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OmniMetrics

Part I: Applications of neural networks (Ma_NN) in Medicinometrics and pharmacometrics

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(Dedicated with profound respects to Dr. S Brahmaji Rao, former professor of chemistry, SKD university, Ananthapur, AP, during on his *sahasra chandra darsanam* (thousand lunar months of life on the lap of mother earth)

ABSTRACT

The sub goals of medicine are diagnosis of a disease, treatment with pharmaceutical preparations/ surgery/intervention and probing into adverse drug effects on treated patients. The confidence in detection of cancer and discrimination from healthy individuals, onset of diabetes, diagnosis of HIV-AIDS, coronary diseases and hypertension are improved with NNs compared to model driven approaches. The prediction of colon cancer from metal ion concentration with NNs is better than even nonlinear-regression procedures.Survival analysis and clinical information of ICU patients improved with NNs.The pharmaceutical research is an iterative cyclic activity of discovering new drug like molecules, phase I to phase III clinical trials, approval, manufacture, quality control and modifying/ looking for new moieties. Both of these disciplines are inter- /intra- disciplinary with diverse paradigms.These sciences in loose/fused hybridization with metrics (information/mathematical/ statistical/ fuzzy/nature inspired protocols/ software/hardware/ robotics/ hyphenated instruments) are state-of-art- medicinoMetrics and pharamcometrics, qualimetrics, with a single ultimate goal of Pareto optimal human health from fetes stage to dot age. Neural networks (NNs), data driven computational second generation intelligent models entered pharmaceutical research and medical diagnosis in 1990s, and are now indispensable information tools. In different phases of product development like experimental design for operating conditions of a process, calibration of two or more compounds simultaneously, prediction of the drug in vivo, in vitro and prediction of dose in control drug design systems, NNs alone or in binary/ternary hybrid mode with other methods is laudable in routine laboratory/industry. Rational drug design (RDD) is more scientific in pruning biochemical/molecular descriptors to arrive at a drug compared to blind fold approaches of synthesis-test-modify cycles. In different stages of drug development like probing into ADME(Tox), drug likeliness, drug activity, toxicity of a compound/metabolites, adverse effects of drugs, high throughput screening (HTS) and virtual libraries, the role of NNs is impressive. Selection of a compound for a drug, optimum safe limits of the dose, toxicity of a compound etc. are not only interwoven complicated procedures, but also inverse problems.It has been realized that modelling from first principles is not

viable, in spite of noteworthy progress in the mechanistic/biochemical models for many of the micro-processes. Intestinal absorption, blood brain barrier (BBB), equilibria of drugs with DNA/active site are complex, but modelling and prediction using NNs do not collapse even with less/ distorted/ redundant/ sparse/ conflicting information. Structure activity/response relationship (SXR) with NN for physico-chemical properties, biological activity, and response to skin/eye irritants pave way to predict the behavior of a compound before synthesis and to develop hierarchical models.

Keywords: Medicinometrics, Pharmacometrics, Artificial Intelligence, Neural network models, Data driven models, Medical diagnosis, Treatment, Surgery, Intensive Care Unit, Non-invasive approach, Supportive tool, Machine-expert-assistant.

I. Medical diagnosis (1-6)

1. Pulmonary & Cardiac diseases
2. Cancer
   - Breast Cancer
     - Genetic factors and family factor
     - Micro calcification
     - Mammograms
   - Ovarian cancer
   - Gastric cancer
   - Cervical cancer
   - Colorectal cancer
   - Prostate cancer
   - Neural cancer
   - Leukemia
   - Brain cancer

3. CNS & Brain
   - Parkinson's disease
   - Dyskinesia
   - Trauma (septic)
   - Alzheimer's decease
   - Brain injury
   - Psychiatry
     i. Addiction
     ii. Drug addictsion

4. Diabetes Mellitus

5. Gynecology & Obstetrics
   - HIV-AIDS

6. Miscellaneous diseases
   - Hearing impairment (Auditory system)
   - Ophthalmology
   - Gastro intestinal diseases
   - Liver Diseases
   - Arthritis
   - Dermatology

Medical Treatment (7-12)
7. Prescribed pharmaceutical preparations
8. Surgery
9. Transplantation
10. Intensive Care Unit (ICU)
11. Hospice and palliative care
12. Recent research outcome for medical treatment (MedTreat) paradigm

III. Pharma industry (13-18)
13. Pharmaceutical product development & quality control
14. Experimental design and RSM
15. Controlled drug release design
16. Calibration of drugs
17. Pharmaco kinetics (PK) and Pharmocodynamics (PD)
18. Performance

IV. Drug Discovery and Design (19-24)
19. Drug likeliness
20. Virtual libraries and virtual screening
21. Biochemistry and metabolism
ॐ Passage of drugs/molecules in the human body
ॐ Intestinal absorption
ॐ Blood brain barrier (BBB)
ॐ Drug-protein-interactions
ॐ Binding of drugs with small molecules/active site/DNA
ॐ Gene expression
ॐ Pre-clinical and clinical trials in drug approval
ॐ Knowledge extraction
22. Structure X Relationships (SXR)
ॐ Multi-dimensional (m-D) SXR
ॐ Data driven models
ॐ Structure activity Realationships (SActivityR)
ॐ Structure Biodegradability Relationship (SBiodegradR)
ॐ Structure Toxicity relationships (SToxR)
ॐ Structure Property Relationships (SPropR)
ॐ Structure response relationships (SRespR)
ॐ Structure parameter relationships (SParR)
23. State-of-knowledge-of-medicinometrics and pharmacometrics Auditory problems
24. Future prospects

INTRODUCTION

According to Bruce Alberts, president of National Academy of Sciences, a biological cell is a huge chemical factory with lot many complicated network of interlocking assembly lines of protein machines.

But, even now, it is analysed as a series of modules and this is the reason for gulf of difference between scientific perceptive and nature's play. Interactomics is an interface of bioinformatics and biology. The focus of this interdisciplinary study is around interactions among proteins, molecules within a cell and their consequences. These results of system biology are of immense utility when perceived with an informed mind [1-395]. We introduced the term omnimetrics [393] in the context of ARTMAP_NNs' (subset of mathematical neural networks) applications in diverse disciplines of science, engineering, commerce etc. Omni_metrics engulfs experimental and computational protocols of local as well as global agencies breaks new ground for next generation of scientists, technologists, those involved in the life cycle of raw materials to finished products, their disposal, waste recycling management, policy makers and governance.

Health versus disease

Life span: Life span on our planet earth is species dependent. Long and short are just relative. Compared to 10^{-43}sec, any process is longer. The age of universe is 13.7 billion years and any time interval is shorter or negligible if compared. The life span of humans is not in the realm of medicine, but dependent up on genomics, environment and life style. It gradually increased and today's prediction is 76 years for female and 81 years for a male born in USA now. Further, perfect health throughout the life span of any living creature is an utopian goal. Birth defects, contagious diseases, epidemic incidents and accidents are random, but ageing and occupational hazards are common in the life cycle (chart 1). Recently, environment, food, consumption of stored energy and mental health has also been considered as vital factors. The incidents pertaining to specific toxic effects due to irritation and allergic reaction of chemicals and chronic exposure to hazardous/toxic compounds increased at a rapid rate in the last three decades [297]. Any perceivable perturbation in the normal functioning of the body, mind and/or memory is an indication of a disease. In earlier centuries there prevailed a belief that disease is due to bad elements/ past deeds and possession of precious materials/ rare herbs keep the person healthy. The curing of the disease was through adoration and prayers. But, modern medicine is now on firm time tested scientific inter- and intra-disciplinary foundation.

Chart 1: Health perturbations and diagnosis in humans

Organ : [**Organ_normal** [Function Components Physiology]
Perturbation;
Organ_disease [Function Components Physiology]
Medical treatment,
Organ_post treatment [Function Components Physiology]
Organ_failure [Function Components Physiology]]

Multiple_organ : [coordination, consequent impairment, failure [one, many]]

[ill]	:	[Unwell; chronically ill, seriously ill; terminally ill]
	:	
[Care]	:	[Out-patient; in-patient; ICU; Hospice; Palliative]
[Medical diagnosis]	:	[Diagnosis; prognosis]
Treatment	:	[Pharmaceuticals; surgery; intervention; counciling]

Smart diagnosis protocols	
	Physical examination
Phase I	Clinical Instrumental ▪ EEG ▪ ECG ▪ ….
Phase II	Specific clinical parameters Sonography MRI Counseling ….
Phase III	Aspirations Biopsies Gold standard tests Biomarkers ….
Prognosis	
Idiopathy	

I. Medical diagnosis (MedDiag)

1. Pulmonary (p$\bar{oo}$l'mə-nĕr'ē, pŭl'-) & Cardiac diseases

Employees indulged for long years of service in hard metal and soft powder manufacturing plants are susceptible to pneumoconiosis and fibratic changes in the lung. If these patients also suffer from IIM (idiopathic inflammatory myopathy) [192], they tend to be in high risk group vulnerable to cancer and a few typical causative factors are in table 1. The predictive NN model with 8 input variables out of 34 resulted in global predictive value of 92.58%. The sensitivity and specificity were 98.4% and 91.0%. The increased risk of lung and stomach cancer and silicosis in these workers was studied with NNs [381] using factors related to profession/occupation [chart 2].

Table 1: Input to NN – prediction of malignancy in IIM patients [192]

Risk factors		Cancer	Healthy
Males		33	67
Female		16	84
Intestinal lung disease	%	8.3	28.9
Age, mean	SD	55.3+19.8	45.9 + 16.94
Duration of IIM mean years	SD	7.3+ 9.56	8.3 + 6.53
Fever	%	22.2	20.2
Dysphagia	%	33.3	14.6
Anti-synthetase or anti-PM – Scipositive	%	0	31.7
Anti-Ro positive	%	7.1	22.0

Chart 2: Factors influencing pneumoconiosis based on logistic regression [381]

- Job title
- Administration
- Furnace
- Molding
- Post-treat Smoking_(pack-year)
- Length of exposure
- Lung disorders
  - Before age 16
  - Family history

Pneumonia: Heckerling et al [72] proposed NNs in prediction of pneumonia from radiographic images. The training set comprises of socio-demographic information, co-morbidity and radiographic data of 1044 patients from the University of Illinois. The system was tested on 116 testing consorts from university of Nebraska. The optimum training parameters as well as hidden layer architectures were arrived from GA. The network parameters viz. number of hidden neurons, learning rate, momentum, presence/absence of layer connectivity are represented by binary chromosomes. In addition to cross over and mutation operators, probabilistic selection using mean square error and average cross entropy were used in optimization. The optimum NN architecture is that obtained after 50 generations of GA is SLP with 9 hidden neurons. The optimum value of both learning rate and momentum is 0.5. It is established that there is no within layer competition connectivity. Elite selection with in generations and inversions of genetic material during combination evolved in less accurate NNs. Simple GA and Grey coding of genes prior to mutation and cross over at different genetic levels resulted with identical NNs.

The discrimination of tracheal-bronchial breath sounds is difficult [68]. The constructive probabilistic NN is better than MLP_NN or RBF_NN in the classification accuracy. SOM is used to find the patterns in sleep related breathing disorders. The rules are generated from the results of NNs by applying machine learning algorithms [94].

Lung nodules: Tan et al. [10] introduced evolving NN with GA as a smart classifier applied for lung nodules in 360 computer tomography image scans from public Lung Image Database Consortium data.

Here feature selection is combined with evolution of topology of NN and optimization of weights. Three to four false positives are observed per scan. The detection sensitivity is 83.0 ± 9.7% for nodules with a diameter greater than or equal to 3 mm.

Mycobacterium tuberculosis: Mycobacterium tuberculosis reappeared in a rampant way [224] due to multi-drug resistant strains and impaired immune system (HIV/AIDS) patients. WHO reported that every year, nearly 460 thousand people are infected with Mycobacterium tuberculosis and 2 million die of it [217]. The data showed that 740 thousand patients suffer with both *TB* and AIDS.

Cardiology

Electrocardiograms (12-lead ECGs) contain information of electrical activity of the heart. The simple pattern recognition by a doctor is used to arrive at preliminary diagnosis of a number of mutually exclusive heart diseases and disorders [80] (table 2). The detection of ischemia from classification of ST-segment and T-wave of cardiac beat [86], heart rate variability dynamics [109], classification of ECGs [108], detection [65]/exclusion [45] of acute MCI discrimination of heart murmurs [64], detection of infarction ischemia [71], prediction of PAF [40] /acute coronary syndrome [110], diagnosis of atheroselerosis [49] /stenosis [102], monitoring the health of heart of adults/ fetus from electro myogram [67], visualization of MCI [45] etc. have been improved with machine learning paradigm particularly NNs. In addition to SLP and RBF, ensembles of NNs, complex valued/ γ-NNs with evidence reasoning mean field minimization, Bayesian regularization in training entered medical diagnostic tools for the analysis of images/digital data in cardiology. The trend is towards acquiring more data from non-invasive procedures to exclude/minimize disease space and at the same to increase the confidence levels of diagnosis with minimum false positives and false negatives. The other dimension is to minimize invasive approaches like catheterization, biopsy etc. Bagged NN ensemble-ADAB-boost-R2 is applied to cardiac risk [90].

Table 2: Classification of ischemia	Classification Accuracy %
Bi-group classification NN+ evidential reasoning	80
NN	68.0
Rule based method	66.7

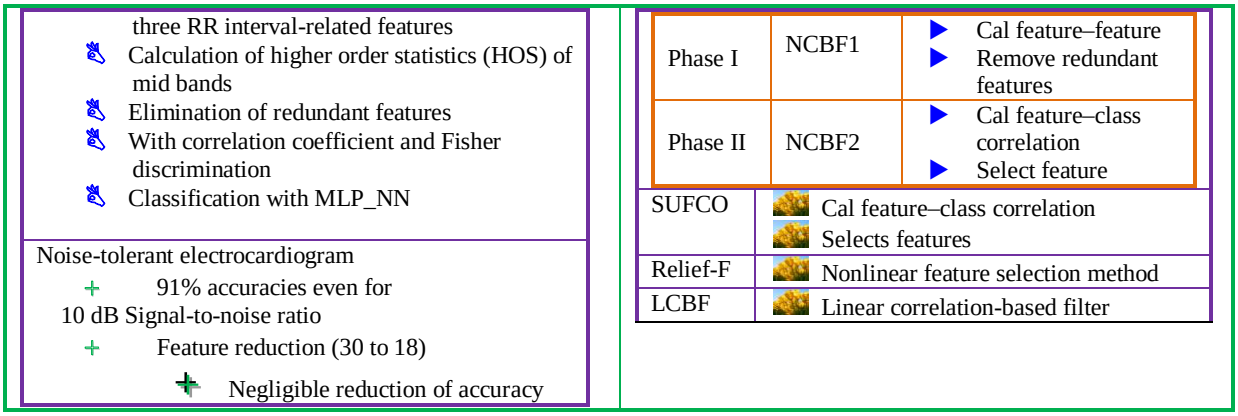
Robust ECG beat classification: A robust ECG beat classification with MLP_NN after feature reduction and elimination of redundant variables using higher order statistics (Alg. 1) of sub-bands was proposed. Discrete wavelet transform was applied to decompose the signals into six sub-bands. The method is robust to (10dB) noise for signal to noise ratios of different kinds while a high accuracy of 91% is retained. MIT-BIH Arrhythmia database and noise stress test database are used. The disturbance is due to white Gaussian noise, baseline wander, power line interference and muscle artifacts.

