for  
881 the utility of ligand-metalloenzyme descriptors in mod-  
882 eling structure-selectivity relationships. Wagner et al. ap-  
883 plied CPNN to structure-activity models for the NF-KB  
884 inhibition by 103 sesquiterpene lactones [130]. The activ-  
885 ity range for NF-KB inhibition was partitioned in six ac-  
886 tivity classes, and the chemical structure was expressed  
887 with autocorrelation descriptors based on atomic prop-  
888 erties. A ten-fold cross-validation shows that the rate of  
889 correct classification is 80.6%, and an external validation  
890 with 14 new compounds has 78.6% correct predictions.  
891 CPNN and  $k$ -nearest neighbors classifiers were applied  
892 to the classification of plants from the Asteraceae fam-  
893 ily based on a set of sesquiterpene lactones isolated from  
894 individual species [44]. The separation of plants in three  
895 tribes and seven subtribes is based on structural descrip-  
896 tors computed from the molecular structure of sesquiter-  
897 pene lactones. This approach can be applied for the au-  
898 tomatic identification of plant species based on chemical  
899 analysis and machine learning.

### 900 Graph Machine Neural Networks

901 Usual structure-activity models consider the chemical  
902 structure only indirect, through descriptors computed  
903 from various representations of molecules. In these mod-  
904 els, the topology of neural networks remains constant  
905 for all training and prediction molecules. All training  
906 molecules, large or small, are represented by a constant  
907 length vector of descriptors, thus restricting the use of  
908 the chemical structure in models. A different approach  
909 is taken in artificial neural networks based on graph ma-  
910 chines which learn SAR and QSAR models directly from  
911 the molecular graph, by translating the chemical struc-  
912 ture into the network topology [32]. In this section we  
913 review four graph machine neural networks, namely re-



Drug Design with Artificial Neural Networks, Figure 5

Representation of congeneric chemical compounds in recursive neural networks: a 2-chloro-1-methyl-4-nitrobenzene b represented as a tree

914 cursive neural networks [5,89,90], the Baskin–Palyulin–  
915 Zefirov (BPZ) neural device [7], ChemNet [69], and Mol-  
916 Net [47,50].

### 917 Recursive Neural Networks

918 Recursive neural networks (RecNN) map a directed ordered  
919 acyclic graph to the real set. All chemical compounds  
920 modeled in a RecNN model must be represented as a directed  
921 ordered acyclic graph. As an example consider 2-chloro-1-methyl-4-nitrobenzene (Fig. 5a)  
922 as a member of series of compounds that have a common  
923 skeleton, which in this case is benzene. The molecular  
924 structure is transformed into an ordered tree as shown in  
925 Fig. 5b. All molecules in the training set are transformed  
926 into ordered tree. Using these structured data as input,  
927 RecNN reflects the molecular topology as encoded in the  
928 ordered tree. The theory and applications of RecNN in  
929 SAR and QSAR are presented in several reviews [5,89,90].  
930 RecNN were applied to several structure-property models,  
931 including models for the glass transition temperature of  
932 polymers [23,24], QSAR for the binding affinities of  
933 ligands to benzodiazepine receptor [91], and for the  
934 Gibbs free energy of solvation in water of organic com-  
935 pounds [8].  
936