Heart rate variability (HRV): Heart rate regularization is a dynamic system operating in chaotic regimes. Heart rate variability (HRV) patterns with time and respiratory sinus arrhythimia are indicators of risk for coronary heart disease in asymptotic subjects [110]. RBF-NN successfully predicted HRV dynamics [109] of not only healthy individuals but also diabetic patients. But, dynamics in patients suffering from pharmacological autonomic nervous system blockade could not be reproduced. Bhatikar et al. discriminated [64] the innocent and pathological heart murmurs and ventricular septal defect in pediatric patients with a high success rate. The treatment with hydroxyurea therapy increases the proportion of fetal hemoglobin and average corpuscular volume of red blood cells. MLP_NN explained HRV from 83 patients' records to a maximum of 86.6% accuracy, while the linear model even with 23 variables was inadequate.

Alg. 1: ECG beat classification resistant to 10 dB SNR

- Decomposition of Signal with Five levels of discrete wavelet transform (Disc.Wavel.Trans) → three midband and

Chart 3: Feature extraction procedures



Chen and Yu [18] reported that the combination of NCBF1 (feature–feature) and NCBF2 (feature–class) correlation variable selection procedures excelled (chart 3) other popular SUFCO, Relief-F and LCBF methods in heart beat recognition. It is modeled with higher order statistics of sub band components based MLP_NN_BP.

Arrhythmia: Although the chronicles are related to cardiac arrhythmias, it is a difficult process. The role of automatic systems starts at this juncture. MITBIH database of ECGs is used with inductive logic programming employing first order relational learning. The confirmation, of course, is by an expert cardiologist. Jovic and Bogunovic [24] reported that random forest model is better than SVM and NNs in two- and four-category classification of ECG data (chart 4) to distinguish Arrhythmia from normal heart beat. C4.5 outputted interpretable and useful rules.

PAF: PAF is a serious arrhythmia leading to high death rate and severe morbidity. The heart rate variability (HRV) dynamics of now–PAF rhythms immediately before PAF event was used [40]. The data consisting of 30-min non-PAF HRV, 45 minute min (distance) from any PAF event and immediately before PAF onset from 51 subjects is analysed with NNs and SVM to classify the patients. NN learned the changes in HRV dynamics immediately before PAF and enabling to detect distinct PAF prognosis. It is sensitive, specific and exhibits positive predictivity compared to SVM which is biased towards the positive cases. Ohlsson [71] reported a software system employing NNs and image processing technique to detect infraction, ischemia from 1320 myocardial perfusion images. The range of ROC is 0.83 to 0.96. due to the lack of harmony between TF in the hidden layer and type of input signal.

A coronary calcium scan with electron beam computed tomography (EBCT) or multidetector computed tomography (MDCT) detects calcium in the coronary arteries and is useful to predict signs of coronary heart disease using National Cholesterol Education Program risk assessment tool kit.

Stenosis: Mobley [63] opines that a significant reduction in unnecessary cardiac catheterization by analyzing the clinical data of patients with chest pain by NN. It can be a supporting tool which can be validated by expert cardiologist. Eleven clinical parameters of 902 patient records with chest pain from national cardiac catheterization data base (year 2004) was trained with NNs. Other 902 data vectors were used for CV and 100 for a test file. The patients with significant coronary stenosis have output > 0.25. NNs successfully discriminated patients with and without significance stenosis. Coronary stenosis often leads to coronary intervention. It is a precautionary measure alarming attention, if an AI system predicts the occurrence of significant (>50%) coronary stenosis from angiography data.

Acute coronary syndrome (ACS): This is a difficult condition for diagnosis. The follow up is needed for a few, while others with minor disorder can be sent home. Green [59] proposed NN ensembles to predict the suspicion of ACS using ECG data of 634 patients in emergency department. PCA was used for preprocessing. Clinical data inclusion in the

ROC	Sensitivity
80%	95%

model did not improve the prediction, but NN ensemble was superior to logistic regression. The current models along with the opinion of emergency personnel ensure the reduction of false negatives.

2. Cancer

Carcinoma (kär s-n m): Cancer and HIV are dreaded diseases that impair normal health and lead to high mortality rate in developing as well as developed nations. Their complete eradication in the world is still incredible challenge and thus remains to be current focus of intra- and inter- disciplinary research. Colon and breast cancer are the most prevalent with high mortality rate even in advanced countries [331]. In mathematical parlance, Sieving cancer into different categories is a multi-valued classification problem, while identifying breast cancer from benign tumors is a discrimination task.

A precise confirmation/ detection/ prediction of tumors is a prerequisite in the treatment of cancer. The volume of the tumor has been found to be a critical parameter in elucidating prognostic information. Histopathological parameters like cell types and differentiation score have both short- and long-term information. Biopsy is a confirmative diagnostic tool. The recent advances in identifying a single molecule with florescence spectrum paved way to probe into the onset of cancer. But, it is not yet in routine practice. Now, gene expression data gained momentum in diagnosis and treatment of cancer.

Neural networks have been proven to yield scrupulous rates of success in all phases of cancer diagnosis and treatment. The established practices in medical diagnosis, prognosis and therapy with proven pharmaceutical preparations are in vogue for lung, colon, breast, ovary, liver and brain cancers [table 3] with NNs. The data on small round blue-cell tumor showed NN identifies high quality cancer clusters compared to k-means and HCA.

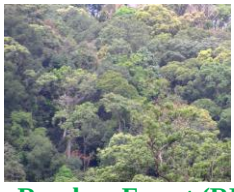
Table 3: NN applications in typical cancer diagnosis

Lung	True nodule Rib-crossing Rib-vessel crossing End vessel Vessel cluster Bone Rib edge Vessel	Accuracy upto 93% False detection < to 7	128
Prostate	Trans rectal / ultrasound T-PSA %F-PSA Age Digital rectal examination Prostrate volume PSA density	NN	117

Chart 4: Discriminating Arrhythmia from normal hear beat

Features from ECG

- S
- DNN
- R
- MSSD
- p
- NN20
- E
- ntropy features
- ApEn1
- A
- pEn2
- **A**
- **pEn3**
- **A**
- **pEn4**
- Correlation dimension central tendency measure (CTM)
- HRV triangular index (HTI)
- spatial filling index (SFI)



Random Forest (RF)

Bold : relevant factors

Liver	MRI Ultrasonography Tomography	Classes hepatic masses Metastatic carcinoma Hepatoma Cavernous hemangioa Abscess Cirrhosis	135

		% accuracy
NN	---	71
Radiologist	Resident	50
Radiologist	Expert	90

Methods	Diagnosis
k-means expectation maximization (EM) C4.5 decision tree Bayesian_NN SVM Random forest	Normal heart rhythm Arrhythmia (any) Supraventricular arrhythmia Congestive heart failure

Model	Performance	
	Two-class	4-class
RF	99.7	99.6
Bayesian_NN	99.1	99.4
SVM	98.9	98.4

The prediction of cancer in IIM patients [192], classification of colon cancerous cells from normal based on gene expression profiles [331], cancerous patients from healthy individuals by nucleoside levels in urine [184], discrimination of malignancy from benign [213] and prostate cancerous patients form healthy individuals by measuring concentration of prostate specific antigen (PSA) [380] are successful with NNs. These models are successful data driven high efficient non-linear models in detection of ovary [43] cervical [39, 44], colon [77], brain [44], lung [87], prostate [122], neural [119] and urinary bladder [122] cancer.

Clinical diagnosis: The presence of chemical and biological markers in blood plasma and lipids is a preliminary diagnostic tool to detect cancer. The clinical methods include monitoring nucleosides [table 4], metal ions (table 5) and PSA [380] in urine and blood plasma (table 6, chart 5).

Nucleoside level in urine: The hybrid inference approach using the concept of voting in the results of LDA and NNs (LVQ_NN, Prob_NN) in discriminating cancerous patients from healthy individuals reaches 100% consistently (table 4) by monitoring nucleoside level in urine [184].

Metal ions in blood serum: Hernandez-Caraballo et al. [179] reported that Prob_NN and logistic regression excelled PCA in sensitivity and specificity in screening cancer based on amount of Zn/Cu/Fe/Se in blood serum (table 5). A word of caution, however, is to employ clinical tests in addition to NN prediction for confirmatory diagnosis.

Histological data: Forgel used evolutionary program (EP) to train NN in detection of breast cancer with histological data and the resultant parsimonious model is statistically significant and outperforms other methods for the same data [126]. EP, a stochastic optimization method has less chance of getting trapped in local optima in weight space compared with popular BP.

Chart 5: Preliminary clinical tests for cancer detection

Total PSA	IMMULITE PSA assays	DPC, Los Angeles, CA
Serum MIF	Enzyme linked immunosorbent assay	DuoSet, Cat no. DY289, R&D Systems, Minneapolis, MN

⇵ MIC-1 serum
⇵ hK11

Table 5: Prediction of cancer from metal ion concentrations in blood serum

Method	Architecture	Sensitivity		Specificity	
		Tr	Te	Tr	Te
NN-BP	4-4-1	94.7	100	100	90
NN-Prob	**4-42-1**	**100**	**100**	**100**	**100**
LR	…..	84.2	87.5	91.3	90

Table 4 : Prediction of cancer with PNN using nucleoside data

Model	Tr	Pred
PNN	100	85
QDA	86.7	85
LV1	86.7	85
LDA	80	80

Table 6: Healthy vs cancerous discrimination

Subjects	Clinical measurements	Model
H:32 C:27	Zn,Cu, Fe, Se in blood serum	MLP (BP) Pr NN
Healthy : 25 (M:12 F:13); Cancer : 25 (M:16 F:9)		Prob NN Spread: 0.3

Tr		Te	
H	C	H	C
10	10	4	8

Gene expression data analysis: The ensembles of classifiers for detection of cancer from gene expression data were proposed. This approach was found superior to a single best classifier in the ensemble as well as classical ensemble construction method ignoring the complexity of the data set. The current ensemble of classifiers selects substituent of features of low complexity. Xu et al. [30] applied feature selection methods followed by Fuzzy_ART to arrive at clusters (Alg. 2) in the small round blue-cell tumor samples using gene expression data. The curse of dimensionality is a stumble block in the analysis of gene expression data with traditional data mining techniques because of high dimensional (genes) variables for relatively a very small number of samples.

Micro array technique: Micro array technique is used to probe into the regulation of activity of the cells in the tumor in different stages [331].

Imaging techniques: The possibilistic neuro-fuzzy-c-means algorithm based NN is used [105] for diagnosis of cancer from images and the results are compared with fuzzy c-means NN.

Prognosis: The precise prediction of cell type, volume and stage of the tumor are the standard indices in the prognosis [212] of the disease.

Breast Cancer

The number of breast cancer cases reported annually is on exponential scale and the rate is threatening. The detection of breast cancer is from clinical/histological data, mammograms and biopsy. Early detection (table 7) has higher chances of successful treatment reducing the suffering and prolonging the life span. Recent improvements in the mass boundary of the tumor masses improved the accuracy in confirmation.

Table 7a: Typical reports on diagnosis of breast cancer with NNs

Tests	NN_model	Ref
Micro calcification clusters Mammography	NN SVM	[62]
Laboratory tests Albumin Cholesterol HDL-cholesterol Triglyceride Apolipoproteins A1 and b Nmr linewidth (the fossel index) Tumor marker C A 15-3 C A 125 Age of patient	59 Benign 45 Cancer MLP_NN I#:6 Sensitivity 55.6 Selectivity 72.9 Tumor marker alone CA 15-3 Sensitivity 61.3 Selectivity 64.4	[130]

Alg. 2: Cluster generation from gene expression data

Input : Gene expression levels

- Statistical analysis → subset of genes
- Eigen functions of Markov matrices as a system of coordinates on the original data set
- Diffusion maps → geometric descriptions of data
- Unsupervised clustering analysis
- Fuzzy ART → clusters of cancer samples

Table 7b: NNs in diagnosis of breast cancer

RBF MLP LDA	SVM LS Min distance	130 Digitized mammogram Malignant vs benign	Non-lin SVM 83.9	[53]
SLP_NN		Digitized mammogram Malignant vs benign	Correct classification Tr 100 Te 94	[44]
SLP_NN EP training		111 Malignant 105 Benign 12 Features radiography	Parsimonious model	[116]
NN		14 Parameters Time intensity profile	NN > radiologist	[122]
RBF MLP SVM	LDA K-means	Boundary	NN is best	[51]

Table 7c: Diagnosis of breast cancer [184]

#Patients	Clinical parameter	Model

Table 8: Mammographic features as input for NN to predict malignancy

H : 14; C : 18	14 Nucleosides level in urine Dhu, Pseu, M1I, m1G	LVQ smoothing par : 1.52 to 6.09 Trn: H 10, C 10; Test: H 4, C 8 100% recognition rate
18 : Cancer 14 : Benign		PCA LVQ LDA stepwise discriminant
25 :Cancer 25 Cancer	12 Nucleosides	

Breast cancer Biopsy proven: #		Factors Relevant Redundant Unimportant Irrelevant Most important
Malignant: 63 Benign: 49		
Mass ○ Size ○ Margin ▪ Well circumscribed ▪ Microlobulated ▪ Obscured ▪ Indistinct ▪ Speculated		No mass
Asymmetric density		None Asymmetry
Architectural distortion		None Distortion
Calcification	Number	None < 5 5 and < 10 > 10
	Morphology	None Not suspicious Moderately suspicious Highly suspicious
	Density	None Dense Mixed Faint
Calcification distribution		None Scattered Intermediate Clustered

The tumor markers, urinary nucleosides etc. permit exclusion of non-cancerous tumors. Mammography is the sought after radiographic detection method for breast cancer, but suffers from high false positive classification. The confirmative test-biopsy, an invasive method is not only emotionally stressful but also costly. A neural network is trained with radiographic data as explanatory variables and biopsy results are the response. The prediction of cancer in new patients from the mammographic features (table 8) using the trained NN model has a very high success rate and is a proven alternative to biopsy [213]. Breast cancer is distinguished from benign ones using 22 factors. The features are selected by GA using class separability criterion. The features studied include 5 shape factors, 3 edge-sharpness measures and 14 texture features computed from 111 regions in mammogram, of which 46 regions related to malignant tumors and 65 to benign masses. The classification is performed with LDA, SVM and strict_two_surface_proximal methods. Nonlinear versions using kernel are also studied. ROC reached 0.95 for Gaussian Kernel. NNs have been used in survival analysis of breast cancer patients [41, 60].

Genetic and family factors: Nattkemper [61] analysed dynamic contrast enhanced MRI time-course data of patients (from U.K multicenter breast screening study) with genetic risk factor for developing breast

cancer by SOM, k-means clustering, SVM and decision trees (DecisTree). SVM and DecisTree attained 74% accuracy and 0.88% for ROC curve. Ronco [113] achieved greater than 94% success to predict breast cancer from familial history, socio demographic, gynec-, obstetric-, dietary factors and age. A noteworthy hierarchical NN in the analysis of MRIs refining center and the width of the display window of image (chart 6) was proposed.

Chart 6: hierarchical NN analysis of MRIs

If	Images are similar to tr. set
Then	RBF estimates functions well
If	Test image is not in tr. set and/or Range of image is wide
Then	Bi-modal linear estimated & Only a reasonable estimate
If	Data fusion is used
Then	Accurate display parameters for trained images & Robust for images not in Tr. set

Task	Method
Feature generator for spatial statistical information of image	Wavelet histogram
Segregation of images into subclasses	Competitive NN Two pairs of RBF
Linear estimator for each subclass	Bi-model
Calculation of parameters for final displays	Data fusion process
Linear estimator for each subclass	Bi-model

Childhood profile: Peterson [84] reported prediction of small round blue cell tumors of childhood and determination of estrogen receptor status of sporadic breast cancer with MLP_NN.

Prognostic breast cancer group: Lisboa [75] put forward partial logistic NN to model low- and high-risk patients and to interpret the prognostic breast cancer group. The automatic relevance determination in NN is done within Bayesian frame. It is better than stepwise selection.

Urinary nucleosides: Dieteru [81] reported that LVQ discriminates between healthy females and those suffering from breast cancer (table 9) better than MLP-BP_NN and SVM from the levels of potential tumor markers. It is recommended to explore LVQ_NN in decision support system.

Table 9: NN for tumor markers AI/med/37

Performance	Test set
Sensitivity	58.8 to 70.6
Specificity	88.4 to 94.2

(+) Unbalanced sizes of different classes.
(+) Fast training.
(+) A few parameters for training.

Enzymatic hydrolysis: The kinetic rate of enzymatic hydrolysis of fluorescein diacetate in live peripheral blood mononuclear cells could successfully diagnose breast cancer in 37 out 40 patients. The normalized mutual information was used to measure the correlation/discrimination of Michaelis-Menton constants (kM and vmax) with breast cancer patients.

Micro calcification: Micro calcification clusters play a vital role in diagnosis of breast cancer. A multistage analysis is applied to data bases from Nijmegen and MIAS. SVM is better compared to NN [62]. The first stage of prognosis comprises of detection of clusters of micro calcification followed by the second phase wherein relevant features of the clusters are picked up. In the classification task NN, SVM and a rule based ES are employed.

Constraint satisfaction NN was used to characterize clusters of heterogeneous breast cancer patients from mammographic data. It was possible to distinguish masses from calcification and further stratification into 7 types of masses and 3 types of calcifications [73]. SOM_NN was trained with 2258 cases and another 2177 held out data were employed for model validation. The benign regions detected by BP-NN do not require biopsy, but a follow up is adequate. It is an instance where it shows that invasive biopsy can be eliminated in typical cases without any threat to the health of the patient.

Mammograms: Digitized mammograms [44] have been used in detection of micro calcification [73, 62, 85] and discrimination of cancerous tumors from benign. A hybrid intelligent system consisting of rule based module to extract the features, PCA for orthogonalising the variables (reducing inter correlation among explanatory factors) and NN for micro calcification [85]. The method was tested with mammograms from data bases of Nijmegen and mammographic image analysis society (MIAS).

The effective shape features of mass boundary in mammograms were studied by multi scale wavelet/FT and fractal dimension analyses. Multiple shape descriptors obtained are the inputs to linear/nonlinear classifiers viz. LDA, k-nearest neighbors, RBF_NN, MLP_NN and SVM [51]. The results are compared with histologically verified clinical diagnosis of each mammogram. ROC was used to present the sensitivity and specificity of the results. NN out performed over other methods.

The classification of mass abnormalities in digitized mammograms to distinguish benign from (malignant) breast cancer cases is performed with NN with an additional neuron in the hidden layer for each output class [44]. It improves memorization ability without destroying generalization. The results on a bench mark data base show the correct classification of 100% on training and 94% on test dataset. The training is performed with a hybrid algorithm consisting of minimal distance based similarity and random weights.

Discriminating malignant versus benign tumors in Breast: A comparison of RBF_NN, MLP_NN, LDA, least squares, minimum distance k-nearest neighbors and SVM methods were made use of in the classification of malignant versus benign tumors from 130 digitized mammograms. [53]. The local texture and fractal analysis are used in deciphering the texture of the masses. The issue is fuzzy and little attention was paid earlier. Fractal analysis was used to compare the information content and dimensionality of the textural features. West and west [101] applied SOM, ensembles of NNs and stacked predictors in diagnosis of breast cancer from a real world data base. The topological ordering properties of SOM are used to define ideal accuracy level similar to Bayes optimal level. These targets are then employed in model selection, determination of variable reduction parameters and assessing adequacy of clinical measurement system.

Fogel [116] et al. successfully trained 12 radiographic features from 216 mammograms and age of patient. The training dataset comprises of 11 patients with malignancy and 105 benign breast subjects. NNs of different complexities were trained with EP and the best evolved one with two hidden nodes was better than more complex architectures reported earlier endorsing the hope of acceptance of the paradigm by the physician as an add-on to the arsenal of clinical/surgical tool box. Abdol maleki et al. [122] reported NN model for detection of breast cancer from 14 parameters derived from time-intensity profile. The results are superior to these of diagnosis by expert radiologist for 120 patients, confirmed with cancer from biopsy of breast legions. NN reached 89% against a human expert radiologist identified 79%. Giger [132] used SLP with two measures of margin of masses to NN as inputs and the performance is rated as equivalent to expert radiologist with 53 breast masses. Abbass [88] used mimetic-Pareto-NN to diagnose breast cancer. It has greater generalization compared to BP-NN. Pareto differential evolution algorithm is augmented with local search to develop evolutionary NNs.

Biopsy: In spite of heuristics to differentiate malignant breast legions from benign, only 20% of masses referred for biopsy are confirmed malignant [132]. The high false positives in initial diagnosis lead to stress and unnecessary surgical biopsy.

MRS

Omlin [74] used integration of symbolic knowledge with NNs to analyze breast tissue from MRS. The database is limited and thus requires reinvestigation.

Clinical + NMR + tumor marker for discrimination of breast cancer from benign: Wilding et al. [130] proposed MLP-NN with six input (clinical and instrumental) variables. The test results have a selectivity

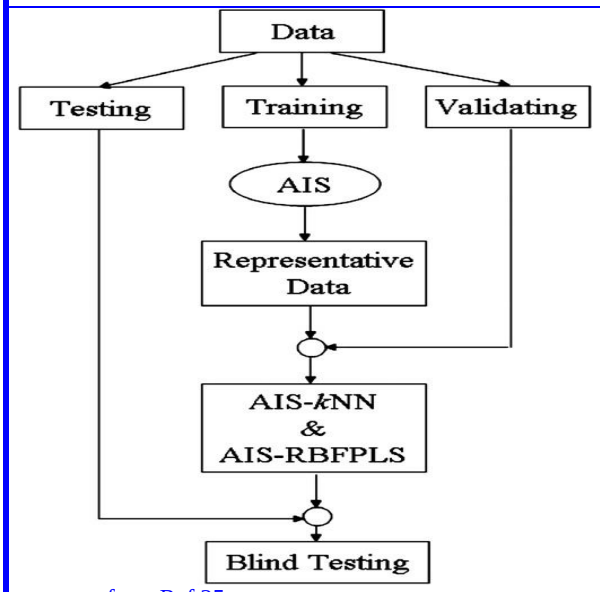
of 73% for breast cancer and 85.5% for ovarian cancer. The multifactor program combing clinical, NMR and tumor marker outcome vividly enhances the diagnosis accuracy (chart 7).

Chart 7: Discrimination of malignant and benign patients

		Sensitivity	Selectivity		
Breast cancer	I#6	55.6	72.9	Breast cancer	45 malignant 59 benign
Tumor marker CA 15-3		61.3%	64.4%	Ovarian	35 malignant 36 benign 27 controls
Ovarian cancer		80.6	85.5		
CA 125		77.8%	82.3%		

Zhao and Davis [25] employed hybrid systems (fig. 1) with RBF_NN, PLS and artificial immune system (chart 8) as components in breast cancer diagnosis. This system excelled ArtImuneSyst coupled with k_NN (table 10) orthogonal RBF and MLP_NN_BP. It exhibited lower misclassification ratio and higher diagnosis stability.

Fig. 1: Hybrid model for breast cancer diagnosis



courtesy from Ref 25

Table 10:Hybridisation of artificial immune system with NN

Dataset	Misclassification rates %	
	AIS-RBFPLS	AIS-kNN
1	3.36	9.07
2	19.18	28.36

Chart 8 : colon cancer diagnosis

# Patients		Model
Healthy : 22; Cancer : 40	Tr : 31 Te: 31	SVM SLP : 30-10-2 KNN

Ovarian cancer

Detection of ovarian cancer in the early stage reduces the high death rate. The current methods although serve the purpose, they are not devoid of limitations. Conventional blood test is neither sensitive nor specific. DNA-micro array and proteomics data are high dimensional and thus analysis is difficult. Tan [43] put forward the confluence of CLFNN–DNA–micro analysis, CLFNN-blood test and CLFNN-proteomic test. It improves the accuracy of diagnosis with higher consistency. It can be a good tool in the arsenal of diagnostic expert and may occupy a niche in clinical expert systems.

Gastric cancer

Droste [125] predicted lymph node metastasis in patients with SLP for data of national cancer center, Tokyo. The sensitivity and selectivity of SLP exceed multi-dimensional scaling (MDS) and logistic regression.

Colon cancer

Futschik [77] proposed evolving fuzzy neural networks to discriminate the cancerous (colon and leukemia) tissues from normal. The rules point to genes responsible for carcinoma. Machine learning studies of cancer improve the existing clinical tests and pave way to new test patterns and treatment procedures. The response of micro array techniques is the gateway of expression of thousands of genes simultaneously.

Gene expression profiles: The gene expression profiles [331] (Chart 9) distinguish colon (epithelial) cancerous cells from normal using evolutionary SLP_NN (30-10-2). The architecture evolves into an unconventional layered structure and some of the hidden neurons are only intermediate and are not connected to output layer. In addition to it, they result in interconnection of hidden neurons, of course, in one direction and direct connection of input and output layers partially. The size of W matrix or total number of connections is 203. The NN experiment was repeated ten times and the accuracy is 94% surpassing MLP_NN, SA_SOM_NN, SEM_(RBF_NN) and k-NN (with 81%). The results (table 11) show two samples are wrongly classified.

Chart 9: 30 Genes selected by information gain [331]

- Human monocyte-derived neutrophil-activating protein (MONAP) mRNA, complete cds
- Complement factor D precursor (Homo sapiens)
- Human desmin gene, complete cds 17 Hsapiens mRNA for p cadherin
- Myosin heavy chain, nonmuscle (Gallus gallus) 18 GTP-binding nuclear Protein ran (Homo sapiens)
- Human cysteine-rich protein (CRP) gene, exons 5 and6
- Prohibitin (Homo sapiens)
- Collagen alpha 2(XI) chain (Homo sapiens)
- Hypothetical protein in trpe 3_region (Spirochaeta aurantia)
- Human gene for heterogeneous nuclear ribonucleoprotein (hnRNP) core protein A1
- 40S Ribosomal protein S6 (Nicotiana tabacum)
- 03001 Transcription factor IIIA
- Small nuclear ribonucleoprotein associated proteins B andB _ (Human)
- Myosin regulatory light chain 2, smooth muscleisoform (Human) contains element TAR1 repetitive element
- Human DNA polymerase delta small subunit mRNA, complete cds
- Mitochondrial matrix protein P1 precursor (Human)
- Human GAP SH3 binding protein mRNA, complete cds
- Human aspartyl-tRNA synthetase alpha-2 subunit mRNA, complete cds
- Human (Human)
- uman cysteine-rich protein (CRP) gene, exons 5 and6

Table 11a : Prediction of colon cancer with evolutionary NNs

Normal		Cancer	
Predicted	**True**	**Predicted**	**True**
9	11	2	0
0	0	20	20
~~84.2~~	~~87.5~~	~~91.3~~	~~90~~

Cancerous	Normal
40	22

Tr	Te
31	31

4x4 SOM of rectangular topology paramters

	Initial	Final
Lr.rate	0.05	0.02
Max iterations	1000	10000
Radius	10	3

Parameters of evolutionary alg.

Population size	20
Max generations	200
Prob. Cross over	0.3
Prob. mutation	0.1
Fitness criteria	Recognition rate

- Tropomyosin, :broblast andepithelial muscle-type (Human)
- Human cysteine-rich protein (CRP) gene, exons 5 and6
- Human serine kinase mRNA, complete cds
- Human homeo box c1 protein, mRNA, complete cds
- Thioredoxin (Human)
- Macrophage migration inhibitory factor (Human)
- 100P Protein (Human)zz
- Human splicing factor SRp30c mRNA, complete cds
- Human mRNA for integrin alpha 6

Connection of hidden neurons to hidden neurons without connection to output layer

Cervical cancer

PAPNET is a cytological screening system with built in NN modeling strategy in recognizing potentially abnormal smears. The system automatically sieves conventional smears leaving the display of images of abnormal smears for rescreening by an expert/qualified/certified cytologist. The abnormalities slipped in manual screening are perceived in the AI-augmented approach. Mat-Isa et al. [39] reported an automated diagnostic system employing hierarchical hybrid MLP to predict the cervical pre-cancerous stage into three classes. The number of features used range between 10 and 20 and the size of patients is from 50 to 400. The quality of data and the rigor of the methods widely differ. The message is that NN, a data driven paradigm will be in the forefront of consultant/expert physician tools in clinic/ICU. The measures of performance and statistics reported are significantly better than many statistical techniques. There is substantial decrease of both false positives ad false negatives.

Colorectal cancer

It is one of the prevalent types of cancers with high mortality rate affecting both sexes. The prediction of anti-colorectal cancer in yester years was limited to a single cell line.

Prostate cancer

Prostate specific antigen (PSA) is a significant biomarker for detection as well as estimation of stage and prognosis of prostate cancer. Stephan et al [117] reviewed the state of art of technology. They [380] reported NN models using several markers viz. total prostate specific antigen (t-PSA),freePSA, macrophase inhibitory cytokine-1 (MIC-1), human kallikrein 11 (HK-11), cytokine macrophase migration inhibitory factor (MIF) along with age, digital rectal examination, trans rectal ultrasound (TRUS), derived prostate volume and PSA density. A study of database of 1188 patients reveal avoiding unnecessary prostate biopsies with a high acceptable accuracy of 75. Regnier-Coudert et al. [19] used NNs, Bayesian networks and linear regression for prediction of pathological stage of prostate cancer. Bayesian nets performed better than Partin tables (developed with US database) when applied to UK patient data (chart 10).

Chart 10a: Database on prostate cancer in UK

- British Association of Urological Surgeons
- 57 centers across UK
- Prostatectomy patients 1700

chart 10b : Prostate cancer

Samples	Markers	Models
371 : Serum samples	➢ Total PSA ➢ Free PSA ➢ MIC-1 ➢ Hk 11 ➢ MIF ➢ Prostate volume	🗁 NN 🗁 Logistic Regression

Neural cancer

Id proteins play a key role during development of nervous system in preventing premature differentiation and terminal cell arrest. Thus they are low or absent in post natal tissues [119]. Gold standard (ref.erence) [106] test is used to assess the discriminatory power. Pizzi [106] used fuzzy gold standard adjustment in classification of human brain neoplasms. The current preprocessing method consistently showed 10-13% improvement. A nonlinear auto associative NN was trained to model (reproduce) the observed EEG tracks. During neural tumor progression [119], Id proteins proliferate resulting in loss of differentiation and neo-angiogenesis. The hall marks of neural cancer can be understood from a deeper study of molecular networks.

Leukemia

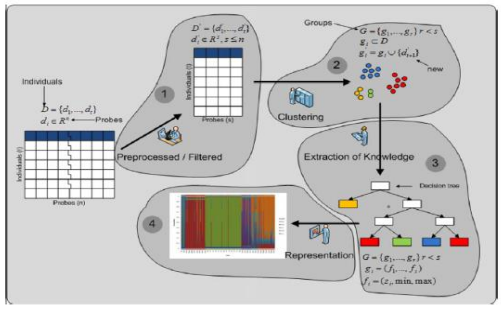
Corchado et al [33] reported mixture of experts' model to detect different forms of leukemia at various stages from the analysis of data from exon arrays. This tool consists of cooperative operation of filtering/ classification/ modeling and rule extraction algorithms (fig.2). The hypotheses of individual experts are combined to generate a system capable of extracting knowledge (CART). It leads to automatic inference of disease comprehensible to medical personnel. This software was developed and tested for patients suffering from different categories of leukemia at various levels of severity under peer supervision medical professionals of cancer institute, University of Salamanca, Spain. The computational intelligence (chart 11) was employed to identify influential prognostic factors for PVL (periventricular leukomalacia, a disorder involving softening of brain white matter) in neonates with congenital heart disease. Samanta et al. [34] arrived at potential prognostic clinical parameters (chart 12) for PVL occurrence in neonates with congenital heart disease. Here, combinations of MLP_NN, Prob_NN, GA and decision trees are used. MLP and prob-NN are used for prediction of PVL. GA picked up six to seven most influential features including systolic/diastolic blood pressures and pCO2. The interpretable rules are generated from decision tree algorithm.