### 937 Baskin–Palyulin–Zefirov Neural Device

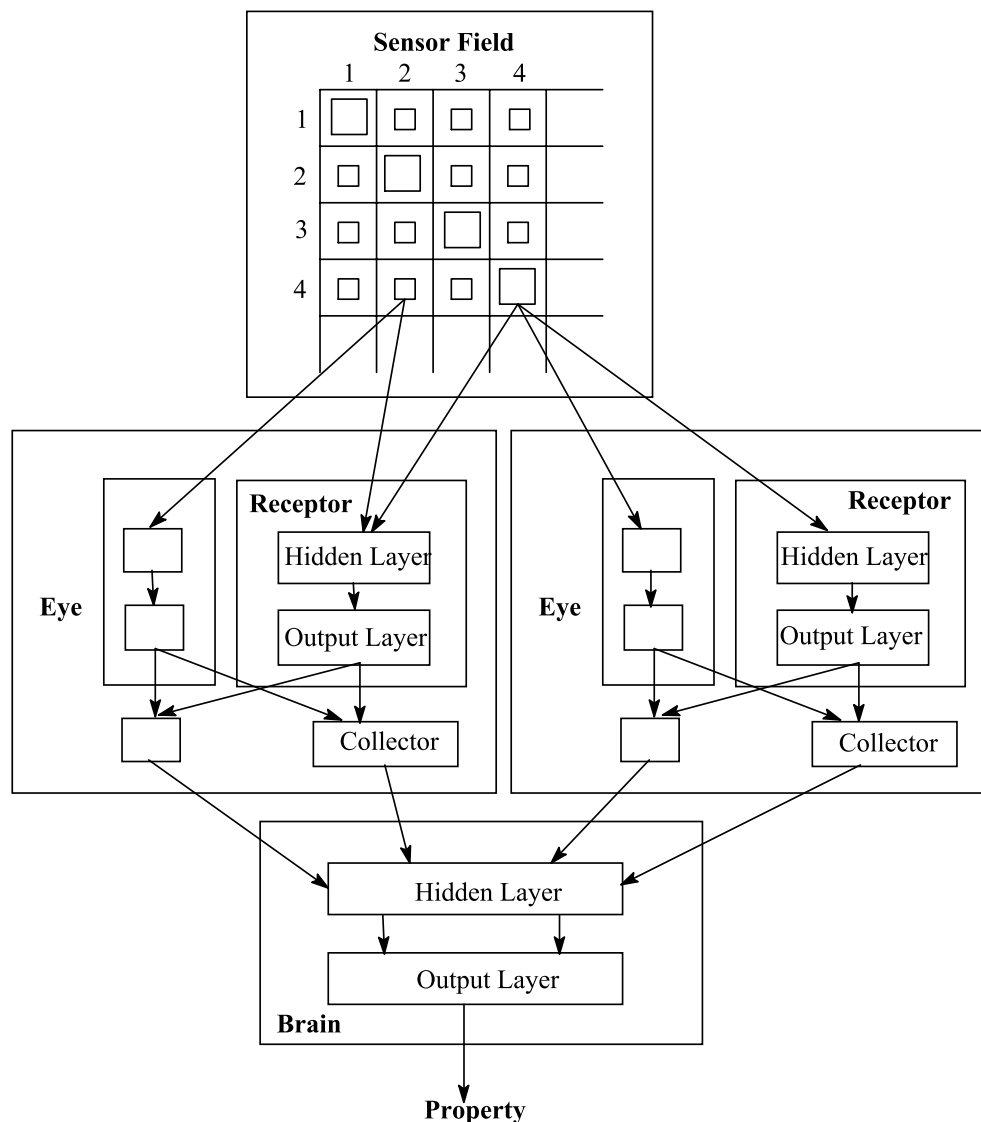
938 The Baskin–Palyulin–Zefirov (BPZ) neural device (Fig. 6)  
939 is a computational implementation of a biological vision  
940 system and contains a sensor field, a set of eyes, and  
941 a brain [7]. A molecule submitted for evaluation to the  
942 BPZ neural device is represented as a molecular matrix  
943 superimposed over the sensor field. The sensor field  
944 receives the network input as a matrix representation of a  
945 molecule, and then sends this information to a set of eyes.  
946 The structural information is process in the eyes by several multi-

947 layer feedforward neural networks, and the output signal  
948 is sent to the brain. The signals received from the eyes are  
949 processed in the brain by an MLF ANN and the output  
950 represents the computed property for the molecule sent as  
951 input to the sensor field. A set of rules is used to translate  
952 a molecule into the structure of the sensor field and of the  
953 eyes.

954 A BPZ neural device with a minimal configuration has  
955 one receptor in each eye, and can be used as a template to  
956 generate a neural device for any molecule presented to the  
957 sensor field (Fig. 7). In the minimal configuration, eye 1  
958 receives signals from individual atoms, whereas eye 2  
959 receives from the sensor field signals corresponding to pairs  
960 of bonded atoms. The information from the sensor neuron  
961 1 goes to neurons 3 and 4 representing the hidden  
962 layer of the receptor R1 from Eye 1. The signal goes then  
963 to the output neuron 7 and then to the collector C1 that  
964 sends the output to the brain. A similar information flow is  
965 similar in Eye 2, with the only difference that the input  
966 signal represents information regarding bonds between atoms.  
967 Neurons 11 and 12 form the hidden layer from the brain,  
968 whereas neuron 13 is the output neuron that offers the  
969 computed molecular property.

### 970 ChemNet

971 ChemNet is an MLF neural network that translates  
972 a molecular structure into the network topology to com-  
973 pute an atomic property [69]. Each molecule is repre-  
974 sented by its labeled hydrogen-depleted molecular graph.  
975 For each atom  $i$  from the molecular graph ChemNet has  
976 two corresponding neurons with the same label  $i$ , namely  
977 one in the input layer and the second one in the hidden  
978 layer. The output layer has only one neuron, represent-  
979 ing the atom from the molecular graph whose property  
980 is computed with ChemNet. The connections between the