Chart 11: Computational intelligence in prognostic analysis

Method	Prediction	Sensitivity	Specificity	Accuracy
MLP+GA	100	60-73	74-84	71-74
DT		80-87	74-79	79-82

DT	Sensitivity	Specificity	accuracy
Tr	60-73	74-84	71-74
Te	87-90	74-79	79-82
	PNN MLP		

Fig. 2: Classification performance
(Courtesy of ref 33)



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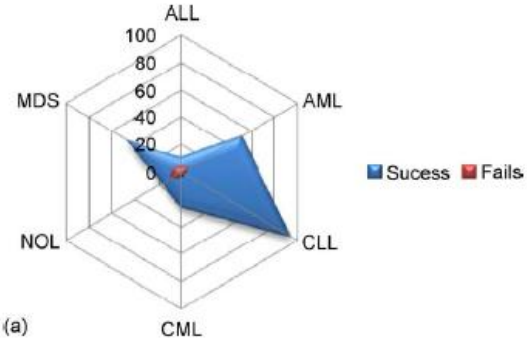


PVL prediction

Hemodynamic features → [MLP_NN prob_NN GA] → Selected Features → Decion tree → Interpretable rules

Chart 12: Performance of NN and combination of NN with DT

Prediction	[NN+GA]	[NN+GA] +DT
Sensitivity	60–73	80–87
Specificity	74–84	74–79
Accuracy	71–74	79–82
Training	100	

	Causes	Cancer in
ALL	Abnormal proliferation of Lymphocytes	Blood and bone marrow
AML	Proliferation of myeloblasts, Red blood cells or abnormal platelets	Bone marrow
CLL	Proliferation of lymphocytes in bone marrow	
CML	Proliferation of white Blood cells in bone marrow	
MDS	Bone marrow does not produce a sufficient Amount of healthy cells → progress to acute leukemia	Group of diseases of blood and bone marrow
NOL (Normal)	**A acute** **C chronic** **L lymphocytic** **M myeloid**	No leukemias
MDS: Myelodysplastic Syndromes)		

Brain cancer

Abdolmaleki et al. [124] found SLP-BP discriminates malignant from benign brain tumors in patients suffering with astrocytic gliomas. The independent opinion of three neuro-radiologists from pre- and post-contrast MRIs resulted in 129 records with 13 parameters. NN model excelled in prediction on 36 new biopsy cases. However, a synergistic improvement was observed when radiologist opinion and MRI data were combined. Bona [82] reported a hierarchical NN to classify the single voxels of 3D brain tissue densities to detect pathological conditions. The tissue density distribution in CT/MRI of brain is related to anatomical or neuro functional regions. A slight difference of density is instrumental to assess pathological conditions. The results are indistinguishable from the reports of expert neuro-radiologist.

3. CNS & Brain disorders

The subcortical brain of a healthy person is active all through performing life-maintaining functions. Even in absence of sensory stimulus or any behavioral task, the cortex functions restless. The electrophysiological and fMRI scans probe into spontaneous activity or "default mode" of operation.

Parkinson's disease (PD)

Sharma and Pienaar [342] reviewed how optogenetics and novel designer receptors, the components of neural-technology-toolbox, paved way for advancement in the knowledge of circuit and signaling properties in Parkinson's disease (PD). Hashizumeet al. [316] reported a case study of a 47 year old patient suffering from severe PD (chart 13). The midbrain dysfunction lead to consequent frontal cerebral cortical dysfunction and was inferred from PET analysis. A neural network called 'corticobasal ganglia loop' formation intimately connecting the frontal lobe and basal ganglia is proposed.

Chart 13: PET in detection of roots of PD

- ^{18}F-dihydroxyphenylalanine PET
- ^{18}F-fluorodeoxyglucose PET
- 99mTc-ethyl cysteinate dimer bicisate single-photon emission computed tomography

PET: positron emission tomography

Dyskinesia

The classification of different types of behavior for one minute interval walking for the trunk (100%), leg (96%) and forearm (61%) is remarkable [326]. The performance with leave one patient out study also exceeds 75%. A careful study indicated that in the worst case, NN rating was in the next class to that indicated by physician.

Trauma (septic)

Marble and Healy [112] came out with a NN model in the diagnosis of complication of sepsis in victims of traumatic blunt injury with 100% sensitivity and 96.5% specificity. The model prediction is not vitiated even for partial incorrect coding of data.

Alzheimer's decease (AD)

Alzheimer's decease is a dotage problem for increasing number of people. The cognitive decline over a period of time detected from visits to clinics at regular/ irregular time intervals and also the family history [56] are indicators of the disorder. The data on l704 people enrolled at Laton aging and research center situated at Oregon health and Science University is analysed with mixed effects-NN with modified B.P. The mixed effected -NN has smaller relative misclassification rate (0.35) compared to SLP (2.74) and linear mixed effects model (0.4). The discrimination between AD and MCI (mild cognitive impairment) patients reaches 92.33% by analyzing resting eyes-closed EEG voltage using NNs. This is in contrast to a low value of 80.43% in the earlier procedures even when blind source separation and wavelength preprocessing was used [48]. Yang et al. [15] reported NN_GA classification tasks from Electrocorticography and EEG data (chart 14).

Chart 14: Classification with NN_GA of Electrocorticography and EEG data

Pre-processing	
least-square approximation	Determines overall signal increase/decrease rate;
Locally weighted spolynomial reg.	Smooths signals → determines the signal strength/variations.
Fast Fourier transform	Periodicity
Model	
GA	Input variable selection
MLP	Fn relation
Rule extraction	White box decisions

Dataset 1: It is a two category task i.e. artificial movements of either a finger or the tongue used in the BCI competition III. Electrocorticography (ECoG) data were recorded using an 8 × 8 ECoG platinum electrode grid at a sampling rate of 1000 Hz. The number of total trials are 378.

Dataset 2: From a 32-channel EEG (operating at 256 Hz), the data are recorded when participant presses left- or right-hand button when left- or right-pointing arrow stimuli is shown. The 960 trials were classified as correct/incorrect responses. After training, 179 regression rules resulted.

Old age problems

Kabeshova, et al. [315] developed predictive model of recurrent fallers in old community dwellers using 15 clinical observations (chart 15)

Chart 15: Application of NEAT for recurrent fallers of aged people

NEAT
Community-dwelling volunteers : 3289
Age: >=65
Number of falls: 0 or 1 fall
2 or more falls

15 clinical characteristics
- Use of walking aid
- Fear of falling
- Use of calcium
- Depression
- Use of vitamin D
- Supplements
- Female
- Cognitive disorders
- BMI <21 kg/m2
- Number of drugs daily taken >4
- Vision score <8,
- Use of psychoactive drugs,
- Lower-limb proprioception score =5,
- TUG score >9 seconds
- Handgrip strength score =29 (N)
- Age =75 years

Inference
Neuroevolution of augmenting topologies [NEAT]) >>
MLP and modified MLP

NEAT	
Sensitivity	80.42%
Specificity	92.54%
Positive predictive value	84.38
Negative predictive value	90.34
Accuracy	88.39
Cohen	0.74

- Age
- Gender
- Body mass index
- Number of drugs daily taken
- Use of psychoactive drugs
- Diphosphonate
- Calcium
- Vitamin D supplements
- Walking aid
- Fear of falling
- Distance vision score
- Timed Up and Go (TUG) score
- Lower-limb proprioception
- Handgrip strength
- Depressive symptoms
- Cognitive disorders
- History of falls Participants

Brain injury

Marcano-Cedeño et al. [14] put forward a MLP_ metaplasticity (MP) model to predict state of acquired brain injury patients after cognitive rehabilitation (chart 16).

Chart 16: Prediction of Acquired brain injury with MLP_metaplasticity model

Model ten-fold CV	Performance %
MLP_MP	91.56
MLP_BP	80.18
C4.5	89.91

MLP_MP Best model	% performance
Specificity	92.38
Sensitivity	91.76
Prediction accuracy	92.07

Psychiatry

Dutta et al. [369] reviewed various state- and trait- abnormalities occurring in cerebellum, lingual gyrus, anterior cingulate cortex (ACC), middle frontal gyrus (MFG), dorsolateral prefrontal cortex (dlPFC), amygdala and insula leading to major depressive disorder. Franchini [96] applied NNs as a supporting therapy decision tool for 416 psychiatric patient data cases. The accuracy of the choice of sertraline is

97.35% for treatment. Brasil et al. [95] proposed a hybrid fuzzy NN for the study of epileptic crisis. The bottle neck of classical ESs is explicit elucidation. Another black hole is a model to infer the human reasoning, knowledge, representation and logic employed in the current task. Resting state-fMRI results are highly relevant in major depressive disorder psychopathology. An immediate or delayed effect of antidepressants on resting state networks are discussed [369].

- Electro encephalogram (EEG)
- Magnetoencephalography (MEG)
- Magnetic source imaging (MSI)
- Positron emission tomography (PET)

Addiction

There is an increased interest in probing into details of changes in different regions of brain for addiction to nicotine, alcohol, drugs ranging from cocaine to LSD. The EEGs, fMRI probes are used for control group and addicts to develop anti-addiction counselling and therapy to bring back their mental and physiological health to normalcy. In addition, the physiology is closely associated with crucial events in life and emotions and their subsequent consequences. A few typical ones are self-destructive habits with false notions of reward/punishment/pleasure. The drug/food addiction at physiological level distills down to brain chemistry. Hippocampus is known to have a pivotal role in the formation of new memories and special navigation. Recently, it plays a key function in drug addiction of opiates and others. The progressive but crucial maladaptive alterations in neural circuit function are the sole reason for neuropsychiatric disorders. The cue-elicited craving for alcohol, cannabis and other drugs is now established.

Nicotine: It is one of the most addictive substances in various forms where tobacco smoke is inhaled. Zhang et al. [334] studied brain areas and grey matter of twenty two smokers with functional arterial spin labeling scanning. The decrease of gray matter density in dlPFC in smokers correlated with cue-elicited activity in this brain area. This widened the scope to understand neurobiological mechanism for the impaired cognitive control for chronic and high level tobacco addiction. This is a case of symptoms of substance use disorders (SUDs). The non-smokers and non-drug addicts (healthy persons) have a natural food cues which trigger hunger and feeding behavior. But, food-addicts have irresistible food cues and consume much beyond a normal person's measure.

Alcohol: Although alcohol is a frequently consumed beverages worldwide, the neural profile at molecular level for a transition from use to misuse is not yet completely figured out [197].

Food: With increased blood oxygen level dependent (BOLD) response in brain has relationship with food cues.

Drug addiction

Behavior components of drug addict

- Conditioning
- Stress
- Attention
- Arousal
- Reward

The genetically developed neural populations, altered distribution of afferent and efferent neural circuit elements as a consequence of repeated exposure and consumption of drugs transform the natural goal directed behavior to compulsive (psychological) reward satisfaction. This trend continues and in some cases unavoidable for the drug addict despite of negative consequences made known to him through counselling or in anti-addiction centers even under pressure [198]. Impulsivity is a pathological hallmark of drug addiction [193]. Paulus et al. [338] reported from imaging (EEG, fMRI, PET, SPET etc.) techniques that insular cortex is hypo- as well as hyper- active in different phases. The diminished cognitive control arises due to its hypo-activity, while irresistible craving for drug-specific and reward-related processes is a consequence of hyper-activity. Bathen [31] correlated clinical data of drug addicts with metabolites present in in vivo.

Cannabis: The cannabis cue-elicited craving is a powerful reinforcer in the brain's reward network. Recently, extensive targeted research results showed that THC's (Tetrahydrocannabinol) effects on the dopaminergic-reward system remain divergent.

Heroin: A higher impulsivity scores and enhanced *i*AFC network activity are noticed in thalamus, right insula and inferior frontal gyrus of heroin drug addicts compared to normal subjects. It is reported (chart 17) that different constructs of the impulsive network operate in HD and control groups. The altered *i*AFC network connectivity in HD-addicts results in loss of impulsive control [193].

Chart 17a: Networks in brain of heroin adducts

Visual food	Resting state fMRI
↑ Twenty two abstinent heroin dependent (HD) subjects ↑ 15 cognitively normal (CN Striatum ↑	abnormalities ↑ intrinsic amygdala functional connectivity (*i*AFC) network activity ↑
↑ bilateral Insula	

Chart 17b: comparision of heroin drug addicts and control subjects

↓ Markedly decreased anticorrelated *i*afc network activity in left precuneus,
↓ Positive correlation pattern in right precuneus, relative to the CN group

↑ Higher impulsivity scores and significantly enhanced *i*afc network activity
▶ Bilateral thalamus, right insula, and inferior frontal gyrus.

Heroin drug addicts	Control subjects
↑ *i*AFC network strengths positively correlated with impulsivity in the ↑ Right subcallosal gyrus, insula, thalamus and posterior cingulate cortex, correlated in left fusiform area.	- Negatively In the CN group, + Left pre-somamotor area-amygdala connectivity was positively correlated, - Right orbital frontal cortex-amygdala and precuneus-amygdala connectivity were negatively correlated with impulsivity scores.

Chart 17c: brain areas –smokers vs. non-smokers

- Dorsal lateral prefrontal cortex (dlPFC)
- Dorsal medial prefrontal cortex (dmPFC)
- Dorsal anterior cingulate cortex/cingulate cortex
- Rrostral anterior cingulate cortex (rACC)
- Occipital cortex
- Insula/operculum

Secondary analysis

- ↑ Resting state functional connectivity (rsFC)
- ↑ Structural
- ↑ Tonic neuronal activity
- ↑ Gray matter density

Chart 17d: Areas activated in brain in food and tobacco cues

Visual food	Smoking cues
↑ Striatum	↑ Striatum
↑ Left Amygdala	↑ Left Amygdala
↑ Bilateral orbital frontal cortex	↑ Bilateral orbital frontal cortex
↑ Bilateral Insula	

Breast feeding woman drug addicts: Despite biological filtration system, narcotic drugs, some pharmaceutical preparations pass from plasma into breast milk causing potential danger to the infants. It is acute when even a lactating mother continues narcotics or maternal medication is indispensable. The distribution of a drug between plasma and milk can be determined from area under concentration time

curve. But, concentrations in milk to plasma (m/p) ratio are not known for many drugs. Thus, it is another area where prediction, although approximate, alone is a guideline in clinical setting viz. drug/dose. Some of the typical earlier models in this pursuit were based on unbounded distribution, membrane diffusion and phase distribution. Now there is an increase in research for efficient and rapid methods to estimate milk to plasma ratio from molecular structure and bio-pharmaceutical properties.

For most of the drugs, average pH values of human milk, plasma, pKa of the drug and extent of binding of plasma-protein are known. But, protein binding in milk and partition coefficient of milk lipid and plasma are known only for a few drugs. Passive transfer and distribution into milk is affected by drug dosage, proportion bound in plasma, maternal clearance rate, half- life of the drug, molecular weight, lipid's solubility, degree of ionization, pH difference between plasma and milk [145].

Clinical analysis

Simultaneous blood glucose and blood pressure from a photoplethysmograph: Monte-Moreno [22] reported (chart 18, chart 19**)** simultaneous non-invasive measurement of blood glucose level (BGL) / systolic (SBP)/ diastolic (DBP) blood pressure by a photoplethysmograph sensor (chart 20) and machine learning algorithms.

Composition of urinary calculi: The composition of urinary calculi by automated/computerized methods facilitates prevention of recurrence of calculi in the urinary tract. Here, factor analysis and NNs are used

Chart 18: Photoplethysmograph for simultaneous BP and blood glucose monitoring

Basis: A functional relationship between the shape of the PPG waveform and the blood pressure and glucose levels is considered as valid.