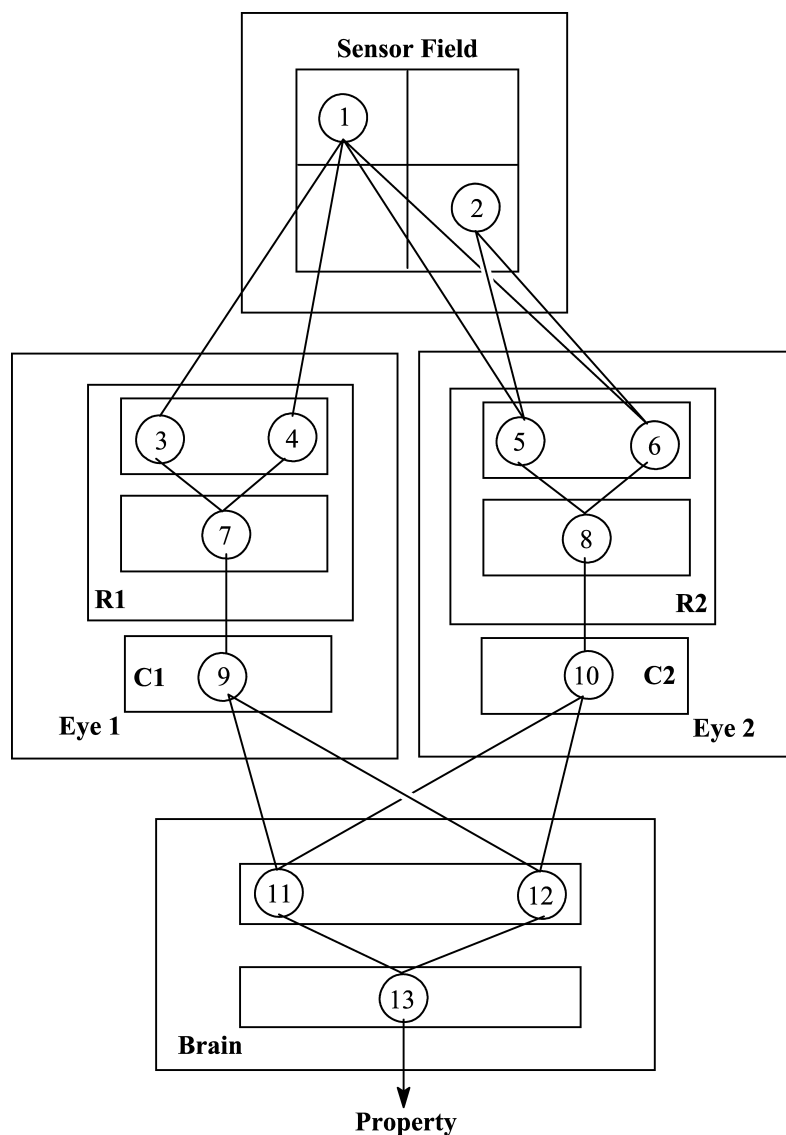


Drug Design with Artificial Neural Networks, Figure 6  
The structure of the Baskin-Palyulin-Zefirov neural device

981 input and hidden layers correspond to the bonding rela-  
982 tionships between pairs of atoms, i. e. two pairs of atoms  
983 separated by the same number of bonds have identical  
984 connection weights. The ChemNet structure is demon-  
985 strated for 2-methylbutane (Fig. 9a). The distance matrix  
986 for the molecular graph of 2-methylbutane is:

$$987 \quad \mathbf{D} = \begin{pmatrix} 0 & 1 & 2 & 3 & 2 \\ 1 & 0 & 1 & 2 & 1 \\ 2 & 1 & 0 & 1 & 2 \\ 3 & 2 & 1 & 0 & 3 \\ 2 & 1 & 2 & 3 & 0 \end{pmatrix}$$

988 Each neuron from the input and hidden layers of  
989 ChemNet corresponds to the atom with the same label  
990 from the molecular graph of 2-methylbutane (Fig. 9).  
991 Input values represent the number of hydrogen atoms  
992 attached to each atom in the molecular graph of 2-methylbu-  
993 tane. All pairs of atoms that are separated by the same  
994 number of bonds are characterized by input-hidden con-  
995 nections with identical weights. The distance matrix de-  
996 termines the connections that have the same weight. All  
997 ChemNet connections corresponding to pairs of atoms  
998 separated by one bond have the same weight (Fig. 9a). The  
999 connections between atoms separated by two bonds are

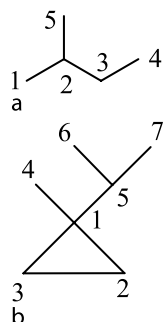


Drug Design with Artificial Neural Networks, Figure 7  
A minimal configuration of the Baskin-Palyulin-Zefirov neural device

1000 shown in Fig. 9b, whereas the connections between atoms  
 1001 separated by three bonds are shown in Fig. 9c. All connec-  
 1002 tions from the bias neuron to the 5 hidden neurons have  
 1003 the same weight (Fig. 9d). The ChemNet structure from  
 1004 Fig. 9 computes a property for atom 1. The connections  
 1005 between the hidden layer and the output neuron corre-  
 1006 spond to the bonding relationships between atom 1 and  
 1007 all other atoms in the molecule, namely atoms situated at  
 1008 distance 1 (Fig. 9a), distance 2 (Fig. 9b), and distance 3  
 1009 (Fig. 9c).

#### MolNet

1010 MolNet is a graph machine that maps the distance matrix  
 1011 in the ANN structure and computes a molecular property  
 1012 using atomic descriptors as input data [47,48,50,51]. The  
 1013 number of neurons in the input and hidden layers is equal  
 1014 to the number of atoms from the molecular graph, and  
 1015 each atom in a molecule has a corresponding neuron in  
 1016 the input and hidden layers. The output layer has only one  
 1017 neuron that provides the computed value for the investi-  
 1018 gated molecular property. The bonding pattern between  
 1019 two atoms is defined by the ordered sequence of atom  
 1020 types and bond types situated on the shortest path between  
 1021

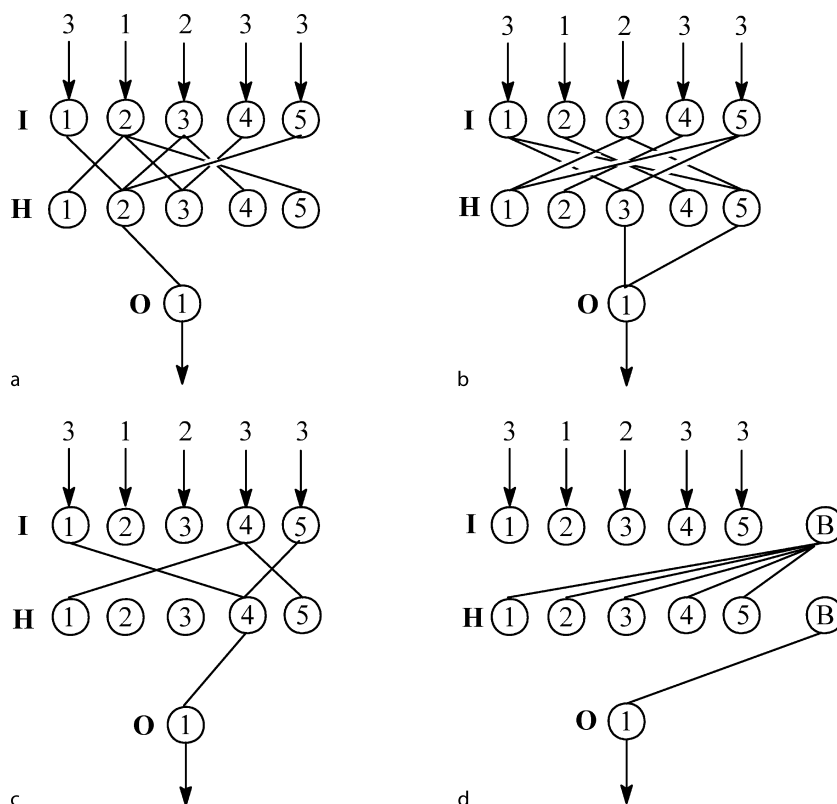


Drug Design with Artificial Neural Networks, Figure 8

Molecular graphs used to generate ChemNet and MolNet neural networks: a 2-methylbutane; b 1-methyl-1-isopropylcyclopropane

1022 the two atoms. All identical bonding patterns correspond  
 1023 to network connections with identical weights. An input  
 1024 neuron  $i$  is connected to the hidden neuron  $i$  with a con-

1025 nection type that depends on the chemical nature of the  
 1026 corresponding atom  $i$ . All  $i - i$  connections correspond-  
 1027 ing to the same atomic species have identical weights. The  
 1028 connections from the hidden layer to the output layer (HO  
 1029 connections) are classified according to the type of atoms  
 1030 represented by the hidden neurons. The atoms are parti-  
 1031 tioned into classes according to their atomic number  $Z$ ,  
 1032 the hybridization state and the degree. All hidden neurons  
 1033 representing atoms of the same type, either in the same  
 1034 molecule or in different molecules, are connected to the  
 1035 output neuron by connections with identical weights. The  
 1036 bias neuron is connected to each hidden neuron with con-  
 1037 nections (BH connections) partitioned similarly with the  
 1038 connections between the hidden and output layers, i. e.  
 1039 according to the atom types as defined above. The bias  
 1040 neuron is also connected with the output neuron (BO con-  
 1041 nection). The MolNet structure of 1-methyl-1-isopropyl-  
 cyclopropane (Fig. 9b) is based the distance matrix com-



Drug Design with Artificial Neural Networks, Figure 9

ChemNet topology for 2-methylbutane (Fig. 8a) that computes a property of atom 1. Each neuron in the input (I) and hidden (H) layers corresponds to the atom with the same label from the molecular graph of 2-methylbutane. The connections between atoms situated at topological distances 1, 2, and 3 are presented in a, b, and c, respectively, whereas the connections from the bias neuron B are presented in d. Input values represent the number of hydrogen atoms attached to each atom in the molecular graph of 2-methylbutane