System	%
Photoplethysmograph sensor, Activity detection module, Signal processing module (PPG waveform) → extracted features Machine learning algorithm Data 410 individuals	Machine learning algorithm **RandForest**s Ridge linear regression, MLP_NN SVM

Chart 19: Advantages and limitations

\+ BP values complied with grade B protocol of British Hypertension society

\+ independent of the patient

\- No need of calibration over time or subjects hypoglycemia or hyperglycemia missed for 1.9% of the cases

Chart 20: Ultimate limits of detection and sensitivity in analysis

Time of introduction	Name		Metric unit (g)	
1960–1970	Nanogram	(ng)	10−9	ppb
1970–1979	Picogram	(pg)	10−12	ppt
1980–1989	Femtogram	(fg)	10−15	ppq
1990–1999	Attogram	(ag)	10−18	
2000–2009	Zeptogram	(zg)	10−21	1000 Da(lton) molecule
2010–2019	Yoctogram	(yg)	10−24	1 Da, 1.7 H-atom
F. Adams, From nano to yocto, and beyond?			Talanta 85 (2011) 1230–1232	

Table 11b: Human urinary calculi-mass fraction of the components [182]

Whewellite		Weddellite		Carbonate apatite	
Expt	NN	Expt	NN	Expt	NN
0.293	0.301	0.339	0.317	0.368	0.382
0.307	0.320	0.537	0.559	0.155	0.121
…..					
0.331	0.339	0.365	0.364	0.305	0.297

from qualitative/semi quantitative IR database. Since the relationship between the absorbance and mass fraction is nonlinear, NNs surpassed standard addition method in the accurate assay of three types of calculi viz. Whewellite, Weddellite and Carbonate apatite (table 11b). The fact that a prior knowledge of the modeling function is not a prerequisite in NNs is the sole reason for the natural choice of this data driven paradigm compared to long cherished non-linear methods. Song [55] applied knowledge based NNs to evaluate thermal function of patients from Glomerulam Filtration Rate (GFR) data. The data consists of 441 GFR data vectors from 141 patients in Australia and New Zealand in 12 sites. KB_NN uses different new regression functions as neurons in the hidden layer and the functions are adopted through incremental learning of the data. Each hidden neuron has a pair of functions associated with it. The regression formulae represent the existing knowledge and one Gaussian kernel function defining the subspace of the whole problem space. All these functions are aggregated and changed through incremental learning. Nine formulas employed are used and the KB_NN model out performs at least by 10% accuracy compared to any of individual regression formulas or a NN model. The present system extracts modified formulas to suit the local profiles of the data space. This approach explains while each of different formulae in practice succeeds/fails for a data set.

Pathology and cytology

The numerical features extracted from images in pathology and cytology are used in classification of diseases by NNs. Becker [127] found that the performance of NN model is better than LDA.

DNA micro array data

Muselli et al. [37] reported recursive feature

Chart 21: Risks of very low birth weight children

Risks of VLBW children

- Brain injury
- Impairments / disabilities
  - Motor
  - Perceptual
  - Cognitive
  - Behavioural

Dataset

Category	Boys	Girls
VLBW children	27	27
Controls	39	25
Total	66	52
# subjects	118	

Clinical assessments

- Visual–motor integration
- Motor coordination
- Stroop test
- Full scale IQ
- Grooved pegboard
- 1H MR of frontal lobe metabolites

Analysis

- Outer product
- PLS discriminant

Models

- Prob_NN

SVM

Wechsler intelligence scales (WISC-III)

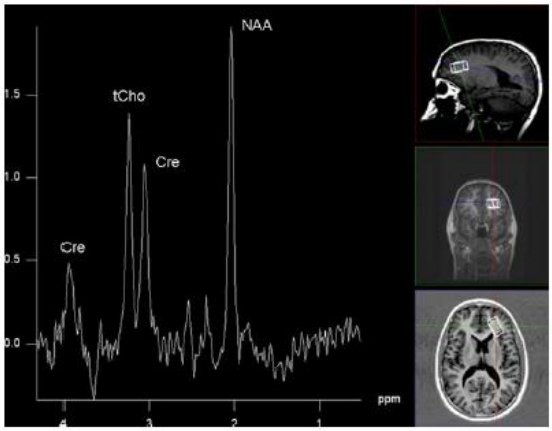
Arithmetic	IQarith
Vocabulary	IQvoc
Block design	IQblock
Picture arrangement	IQpicArr

Psychiatric assessments

- Autism spectrum screening questionnaire
  - Mother report
    - Attention deficit
    - hyperactive disorder

Fig.3: ^{1}H MRS of VLBW male adolescent
(Courtesy from Ref. 31)

selection followed by switching NNs in the analysis of DNA micro array data. The identification of the subset of genes involved in biological process (normal or diseased) is a difficult task. The SNN RFA procedure is better than SVM as signal to noise ratio approaches a low value. However, in gene expression datasets, the large number of measured (genes) variables versus a small number of samples poses a potential computational challenge due to curse of dimensionality.



4. Diabetes Mellitus

Onset of Diabetes: National institute of diabetes, digestive and kidney diseases continuously monitored the Indian female population residing in Phoenix, AZ over five years due to the high incidence rate of diabetes among the set since 1965. This database has been analysed over years by a large number of researchers proposing newer NNs and significant modifications are made in the solution strategies. The prediction of (onset of) diabetes Mellitus in PIMA database was done using SLP with a success rate exceeding 80%, which is larger compared to linear regression (MLR) and ADAP procedures. From a data base of 6142 case sheets, the time sensitive risk factors to predict diabetes is analysed by MLP with back propagation. The model outperforms compared to regression methods. Tafeit [107] et al. used factor analysis and NNs to determine pre-subcutaneous adipose tissue compartments in non-insulin-dependent diabetes mellitus. Lipometer, an optical noninvasive device gives subcutaneous adipose tissue topography (SAT-TOP) compared to the healthy individuals who have higher upper trunk and lower leg (apple type) obesity. The factor analysis and NN outputs similar results.

5. Gynecology & Obstetrics (Ob-stet'riks, ob-)

Nine classification techniques are compared to predict the outcome of three types of pregnancies viz. ectopic-(EP), intra urine- (IUP) and failing pregnancies. With a training set of 508 and testing data of 348, Bayesian LS_SVMs with radial basis kernel was always on the top among multi-class LR, multi-class-kernel-logistic-regression, PCR, Bayesian MLP, binary logistic regression etc. It is one among a promising decision support tools for clinical practice. In obstetrics, CTG and non-stress test readings are complex. CAFÉ (computer aided fetal evaluator) is an intelligent tightly coupled hybrid system integrating rule based methods, NNs and algorithmic procedures to automate real time antenatal monitoring using the data from cardiotocography (CTG) [43]. The analysis of 3450 minutes of signal time from 53 different patients is comparable with the expert's opinion. Alonso-Betanzos [114] et al. proposed NNs to evaluate a pregnant women antenatal status. The results compared well with LDA and Baye's model. NNs played a role in controlling treatment of patients with drug abused, monitoring the status of fetus health antenatal condition combating with epileptic crisis.

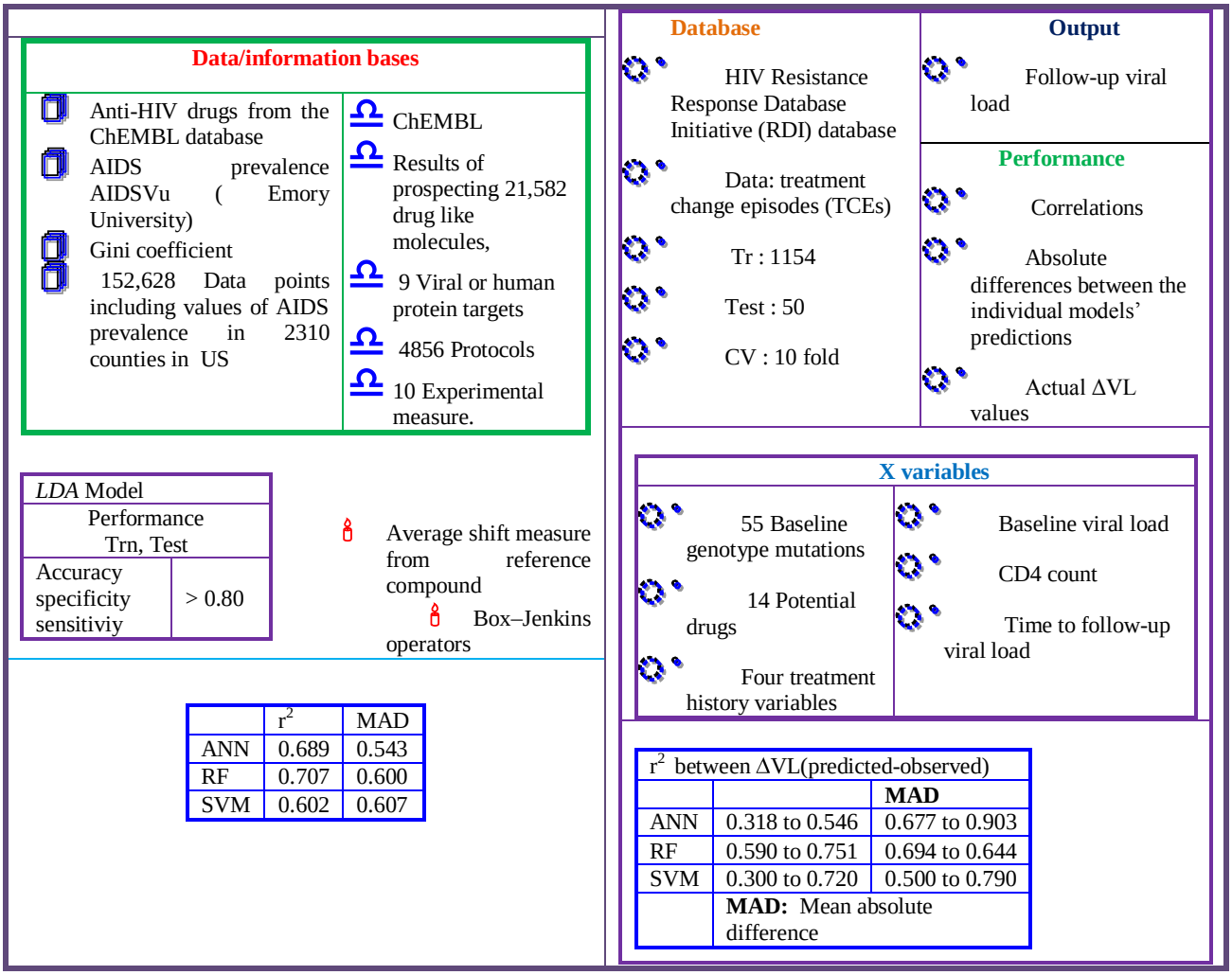
In vitro fertilization (IVF): An in vitro fertilization prediction system was proposed with NNs and k-fold cross-validation. The prediction by ensemble of NNs was better.

Chart 22a: Mapping of AIDS in US using ChEMBL database

Input

- Shannon information invariants of molecular graphs for drugs
- Social networks of income inequality

Chart 22b:HIV treatment change episode models



	r^2	MAD
ANN	0.689	0.543
RF	0.707	0.600
SVM	0.602	0.607

r^2 between ΔVL(predicted-observed)		
		MAD
ANN	0.318 to 0.546	0.677 to 0.903
RF	0.590 to 0.751	0.694 to 0.644
SVM	0.300 to 0.720	0.500 to 0.790
	MAD: Mean absolute difference	

Low birth weight children: Cerqueira et al. [1] developed an open source simulator for prognosis of survival of premature newborns. This machine learning software (NICeSim) predicts outcome (probability of death) of newborns undergoing treatment in neonatal intensive care units (NICU). The low gestational age and low birth weight (chart 21) with consequent respiratory distress syndrome is a risk factor. The prediction reached an accuracy of 86.7% under ROC of 0.84 for the positive class of data from a Brazilian hospital. There is a provision to add/delete influential variables and their ranges by neonatal nutritionist or pediatrician to probe into extremes. Bathen et al. [31] analysed the risks of very low birth weight (VLBW <1500 g) survived children comparing clinical, psychological test parameters and MRI with those of control group (birth weight >10th percentile). The VLBL children were in neonatal ICU of University Hospital in Trondheim, Norway for two years (1986 to 1988) and belong to high risk category for neurological impairments (fig. 3). This threat mostly continues even in adolescent and adulthood periods. The children chosen as control were born to mothers living in the Trondheim region. The magnetic resonance brain spectra of 54 VLBW survivors of 14-15 years of age and 64 control subjects were scanned for localized volumes in the left frontal lobe containing mainly white matter. The relationship between clinical parameters with the metabolites in MR spectra is probed for subjects of 14 to 15 years age group. Prob_NN and SVM classify the two categories efficiently. MR brain spectra were obtained from volumes localized in the left frontal lobe and contained mainly white matter. The clinical factors used in the classification were visual-motor integration using motor coordination stroop test, full scale IQ and grooved pegboard.

HIV-AIDS

The survival period and quality of life of HIV infected patients are notably increased with combination-drugs based on highly active antiretroviral therapy (HAART). Herrera-Ibatá et al. [218] prepared a complex map of networks of prevalence of AIDS in US. The chemical structure, molecular target, organism, along with preclinical results for effect of prospecting drug molecules and their cocktail are considered (chart 22). However, the treatment failure for HIV patients is primarily due to resistance of virus to the drug. Then, the genotype resistance test guides the new regimen in the course of therapy. Wang et al. [36] reported RF, SVM and NN models for predicting virological response (chart 22). The predictions of the committees of NNs, random forest and SVM are statistically significant and they are similar in accuracy. But, the combination of output of three committees improved further correlations (r = 0.72) between computed and measured virological responses. Merck focused 250,000 structures to find diketoacid-like HIV-integrase inhibitors. NNs are compared with random forests and SVM in predicting in virological response to HIV therapy. The failure in treatment of HIV is due to drug resistance (chart 23). The selection of new regime is guided by genotypic resistance testing, but the interpretation of complex genotypic information poses a major challenge. Treatment change episode dataset from HIV resistance response database initiative (HIV-RRDI) is divided into 1154 training and 50 testing cases. The training set was divided into 10 groups. Seventy six input variables are used and the output was followed up vival load. NN models are inferior to RF and SVM in simple single models. Using committees models all the three methods improved. The next phase is combining the committees output which gave a correlation of 0.728 between predicted and actual virological responses. A committee of NNs models is equal to RF and SVM models. Combination of results from different methods is a successful technology in the hands of experts. It should be carefully designed and implemented without subjective prejudices and bias towards a goal/sub goal. The combination of NN and RF models is under clinical evaluation.

Chart 23: $$$Drug-resistant virus/bacteria	
Multidrug resistant	MDR
Extensively	XDR
Totally drug-resistant	TDR

6. Miscellaneous diseases

ॐ Hearing impairment (Auditory system)

Davey [47] et al. developed an automated detection system for ABR (auditory brainstem response) wave form. The dataset of varying hearing ability of 85 persons consisted of 550 wave forms depending upon the stimulus employed. The NN and C 5.0- decision-tree-algorithms resulted in 95.6% and 85% accuracy of two_stage_classification. In the first stage a ratio of post-stimulus to pre stimulus power (200, 500, 900 Hz in frequency domain) in the time domain is used to classify strong responses from others. The outputs of classification time, frequency and cross correlation procedures using Dempster-Shafer information theory are affected in the second stage. This hybrid approach is robust, exhibits high classification accuracy and emulates an expert audiologist in diagnosing hearing impairment from ABR wave characteristics. The SLP_NN was trained with 120 NRT traces and tested with 550 independent traces from 11 cochlear implant subjects. The performance is statically comparable with that of expert physician [69].