1042 puted from the molecular graph:

$$1043 \quad \mathbf{D} = \begin{pmatrix} 0 & 1 & 1 & 1 & 1 & 2 & 2 \\ 1 & 0 & 1 & 2 & 2 & 3 & 3 \\ 1 & 1 & 0 & 2 & 2 & 3 & 3 \\ 1 & 2 & 2 & 0 & 2 & 3 & 3 \\ 1 & 2 & 2 & 2 & 0 & 1 & 1 \\ 2 & 3 & 3 & 3 & 1 & 0 & 2 \\ 2 & 3 & 3 & 3 & 1 & 2 & 0 \end{pmatrix}$$

1044 The MolNet connections between the input and hidden  
1045 layers corresponding to 1-methyl-1-isopropylcyclo-  
1046 propane are shown in Fig. 10. The neural network is sep-  
1047 arated into four sections, each corresponding to a bond-  
1048 ing relationship. Because the molecule considered here has  
1049 only carbon atoms and single bonds, all connections depic-  
1050 ted in a section from Fig. 10 have identical weights. In-  
1051 put values represent vertex degrees, but any atomic index  
1052 may be used as input to the network. The network con-  
1053 sists of connections between atoms with the same label  
1054 (Fig. 10a), and between atoms situated at topological dis-  
1055 tances 1 (Fig. 10b), 2 (Fig. 10c), and 3 (Fig. 10d), respec-  
1056 tively.

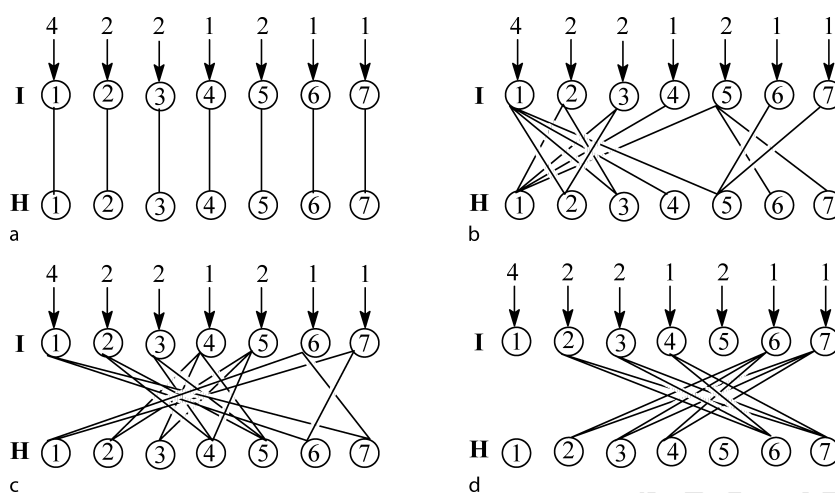
1057 The connections between the hidden and output layers  
1058 (HO connections) are determined by the structure of the  
1059 molecule presented to MolNet. HO connections in alkanes  
1060 are classified according to the degree of the carbon atoms:  
1061 hidden neurons representing atoms with identical degrees  
1062 are linked to the output neuron with connections hav-  
1063 ing identical weights. The connections between the bias

1064 neuron and the neurons in the hidden layer (BH connec-  
1065 tions) are classified according to the same rules used for  
1066 HO connections. MolNet connections between the hidden  
1067 and output layers for 1-methyl-1-isopropylcyclopropane  
1068 are presented in Fig. 11.

### 1069 Other Neural Networks

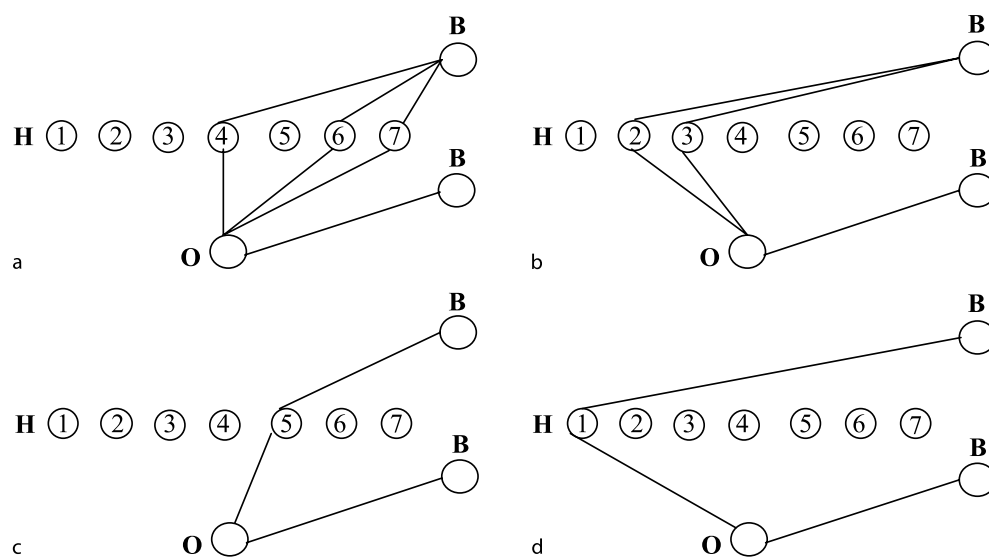
1070 In this section we present an overview of other artifi-  
1071 cial neural networks applied in structure-activity models  
1072 and in drug design. A Bayesian regularized neural net-  
1073 work (BRNN) was evaluated in QSAR for  $K_m$  values of  
1074 cytochrome P450 3A4 substrates [133]. Correlations with  
1075 electrotopological state indices give predictive and robust  
1076 models. Bruneau and McElroy applied BRNN to mod-  
1077 els for the distribution coefficient  $\log D_{7,4}$  computed for  
1078 a set of 5000 compounds [14]. The neural model obtained  
1079 is stable and can be applied for compounds in different  
1080 ionization states. The steady-state volume of distribution  
1081  $V_{ss}$  for drugs and drug-like chemicals was computed with  
1082 BRNN for a set of 199 compounds (human  $V_{ss}$ ) and a sec-  
1083 ond set of 2086 compounds (rat  $V_{ss}$ ) [31]. Both models  
1084 have good predictions statistics, and can be used to filter  
1085 chemicals in the early stages of the drug discovery pro-  
1086 cess. Caballero et al. computed a BRNN model for the in-  
1087 hibition constant of 46 inhibitors of the cysteine protease  
1088 cruzain [16]. The neural network was also used to rank the  
1089 importance of the structural descriptors.

1090 Probabilistic neural networks (PNN) and general regression  
neural network (GRNN) have similar architec-



Drug Design with Artificial Neural Networks, Figure 10

MolNet connections between the input (I) and hidden (H) layers for 1-methyl-1-isopropylcyclopropane (Fig. 8b); each neuron corresponds to the carbon atom with the same label from the molecular graph of 1-methyl-1-isopropylcyclopropane. The connections between atoms with the same label are presented in a, whereas the connections between atoms situated at topological distances 1, 2, and 3 are presented in b, c, and d, respectively. Input values represent vertex degrees



Drug Design with Artificial Neural Networks, Figure 11

MolNet connections between the hidden (H) and output (O) layers for 1-methyl-1-isopropylcyclopropane (Fig. 8b); the bias neuron is labeled with B. The bias-hidden and hidden-output connections to/from hidden neurons representing atoms with the degree 1, 2, 3, and 4 are presented in a, b, c, and d, respectively