Malodor: Nakano et al. [8] used NN, SVM and decision trees to classify malodor from oral microbiota in saliva. The malodor in mouth air is due to methyl mercaptan, a volatile sulfur- compound. T-RFLP (terminal restriction fragment length polymorphisms) analysis (chart 24) outputs fragment lengths/ peak areas information on microbiota. It corresponds to bacterial strains.

Chart 24: T-RFLP analysis with the DNA fragments for oral malodor	
No of patients:	309
Peak area	Equivalent to frequency of a specific fragment if one molecule is selected from

	terminal fragments gene
Response	Peak areas of terminal restriction fragment (T-RF) length polymorphisms (T-RFLPs) of the 16S rRNA

QC parameters	Performance %
Accuracy	81.9
Sensitivity	60.2
Specificity	90.5

ॐ Ophthalmology

The physiological processes linking the visual stimulating sensations in the visual field and the concept of the object are complex [66]. It is much more in the case of blind people. The modelling of such partially understood/ misunderstood information/ concepts is beyond the state of the art of technology of AI and physiology.

A substance is classified as irritant to eyes if it causes a particular level of trauma in the Draize rabbit eye test i.e., if the mean scores at 24hr, 48hr, 72 hour exceed documented symptoms. The irritant substance partitions into membrane. Thus, a chemical with high dipole moment has lower hydrophobicity (logP). In effect, it cannot not pass through the membrane [384]. However, a small dipole moment is necessary for the passage. The chemicals perturb the transport of ions across the cell membrane in the eye by changing the electrical property. It is the cause of eye irritation when exposed to neutral organic compounds. Barratt [385] employed 34 alcohols in the model with PCA and MLP_NN_BP. The classification into irritant and non-irritant are assigned the values of 1 and 0. The descriptors employed are dielectric constant, logP, dipole moment, RY and RZ. The NN is accurate to an extent of 97.27% in training, but the predicted values are widely different especially in the middle of the range (0-10). Archambeau [66] developed grey box and black box NN models to restore partial vision of some categories of blindness. The Grey box model makes use of up to date new-physiological knowledge in MLP or RBF NNs. It is 25% more efficient than LLS. It is worth noting that black box model i.e. NN without a priori knowledge has similar prediction accurately. Hung et al. [26] proposed suppressed fuzzy-learning vector quantization (supp.fuz.LVQ) (chart 25) for segmentation of MRI images. It is applied as supportive diagnoses of ophthalmic diseases. The fuzzy function in fuzzy_LQ approximates lateral neural interaction in SOM. The suppression in supp.fuz.LVQ is affected with a parameter learning schema.
Data.simul: The numerical data are generated by a mixture of normal distributions.

Data.patient: The ophthalmic MRI images of two year old female patient with retinoblastoma of her left eye are analyzed. She has an inborn malignant neoplasm of the retina with frequent metastasis beyond the lacrimal cribrosa. The intra-muscle cone tumor mass with high T1-weight signal images and low T2-weight signal images in the left eyeball are detected. The 20mm (diameter) tumor occupied nearly the entire vitreous cavity. Further, there was a shady signal abnormality all along the optic nerve reaching the optic chiasma near the brain.

Chart 25: Segmentation of MRI images with LVQ_NNs

LVQ	Learning vector quantization
FLVQ	Fuzzy LQ
S-FLVQ	Suppressed FLQ
ALVQ	Alternative LVQ
GLVQ	Generalized LVQ
RGLVQ	Revised GLVQ
FGLQ	Fuzzy GLVQ

ॐ *Gastro intestinal diseases*

Acute gastro intestinal bleeding (GIB) requires immediate intervention. The results of endoscopy and prediction of bleeding source are helpful in looking for scarce healthcare resources [46]. The random forest model, NN etc. successfully identified the source of GIB. RF model predicted with 80% accuracy while endoscopy reach only 75%.

Small bowel tumors: Li et al. [21] proposed color texture features and classifier ensemble (chart 26) to diagnose small bowel tumors from images of capsule endoscopy.

Diarrheal diseases

The number of deaths in children below the age of five is 760,000 per year.

Chart 26: Diagnosis of tumors in small bowl with capsule endoscopy

- k-NN
- SVM
- MLP_NN
- Ensemble

Patients	10
Capsule endoscopy images	1200

Performance	%
Accuracy	90.50
sensitivity	92.33
specificity	88.67

Liver Diseases

Liver is the largest internal human organ/ gland with unique characteristics of regeneration and expansion in case of biological emergency. The semi-automatic and automatic liver segmentation techniques are recently reviewed. Hepatic (liver) masses are differentially diagnosed by radiologist with data from ultrasonography, computed tomography (CT), MRI and clinical tests. CT images are the prime source in automatic liver disease diagnosis, liver volume measurement and 3D-liver volume rendering. A noteworthy increase in accuracy is possible by combining data from all sources and increasing number of patients in data acquisition phase. GA, EP etc. are to select relevant variables and to train the NN. The preprocessing and filtering techniques in model development have positive effect. However, the interpretation is difficult. A grey level based NN-method is tested on 40 patients with great success. The status of currently available hepatocellular cancer markers which include single protein, complex proteomics features and tumor-specific auto anti bodies are reviewed. Yet, a new generation of markers are needed confirming to the stringent criteria stipulated by early detection research network. Wang [52] proved earlier the convergence and global stability of AdvFuzCell_NN based on NDA algorithm and applied for detection of white blood cells and segmentation of microscopic white cell images. They achieved higher boundary integrity and recall accuracy of CT liver images with advanced fuzzy cellular NNs (AdvFuzCell_NN) over fuzzy cellular NNs. Maclin [135] achieved 71% accuracy (51 out of 72 cases) with SLP_NN (BP) using ultrasonic data. Hayashi [103] et al. used NNs for diagnosis of hepatobiliary disorders from nine continuous real valued clinical parameters. With piece wise LDA classification, rules are generated. Chuang [23] reported MLP_NN_BP hybridized with case based reasoning has good predictability of liver diseases. This model exhibits low false negatives in diagnosis.

Table 12: Hybrid and component models for Rheumatoid Arthritis

Model	Accuracy	Model1	Model2	Accuracy
BPN	93	BPN	CBR	95
CART	85	CART	CBR	91
DA	76	DA	CBR	84
LR	86	LR	CBR	86
CBR	89			

Arthritis

Rheumatoid arthritis and Spondyloarthropathy lead to functional impairment. Wyns [70] proposed SOM to predict early arthritis. MLP_NN with B.P and quest decision tree program are inferior to the present system (table 12).

Dermatology

The skin is the principal barrier against environmental insult preventing health hazards. According to EC stipulation [386] the extent of corrosivity of chemicals is measured by the development of necrosis (irreversible damage to the skin tissues), when a chemical (500mg of a solid or 500ml of a liquid) is applied to the skin of a rabbit for a period of 4hrs. The other measures of severity are causing burns within three minutes or severe burns instantaneously. The permeation/transportation of the chemical from the site of administration/ exposure/ contact to the site of attack is the prerequisite for either biological/ drug/ toxic action. This is beyond well explored physical, chemical and biological forces, many being non-linear [141]. The binding or reaction with the receptor or target is responsible for the reaction.

Severe burns: Jiménez et al. [7] proposed a multi-objective evolutionary fuzzy classification system (Alg. 3, chart 27) to predict survival or mortality of patients with severe burns.

Chart 27: MOO for severely burnt patients

- $$$_multi-obj algorithm
  - Evol alg
  - Niched pre-selection
  - Elitist Pareto-based
    - \+ Algorithm for diversity reinforcement (ENORA)
- Non-dominated sorting genetic algorithm (NSGA-II)

ENORA

- Decision trees
- Artificial neural networks
- Naive Bayes
- And case-based reasoning)
- Niched pre-selection
- NSGA-II algorithms

\+ MOO-EvolAlg is non-combinational

\+ Real parameter optimization

ENORA performance

Classification rate	0.9298
Specificity	0.9385
Sensitivity	0.9364
Interpretable fuzzy rules	Approx. 14

Alg. 3: Multi-objective constrained optimization

Data: Severly burnt patient's parameters

Multiple ObjFns

- Minimize #rules of classifiers
- Maximize accuracy

Iterate

MO-Evol.Alg.
Pareto-based elitist
→set of alternative (Pareto) classifiers
Assign a linguistic label (for interpretability) to each fuzzy set of classifiers
Decision making
If classifier comply with preferences of decision maker
Then choose classifier
If no classifier is satisfactory for decision maker
Go to iterate
else

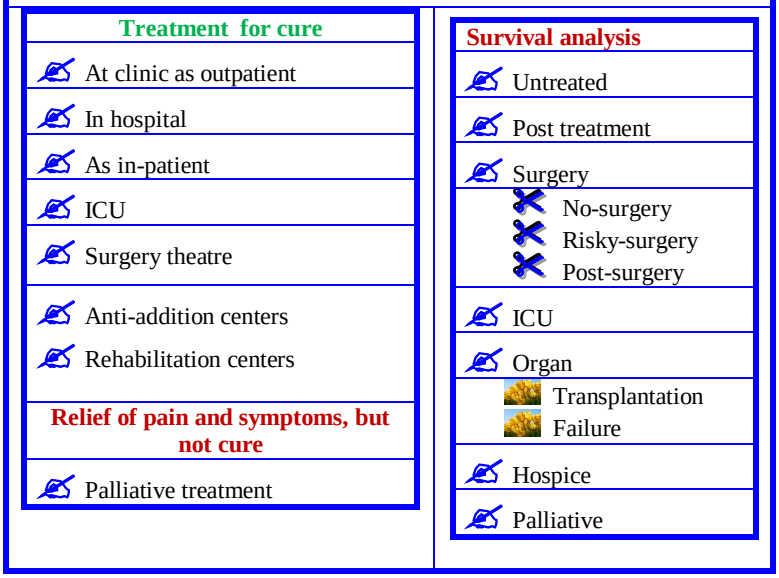
End iterate

II. Medical treatment (MedTreat) (7-12)

The eras of staunch beliefs like possession of precious stones/ metals/ mercury and practices for curing the diseases had a natural extinct. The present medical science evolved to a stage of near perfection. There is hierarchical and parallel renaissance in prevention, diagnosis, curative treatment, and follow up associated with adaptive intervention.

The Therapeutic programs range from general to specific case by case. It starts with prescribed pharmaceutical preparations, intervention/ surgical protocol and treatment in ICUs (chart 28). In the case of brain/psychic disorders counseling, rehabilitation and physiotherapy are integral part of restoring normal health to the possible extent. A chemical that alleviates the ailment is called a medicine or a drug. The current practices of medical treatment include administration of drugs, surgery, implants, transplantation and intervention. The typical nascent medical technologies include intervention nephrology, intervention cardiology etc.

Chart 28: Medical treatment and survival analysis

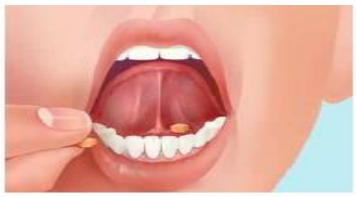


7. Prescribed pharmaceutical preparations

The objective of intervention is to compensate/nullify/reverse the disease process in different organs (chart 29) with molecules called drugs. The interaction with diseased cell/ (direct/indirect) causative agents is the basis of drug action. The theoretically feasible chemical space is 10^{100} and corporate data bases consists of 10^6 molecules and all types of chemo-bio-toxicological information is not available even to this small fraction [155]. Due to limitations to find the best with all available tools, we resort to short cuts, simplification, elimination etc. in irrational/rational /knowledge based intelligent drug design. Now, non-prescribed medicines for common ailments are available across the counters at pharmacy outlets. The preventive measures include flu shots in cold regions, polio vaccines for infants and so on. The mode of administering the drug is internal viz. oral, intravenous and external though dermis (ointments, pouches). Further, pre- and post-surgical treatment involves typical medicines with dosage restriction. In spite of the advancement and near perfection of pharmaceutical industry, there is no unique drug without marked side effects.

Chart 29: Administration of pharma_drugs into human body

Drug administration	: [	Oral Respiratory tract [Ophthalmic/ Otologic /Nasal] Urogenital Rectal]
Oral	: [	Digestive tract (enteral) Buccal(Sublabial) Sublingual]
Respiratory tract	: [	Inhaled Intransal Nebulizer]



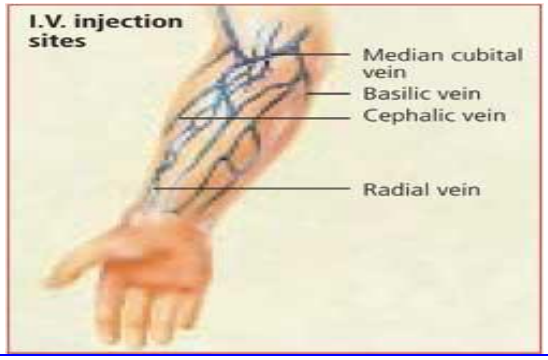
Sublingual Route

Oral	Digestive tract
Intravascular/intravenous injection into	Circulatory system
Drug releasing implants	Stunts

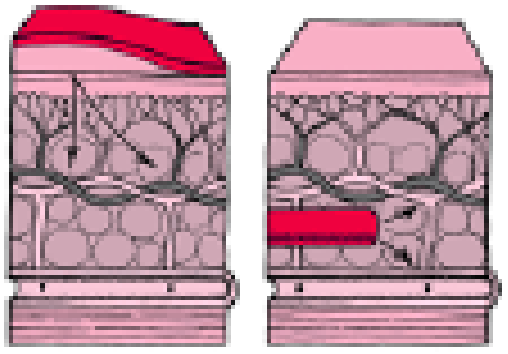
Preventive care
- vaccines
- Life style
- Food/water
- Environment

Drugs
- Pharmaceutical preparation
- Placebos (not recommended)

Injection	into
Hypodermic	Subcutaneous
Intracutaneous	Intradermal
Intradermal	Dermis or substance of the skin
Intramuscular	Muscle
Intrathecal	Subarachnoid space through theca of spinal cord (Epidural)
Intravenous	Vein
Subcutaneous	Subcutaneous tissues



Organ in human body	Science (Pronunciation)	Medical expert	Medicine+ Information science + Expert knowledge + Hardware/software
Lung	Pulmonology (p͝o͝o ˈl mə-nˈäl ə-jē)	Pulmonologist	PulmonoMetrics
Heart	Cardiology (kɑ r di□ɒ l ə dʒ i)	Cardiologist	CardioMetrics
Bones, joints	Orthopedics	Orthopedician	OrthopedoMetrics
	Gynecology	Gynecologist	GynecoMetrics
	Gastroenterology	Gastroenterologist	GastroenteroMetrics
	Diabetes	Diabetologist	DiabetoMetrics
All	Medicine	Medical practioner	MedicinoMetrics



Transdermal Implantation

Placebos: Placebos are not recommended and legal sanctions were also restricted. But, recently there is a surge from the perspective of viewing them as melting pot of concepts and ideas for neuroscience [253].

Anticancer drug administration: Díaz-Rodríguez and Landin [267] developed NN based smart design considering the amount of solubilized drug and gel temperature for anticancer drug β-lapachone to be administered as injectable formulations into intratumoral region.

Dose prediction of Simvastatin and atorvastatin: Moon et al [229] conducted a feasibility study to adopt NN prediction to prescribe the dosage of drugs. Two data sets from 17 patients in the age group of 40-67 receiving drugs, simvastatin and atorvastatin, were analysed with Neural SIM software. The input to the model is lipid panel data viz. LDL-C (low density lipoprotein, cholesterol), TC (total cholesterol), HDL-C (high density lipoprotein cholesterol) and TG (triglycerides). The correlation is high (table 13a) and the model prediction and experts' prescription (table 13b) are similar in 14 out of 19 cases. The improvement in prediction requires larger size of data set and additional influencing factors like age, body weight, life style, sex, medical history (like presence of diabetes mellitus and use of anti-retroviral drugs) etc. The dose determination of HMG-CoA-reductase inhibitors was modeled with NN within the pharmaco-dynamic framework. This study demonstrated the successful prediction of appropriate dose. These authors suggested acquisition of a larger sample size is a necessity for the development of more accurate models [159]. Earlier NNs were used in determining the dose of heparin in inducing anticoagulant effect and N-acetyl cysteine to prevent the toxicity of acetaminophen.

Table 13a: Correlation of NN model for lipid data with drugs

Drug	Correlation coefficient			
	Data set 1		Data set 2	
	Tr : 31	Te:45	Tr:20	Te:29
Simvastatin	0.99	0.89	0.77	0.83
Atorvastatin	0.95	0.88	0.91	0.92

Table 13b: Comparison of NN predicted and expert prescription of doses in mg

Data set 1			
NN		Expert	
Simvastatin	Atorvastatin	Simvastatin	Atorvastatin
81	0	80	0
79	40	80	0
2	46	0	40
18	32	80	0
Data set 2			
58	6	80	0
2	80	0	40
53	16	40	0
62	0	80	0

8. Surgery

Anesthesia: Linkens and Mahfouf [92] emphasized the application of hybrid intelligent algorithms with fuzzy logic, NNs and EPs in anesthesia. Allen and smith [93] reported MLP_NN with B.P to a fuzzy logic infusion controller of general anesthesia. Auditory evoked potential (AEP) is the response to an auditory stimulation. AEP obtained from electroencephalogram (EG) indicates the depth of anesthesia. El-Nagar and El-Bardini [3] reported an interval type-2 (IntervTyp2_) fuzzy neural network (Fuz_NN) controller to maintain multi-variable anesthesia system. Here, the effects of surgical stimulation are minimized and uncertainty consequences due to large patient parameters change (due to inter-individual variability) are surmounted. It consists of interval type-2 fuzzy (IntervTyp2_Fuz) linguistic process in the antecedent and an interval neural network in the consequence part of first order logic driven processing.

Optimum needle insertions: Vaughan et al. [6] proposed patient specific simulator for optimum needle insertions accurately based on epidural model using body mass,

- Structure of type-2 fuzzy logic systems (FLSs) is superior to type-1
- Minimize numerical and linguistic uncertainties of I/O values

height and age. NN is trained with 23,088 patients' clinical data and prediction accuracy is in table 14.

Tonsillectomy (ton·sil·lec·to·my): Pizzi [98] applied NN with fuzzy inter quartile encoding as preprocessing in the analysis of blood sample test results of tonsillectomy patients and data sheets oqueries related to bleeding tendency of adenoidectomy (ă'd-oi-dĕ'k-mē) patients. A clear improvement of 11% in classification accuracy is observed. Fuzzy inter quartile encoding is a preprocessing method applicable for classification. It indicates the extent of belonging of a feature in a set of overlapping correction. This transformation is robust to feature outliers and normalizes the feature space.

Prosthetic surgery: Sewell et al. [20] developed a procedure to assess distribution of pressures within prosthetic socket using MLP_NNs with BP. This "right first time" approach increases comfort to both patient and prosthetist. NN predicted the interfacial pressures at the residual socket interface from strain data on 16 patches within an accuracy of 8.7%, adequate in this venture.

Case study: The interfacial pressures of limb were measured from unilateral transtibial (below-knee) traumatic amputee who was 45-year-old and had been on prosthesis for 22 years. This data driven AI addresses design issues of future of smart lower-limb prosthetic socket fitting processes.

Surgery simulation: Modeling of soft tissue deformation is still crucial in simulation of surgery. But, it an unsolved task yet. A cellular SLP to solve reaction diffusion model for real time simulation of soft tissue deformation is reported. The NN model predicts typical behavior of living tissues. It also accepts local as well as large range deformations.

Table 14: Simulator for optimum injection needle insertion

Prediction of	Error	
	NN	Regression
Skinfold thickness		
Subscapular	3.54 mm	3.75 mm
Triceps	3.43 mm	3.89 mm
Circumference		
Waist	3.92 cm	3.84 cm
Thigh	2.00 cm	2.16 cm
Arm	1.21 cm	1.34 cm
Calf	1.40 cm	1.46 cm

Survival analysis of post-surgery

Post-surgical breast-cancer patients: The post-surgical survival of breast cancer patients is complex. A decision support tool for the prognosis of relapse of breast cancer using an ensemble of NNs is reported. Control of induction by sample division method and different sets of variables are used and Bayes optimal error is estimated from NNs. The clinical data is from medical oncology service of the hospital, Spain.

Post-surgical thoracic transplantation: Delen [29] studied the survival time prediction for dataset obtained from united network for organ sharing (UNOS). The predictor variables obtained from machine learning techniques are more effective. AI methods play a key role in allocation policies in the field of organ transplantation (table 15, table 16). The three risk groups are identified by Cox survival model using the input factors obtained from integrated machine learning techniques. When MLP_NN is trained with R-prob. algorithm, ROC of prognostic model is the range 83.9 – 87.1%.

Table 15: Survival analysis of post thoracic transplantation surgery

Model	R^2
MLP_NN	0.847
Reg_Tree	0.785
SVM_+ RBF kernel	0.879

Table 16: Performance measures of models in thoracic transplantation data

Model	R^2
SVM with RBF kernel	0.879
MLP_NN	0.847
M5	0.785

9. Transplantation

The high accurate prediction of survival time and prognosis have become mandatory in transplantation of organs like kidneys, liver and heart where the lifesaving demand is much more than donors. Delen et al. [29] analyzed the dataset of a nation-wide thoracic transplantation instances from United Network for Organ Sharing—UNOS with NN, SVM etc. to select the dominant variables. Cox-regression derived and Kaplan–Meier prognostic indices used to predict survival times of patients with terminal illness waiting for cardiac and pulmonary transplantation.

Hospital and patient management systems

A Bayesian NN method was used by WHO/UPPSALA monitoring center to detect early signals of potential safety problems of marked drugs [146]. It probes into unexpected patterns in the response and their trend over the time. WHO pooled up a database with more than two million adverse drug reactions emanated from 27 countries. The quarterly updates exceed 35 thousand new entries.

10. ICU (Intensive Care Unit: Immune Contact Urticaria)

Also called intermediate care unit/ critical care unit/ infant care unit comprises of special equipment for continuous monitoring of seriously ill patents. This emergency unit prevents or reverses the organ failure processes through timely intervention [42]. The function of ICU is through cooperative and distributive efforts of super-specialists, expert doctors and para-medical staff. The pharmaco kinetics and pharmocodynamics of drugs for the severely ill patients with multiple diseases is critical, many a time differing from case to case. The choice of alternate drugs, dosage and intervention procedures are adaptively implemented without losing time. The reaction of the drugs and onset of opportunistic diseases are intelligently combated through time tested protocols.

Hospital management systems
ICU
Surgical theatre
Palliative care
In patient

SOFAR (sequential organ failure assessment) is an expert driven index widely employed in European ICUs. This index quantities the disorder of the organs. The database consisting of survival times, clinical/pathological parameters, unexpected/unforeseen conditions etc. is useful to develop predictive models, which are lighthouses in enhancing the survival period with less suffering and decreasing mortality rate. The applications of classical AI are rampant in biomedical instruments [51]. Real time applications are all pervading. Intelligent alarms/ monitoring/ diagnosis in I.C.U., Pre-/post- operative care and prediction of emergences/survival are only a few instances in routine practice. NNs are superior compared to MLR and Multivariate logistic regression in predicting the severity of patients' condition [159]. The prediction of NN model, based on patients' data and case histories joined the bandwagon of medical system ensuring the achievement of the possible health and comfort utilizing the doctrine of swarm intelligence. Successful literature citations (chart 30) endorse the use of NNs (ensembles, mixture-of-experts) in emergency situations/ ICU with better outcome compared to Cox/logistic regression. Simulation studies also found a niche in ICU activities. Silva [42] proposed NNs to predict the risk of ICU organ failure from monitored biometrics and adverse events. Lapuerta et al [260]
used NNs to measure the severity of illness in alcoholic patients with severe liver disease from laboratory and clinical test results. The outcome of NN is comparable with Maddrey discriminatory function. It is a commonly employed prognostic indicator for alcoholic liver disease based on bilirubin and prothrombin test. NNs play a role in oncology critical care and cardiovascular medicine since the rapid and precise predictive outcome is immediately needed [50].

Chart 30: NNs in survival analysis of patients in ICU

- Prediction of length of stay in ICU
- Organ impairment/disfunction/failure
- Forecasting effect of atmospheric changes on respiratory symptoms [ ]
- Detecting emergency condition in neuro-surgical patients
- Survival prediction of patients
  - Severe burns
  - Post-surgery of non-small cell lung carcinoma
  - Cardiac disorders,
  - Alcoholics suffering from severe liver
  - Patients vulnerable for spectic shock
- Data from bed side alarms

The range of data for severely ill patients is large, but full range of all factors for a patient for prediction of an ailment may not be available. The pharmaco kinetics of two drugs (arbekacin sulfate (ABK) and Amikamycin (AMK)) was studied from physiological data obtained from ICU patients. The ABK concentration in blood plasma was measured with polarization immuno-assay and predicted with NNs. The data in table 17 describes the number of cases where the drug concentration in

plasma is below and above the effective level. This is a big handicap resulting in poor prediction, which may even be misleading. The pre-requisite is thus pre-evaluation of the predictable region as well as full cognizance of data structure. The caution here is not to hamper on prediction with extrapolation in life saving situations.

Renal failure: A large database of 25,215 daily records of 4,425 patients from 42 European ICUs [42] is considered. NN excelled with multinomial logistic regression both in discrimination and calculation criteria and the system works better for renal failure (ROC-76%). Data mining methods obtained knowledge of emergency from easily obtainable data. It makes room to develop intelligent clinical alarm monitoring.

Septic shock: It results in high mortality and thus of prime concern in intensive care medicine. Paetz [79] proposed a NN with growing trapezoidal TF to classify the patients in ICU vulnerable for development of septic shock. This approach alleviates the black mark of NNs as black box models.

Table 17: Prediction of drugs in plasma levels of severely ill patients by NNs

If	Conc of drug in plasma is below the effective concentration
Then	positive
Else	negative
If	correctly classified to be 'positive', then true positive (TP)
If	correctly classified to be 'negative', then true negative (TN)
If	incorrectly classified to be 'positive',then false negative (FP)
If	incorrectly classified to be 'negative',then false negative (FN)

Length of stay in ICU

Ng [57] proposed mixture experts NN to model in-patient length of state (LOS) of infants born during 1995-1997 and their subsequent admission for Gastroenteritis (n=692). Incremental expectation maximization algorithm is used to train the NN in online mode. LOS is complicated and changes dynamically. The demographic and co-morbidity data are used. The mean absolute difference is the criterion comparing the methods for prediction of the length of stay. Incremental learning is better than batch mode.

Mortality in ICU

Silva [54] reported NN model to predict the mortality of a patient in ICU from a large (13,164 cases of) adult patient database pulled up from 42 ICUs spread over 9 European countries. The features employed are adverse events recorded from four bed-side alarms and 17 static variables like serum sodium collected within 24 hours of the admission of the patient.

Model	%
ANN	82.6 to 85.2
LR	80

Post-operative care in ICU: Rowan et al. [50] reported ensemble of NNs to predict length of stay of post-operative cardiac patients in ICU. The 15 preoperative and 17 operative/post-operative risk factors are considered to develop integrated multi-functional software. ROC analysis was used to discriminate the function of single and ensemble of NNs. The consolidated output of ensemble of three NNs is 0.9 while the highest discriminating power of individual NNs in the set is 0.819.

Table 18: Survival analysis of post-surgical patients at ICU

	NN	Radiologist
ROC area	0.94 (0.01)	0.91 (0.01)

GA-NN > logist reg

- Age (years)
- Tumor volume
  - Rectangular prism (cm3)
  - Surface area of sphere equal in volume rectangular prism (cm^2)
  - Natural logarithm of volume of rectangular prism (cm^3)
  - Radius of sphere equal in volume to rectangular prism (cm)

Lung carcinoma: GA-NN was proved better than logistic regression for survival analysis of a database of 620 patients who underwent surgery with

Non-small cell lung carcinoma (NSCLC) during the period 1987 to 1992 at the Regional Thoracic Surgical Unit for the Mercy region, UK (table 18).

Survival analysis in ICU:
Laurentiis and Ravdin [129] showed the prediction by NN is better than Cox regression method in survival analysis. With simulated data sets mimicking realistic scenario, the interactions between factors and relevant variables have been identified. The highlight of the contribution is that NN is not a black box approach but shed light into the role played by different prognostic factors in the hazard of death.

Breast cancer patients: Delen [60] compared NNs, decision trees and logistic regression to predict survival period of breast cancer patients from a data set of 200,000 cases. The performance order using 10-fold CV is C5 (93.6%) > NN (91.2%) > logistic regression (89.2%). The sensitivity analysis of NN projects the prioritized (important) prognostic factors variable in data/model space. An integrated decision support system using logistic NN with automatic relevance determination is developed with a data base consisting of 2100 patients with breast cancer. Monte Carlo sampling of post-surgical intervention predicted survival of individual with 95% confidence interval.

Pain

The physiology, psychology and comprehension of pain are very complicated, but demand high price. The quality of not only personal life diminishes, but also a drastic down fall of professional output. Pombo et al. [2] reviewed positive benefits in pain management by machine learning and nature inspired algorithms in clinical decision support systems. They assist with complimentary/unique/ contrasting knowledge to clinical practitioners for rapid preliminary diagnosis for follow-up treatment and gold standard measures for exclusion and confirmation of even rare critical disorders/syndromes. The proper pain management and counseling avoids the pitfall of running in suffering, schizophrenia and psychic phenomenon of suicidal tendency.

Chart 31: Computer technologies impact in pain management systems

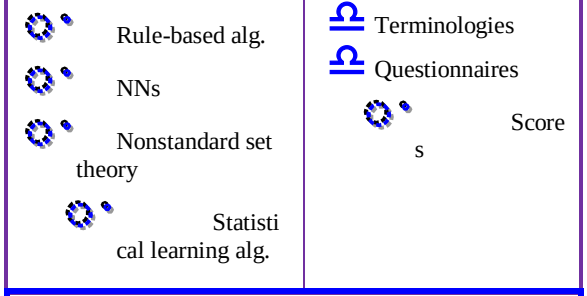


Chart 32: Microarray data for classification

# classes	Data description	Disease
2-class	Oligonucleotide data	Acute leukaemia
4-class	Complementary DNA dataset	small round blue cell tumours

From a search of electronic databases for CDSSs for pain showed 1245 citations during the period 1992 to 2011 and 32 publication data sets are analyzed for clusters denoting the computer technologies employed. This study showed that computer technologies alone are not determinant factors in improving systems' accuracy and clinical practice, although they have impact in development of patients (chart 31) symptoms based systems. The same criticism was there earlier in drug discovery with a slogan 'Is there a drug completely discovered by computer alone? This was retarded with a soft touch that 'Is there is drug that is discovered without use of computer at any stage during last half a century? The lesion is a single technology is not whole and soul, yet it is not even dispensable altogether.

11. Hospice and palliative care

Palliative care aimed at comfort and pain relief for terminal diseases. It has grown in India also recently.

12. Recent research outcome for medical treatment (MedTreat) paradigm

Brain computer interface

EEG based brain-computer-interface provides a new communication channel to monitor and treat brain disorders and old age problems.