1091 tures, with the difference that PNN perform classification  
 1092 whereas GRNN perform regression. Niwa applied PNN to  
 1093 identify the biological target from the chemical structure  
 1094 of their ligands [96]. The neural network was trained with  
 1095 a set of 799 compounds having activities against seven bi-  
 1096 ological targets. On average, 90% of the compounds were  
 1097 correctly classified. PNN classification models were de-  
 1098 veloped for the genotoxic potential of 85 quinolones and  
 1099 115 quinolines [38]. The quinolone dataset contains 23  
 1100 genotoxic and 62 nongenotoxic compounds, whereas the  
 1101 quinoline dataset contains 44 genotoxic and 71 nogeno-  
 1102 toxic chemicals. An ensemble of nine PNN models was de-  
 1103 veloped for each classification model, and the final class  
 1104 attribution (genotoxic/nongenotoxic) was decided by  
 1105 a majority vote of the trained classifiers. Simulated an-  
 1106 nealing was used to select between three and ten struc-  
 1107 tural descriptors for each PNN classifier. The ensemble  
 1108 PNN model for quinolone derivatives was able to predict  
 1109 correctly 16 of the 23 genotoxic chemicals and 60 of the  
 1110 62 nongenotoxic compounds, with an overall accuracy of  
 1111 89.4%, an overall accuracy for genotoxic class of 69.6%,  
 1112 and an overall accuracy for nongenotoxic class of 96.8%.  
 1113 Other structure-activity and drug design applications of  
 1114 PNN include the prediction of estrogen receptor ago-  
 1115 nists [78], identification of drugs that penetrate the blood-  
 1116 brain barrier [79], estimation of the genotoxicity [77], pre-  
 1117 diction of P-glycoprotein substrates [140], classification of  
 1118 chemicals that are toxic for *Tetrahymena pyriformis* [139],

and identification of factor Xa inhibitors [80]. The general  
 regression neural network was applied for the computa-  
 tion of the total clearance  $CL_{tot}$  of 503 compounds [141].  
 The  $CL_{tot}$  of a drug characterizes its bioavailability and  
 elimination, and thus may be used to determine its dose  
 and steady-state concentration. Based on the statistics ob-  
 tained for a validation dataset of 105 compounds, the best  
 predictions are obtained with the support vector regres-  
 sion followed by GRNN. The percent human intestinal  
 absorption (%HIA) of 86 drug and drug-like chemicals  
 was computed with GRNN and PNN [95]. For an exter-  
 nal prediction set, GRNN has a root mean square error  
 of 22.8%HIA and PNN has 80% rate of correct classifica-  
 tion. The models for human intestinal absorption are  
 based on topological indices, thus making the GRNN and  
 PNN models strong candidates for screening in large vir-  
 tual libraries.

### Future Directions

Artificial neural networks have a unique appeal in struc-  
 ture-activity predictions because they promise to deliver  
 superior modeling power inspired by the functions and  
 mechanisms of the human brain. Although the initial ex-  
 aggerated expectations never materialized, and artificial  
 intelligence is still a faraway dream, the drug design ap-  
 plications reviewed here provide compelling evidence for  
 the exceptional modeling abilities of artificial neural net-



works. Current applications span all major SAR and QSAR properties relevant to drug design and discovery, and new applications are reported in the literature. Future developments should consider an integrated development of optimally predictive models, in which feature selection, network topology optimization, network training, and validation form a single optimization problem. We anticipate significant improvement in the optimization algorithms used in ANN training, inspired by the remarkable results obtained with particle swarm optimization and ant colony optimization. Novel ANN algorithms and procedures should be adopted from the disciplines of computer science and machine learning. It is expected that the continuous increase in computer power will make feasible applications of ANN ensembles for datasets relevant to the pharmaceutical industry. Significant improvement in SAR and QSAR models may come from graph machine applications that incorporate structured data into the ANN topology.

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