Partin tables

The physician's choice of best treatment strategy for clinically localized prostate cancer case by case made use of Partin tables and their updates. The experience clearly showed non-linear and data driven techniques are indispensable to long cherished linear methods for over half a century. Further, knowledge extraction tools and self-adaptive systems are good companions in the tool-kit.

Nanotechnology

Fond et al. [251] reviewed the benefits of nanotechnology and products in the treatment of psychiatric ailments. The in vivo imaging, metabolome analysis and smart devices for diagnosis underwent renaissance with rapid growth of nanoscience. Yet, a word of caution is spelled out to probe further, as the proof of safety.

Nanorobots in nanomedicine

Santagati and Melodia [327] modeled generation, propagation and detection of opto-ultrasonic waves and their applications in biological tissues. The communications amongst nanorobots of size in the range of one to hundreds of nanometers are through intra-body opto-ultrasonic signals. Interconnected dense wireless nano-devices widened the scope of in-vivo monitoring of cellar processes enhancing diagnosis and adaptive drug-delivery in treating dreaded diseases.

Tele operated flexible endoscopes: Bell et al. [12] reported prospects of tele operated flexible endoscopes, an emerging technology, based on image-based tracking. NBI (narrow band illumination) with lumen-centered partitioning is considered as for vision-based pose estimation. It uses components now available in commercial gastrointestinal endoscopes. They give accurate feedback of motion of the tip of the endoscope. This system still awaits viability in clinical settings.

PET: Zhong et al. [35] employed SLP_NN to solve reaction-diffusion equations of real time soft tissue deformation. It is integrated with haptic feedback to simulate soft tissue deformation resulting in a haptic device. Soft tissue deformation modeling is still a challenging task in spite of the fact it is an important component in simulation of surgery for exploration research as well as pedagogic training.

Genes of significance

Tong and Schierz [27] reported a hybrid GA_MLP-NN to extract biologically and statistically significant genes from unpreprocessed microarray data (chart 32). The fitness function of GA is calculated from correct number of samples labelled by FF_NN. The weights of NN and fitness of GA are coevolved leading to selection of genes with high information. Muselli et al. [37] arrived at subsets of genes involved in a biological process with switching neural networks employing real and simulated gene expression datasets. NN assigns a relevance value to each gene and proceeds with recursive feature addition. A mathematical model with both biological and statistical plausibility is used to generate data.

Missing data imputation: The revolution in evolution of imputation of missing data in multi-variable records over the last forty years is exemplary in disciplines like drug discovery, prognosis, prediction of recurrence of a treated disease and environment. Missing data imputation is performed by statistical data machine learning techniques. Mean, hot-deck etc., belong to statistical category. MLP, SOM, k-NN are examples of machine learning methods. Jerez et al. [28] applied data driven (model free to start with) methods (chart 33) in predicting relapse of breast cancer. NN based imputation approach is superior to

that on statistical methods as was practiced in yester years. The breast cancer data set comprising of 3679 recurrence-survival information invasive breast cancer cases diagnosed in 32 hospitals in Spain. The prediction by NNs is better than list-wise deletion method.

Chart 33: Comparison of imputation methods for breast cancer relapse

Statistical	Database
Mean, hot-deck, multiple imputation, Machine learning MLP SOM KNN	3679 Patients Demographic, therapeutic 32 different hospitals Spanish Breast Cancer Research Group

Model	AUC of ROC-curve
MLP	0.0053
k-NN	0.0048
SOM	0.0071
NN {SOM>MLP} > k-NN	

Animal experiments

Chauveau et al. [339] performed animal experiments on mice using ciproxifan. In the case of sleep disorders, histamine receptor type 3 (H3) antagonists are gaining momentum as awakening drugs.

III. Pharma industry (13-18)

13. Pharmaceutical product development & quality control

The continual production of certified drugs involves quality control at each and every phase of production line [257]. There are no established theories to account for all the interactions between excipients and the drug. The relationship is complicated and non-linear in many factors. In yester years, empirical models based on correlation between the response and assumed causative variables were inevitable. Expert systems, fuzzy inference systems, data driven NNs and evolutionary algorithms/ programs, nature inspired swarm intelligence methods altogether changed the scenario. The statistical experimental designs, quantitative assay of active constituent in the formulation and the manufactures' adherence to the stipulated quality assurance measures of different batches have all increased accuracy/precision and robustness by NN paradigm. The chromatograms of samples from different manufacturers are modeled with ensemble NNs. Tetko [297] vary the number of NNs from 1 to 10,000 and final ensemble consists of 200 NNs.

Authentic and unauthentic drug samples

It is important to monitor whether a product marked is the same as that originally approved. NN is a trust worthy tool in pharmaceutical finger printing compared to other chemometric techniques. Anzanello et al. [238] applied a set of unsupervised and supervised models to sort out authentic and unauthentic samples among seized drugs (Cialis and Viagra). The Fourier transformed IR signals are further transformed in PC space and subsequently subjected to discriminant analysis (table 19). An ensemble of 200 NNs is used to compare L-tryptophan from six manufacturers [297]. MLP_NN was trained with BP/ superSAB using 253 chromatographic profiles. The variation in chromatographic profiles is due to differences in the production lots, HPLC columns and experimental design. The results (table 20) show that the chromatogram 2 belongs to manufacturer B as well as E, while others are unambiguous.

Table 19: Discrimination of authentic and unauthentic seized drugs

- FT-IR (Y)

Discriminating models

- *Supervised*
  - *kNN*
  - *SVM*
  - *Prob_NN*
  - *LDB*
- *Unsupervised*
  - *k-means*
  - *Fuzzy c-means*

Table 20 : Comparison of a pharmaceutical product from six manufacturers with NN-ensemble

Chromatogram	Manufacturer	probability
1	A	$< 10^{-6}$
2	B, E	>0.3
3	D	$< 10^{-8}$
4	E	$< 10^{-17}$

14. Experimental design and RSM

In the development of a pharmaceutical formulation, several influential design factors, process variables and responses are involved (table 21). Takayama [143] reported some of the responses are effectiveness, usefulness, stability and safety. The excipients, matrices, preservatives and other moieties are indispensable for ointments, capsules, syrups and even for many tablets. Further, the controlled/ sustained/ extended release of the drug involves a few more matrices. Quantitative prediction of performance of a formulation from basic physico-chemical properties of the drug and components is out of scope. Hence, the optimum values of process parameters, composition of ingredients, physico-chemical characteristics have been achieved through statistical experimental design instead of age old one variable at a time (OVAT) procedure. The optimum values are obtained from developing a multi-response multi-explanatory factor models and calculating the numerical values of the factors at the maximum of the response. The statistical experimental designs popular in pharmaceutical preparations are D-optimal/ uniform/ central composite design, its variants and hybrid ones with simplex method. The full quadratic or rarely polynomial models were in practice nearly over four decades and it is referred as response surface methodology (RSM). But, data driven NN models in RSM of experimentally designed pharmaceutical data revolutionized potential applications in pharmaceutical product development. The obvious reason is NNs discover non-linearities in the response surfaces missed by simpler nonlinear methods of yesteryears.

Table 21: ED and NN in optimization of formulations

ED	NF		Drug
Composite	2	Spherical	Transdermal drug
Composite	3	NL:2	Sustained matrix release matrix tablets
Simplex + Centroid design	4		Controlled release Chloropheniramine maleate
Face centered CCD	3	NL:3	Controlled bead formulation

Synergistic drug action: Pivetta et al. [377] reported NN model for experimentally designed combination of two (chart 34) or more drugs to look for synergistic drug action and increased inhibiting resistance to drug. The method is validated with success by experimentally preparing and testing the combination with highest synergistic effect from predictive model.

Chart 34: Binary mixtures of cisplatin in prediction of synergism of drugs

- [Cu(1,10-orthophenanthroline)2(H2O)](ClO4)2,)2
- Cu(1,10-orthophenanthroline)(H2O)2(ClO4)2
- [Cu(1,10-orthophenanthroline)2(imidazolidine-2-thione)](ClO4)

Response

- Human acute T-lymphoblastic leukemia cells

Dissolution of drug: Mendyk et al [257] put forward a neural model for ketoprofen for the dissolution from solid dispersions (table 22, table 23) and physical mixtures for development of formulations (table 24). NN modeling of RSM for the data gathered from statistically designed experiments has optimal percutaneous absorption as well as acceptable skin damage in the development of ketoprofen hydrogel [295].

Table 22 : Factors influencing ketoprofen solid dispersions [257]

Response > 1	
y: Expected % of dissolved ketoprofein at specified time in the input	
X : 6	
➢ Formulation of solid dispersion (SD) or physical mixture (PM)	➢ Cooling on ice or ambient temperature
➢ SD previously mixed or not	➢ % Amount of ketoprofen
➢ Method of preparation evaporation or melting	➢ Time of dissolution test
Model : MLP_NN: 7-3-2-1	

Table 22b: Transdermal ketoprofen hydrogel [142]

X : 2	**Response : 3**
➢ Amount of ethanol	🗁 rate of penetration (R_p)
➢ MET	🗁 Lag timeb(t)
	🗁 Total irritation score
NN ; Generalised distance function for optimization	

Table 23 : Transdermal ketoprofen hydrogel script

X : 4	**Response : 2**
➢ HEC	🗁 Release exponent
➢ HPC	🗁 time for 50% drug to be released
➢ HPMC	
➢ CMC	
H# : 8; Lr : 0.25; mom.: 0.9	

Table 24: Prediction of acrylic microspheres

X : 3	**Response : 2**
➢ Concentration of sucrose stearate (dispersing agent)	🗁 Particle size of microsphere
➢ Stirring rate of emulsion	🗁 Time at which 63.2% of drug is released
➢ Ratio of polymer	
Tr: 13 Te : 4 Software : Neuroshell easy predictor v(1.01)	

15. Controlled drug release systems

The design of controlled release drug delivery systems reached a matured state in this decade. The nanosomes, nanoparticle polymers, nanobubbles and nanoshells have significant role. The experimental variables are optimized to get the desired in vivo drug concentration profile in plasma with time. It is not only costly, but also impracticable to carry out the experiments in vivo. The alternative is to perform in vitro experiments, if the correlation between in vitro and in vivo processes is known. As these results are generally unavailable, data driven NNs come to rescue. The present day technology is to correlate in vitro release profiles with in vivo absorption trends. These are obtained by deconvoluting the desired in vivo plasma concentrations. The design of controlled release dosage formulations (table 25) with CAD/chem software based on % release of drug at ten different time intervals were studied. The formulation factors viz. molecular weight of drug, intrinsic dissolution rate, pKa, salt type, drug to polymer ratio and polymer hydration rate were correlated with release profile of the drug using enhanced delta back propagation as learning algorithm for NN with six hidden neurons.

Table 25a: Concentration release profile	
X : 10	**Response : 10**
➢ 10 formulation factors	🗁 Cumulative % of drug released at 10 different times
SLP ; H# : 9; Software : CAD/Chem software (v4.6)	

Table 25b: Prediction of physico-chemical	
X : 3 (Prediction)	**Response : 2**
➢ Water uptake	🗁 Composition of polymer
➢ Glass transition temperature	🗁 Moisture content
➢ Viscosity	
Software: CAD/Chem software (v5.0) pred_err : 0 to 8%	

Table 25c: Optimal composition of formulation	
X :10	**Response : 10**
Tablet variables	Cumulative % of drug at (ten) different time periods
➢ Moisture	
➢ Particle size	
➢ Hardness	
Formulation variables	
➢ Seven	
Software : CAD/Chem (v 4.6)	

Table 25d : Controlled drug release

- Sustained
- eXtended

- Considerable decrease in dosing frequency
- Improved patient compliance
- Reduced in vivo fluctuations from a maximum to a low concentration level
- Localized release of the drug
- Concentration is within desired range throughout the day →
- Reduced side effects

Prediction of properties of matrix materials in control drug release: The prediction of hydration characteristics, glass transition temperature, rheological characteristics of hydrophilic polymers with NN are reported. These materials are used in controlled release matrix tablets. The optimal pharmaceutical formulations predicted by NNs gave satisfactory release patterns of trapidil when tested in real laboratory experiments.

Uniform design in controlled drug release: Xu et al. [158] studied controlled drug of release rate of salvianolic acid B and that of the total salvianolic acid with NN employing uniform design (chart 35).

Chart 35: Experimental design of controlled porosity osmotic pump tablets (CPOPT) for salvianolic acid (SA)

Explanatory factors	Response
⤵ Drug ⤵ Osmotic pressure ⤵ Promoting agent rate ⤵ Coating ○ Content in solution ○ Coating weight	⤵ The linear correlation coefficient of the accumulative amount of drug release and the time of 12 h, r(Y1), ⤵ Sum of the absolute value between measured and projected values, Y2, 2 and 8 h Time at which 90% of the drug was dissolved
Models ⤵ ANN uniform design ⤵ Genetic programming (GP)	Inference : ANN projected the outputs better than the uniform design

D-optimal ExptDes for controlled release of nimodipine: Barmpalexis et al. [250] optimized compositions of constituents of controlled release floating tablet of nimodipine formulations using D-optimal experimental design and NN / GP models. Advanced instruments (differential scanning calorimetry, powder X-ray diffraction, FT-IR spectroscopy and polarized light microscopy) determined the physical state of dispersed drug in polymer matrix (chart 36). The concomitant operation of swelling and erosion of the polymer matrix results in controlled release of drug. Barmpalexis et al. [225] inferred that symbolic regression through GP with multiple populations is superior to NN in matrix release of % nimodipine from polymer bases (chart 37)

Chart 36: Effervescent controlled release floating nimodipine tablet formulations in polyethylene glycol solid dispersions

Optimum mixture proportions
- Polyethylene glycol
- Polyvinyl-pyrrolidone
- Hydroxypropyl methylcellulose
- Effervescent agents
- Drug
  - Nimodipine

Expt Design
- D-optimal design
- 25 experimental points

Response
- Drug release
- % release at 60 min
- Time at which the 90% of the drug was dissolved
- Floating properties
  - Tablet's floating strength
- Duration

Chart 37: optimization of a pharmaceutical zero-order release matrix tablet

- Amounts of polymers
  - PEG4000
  - PVP K30
  - HPMC K100
  - HPMC E50LV

Response
- Percentage
- % Nimodipine released
  - 2 and 8 h
  - Time at which 90% of the drug was dissolved

Objfn: min(euclidian distance between predicted and optimum release parameters)

Inference : GP >> ANN

Models
- Symbolic regression
- genetic programming (GP)
  - Single populations
  - Multiple populations

	Gp	Similarity factor
Multi-population		85.52
Single-population + extended function		84.47

Global optimum

%	
PEG = 9	PVP = 30
HPMC = 36	EFF = 11
Nimodipine = 14	

Controlled release of theophylline: Controse acts as a controlling agent in the release of theophylline from the tablet, while different starches accelerate the process. FF-NNs adequately explain the non-linear relationships between the explanatory (causal) factors and release (response) parameters. The limitation is that second order polynomial RSM showed relatively plane surfaces. It predicted negative values for explanatory factor values in the boundary regions. The prediction of release profiles of theophylline in controlled drug release tablets are nearer to the experimental ones. But, polynomial modeling of RSM leads to inaccurate/wrong conclusions. The controlled release of theophylline (Table 26a, 26b) prepared with controse using NN paradigm was optimized. The dissolution profiles [Table 26c] of theophylline in tablets containing microcrystalline cellulose and glyceryl monostearate using NEURAL program were predicted. NN model [Table 26d] was proposed to predict the release profile of sustained drug, diclofenac sodium in formulation. NN successfully resulted in optimum concentrations of OEBC and sum of DIA and PA for the simultaneous optimization of RP and TIS. Here also, full quadratic model failed. It is desirable to provide an option, if not replacement of polynomial models by NNs, as they have made a significant impact in pharmaceutical industry earlier.

Table 26a : **Statisitcal experimental design for Controlled release of theophyllline tablets**

		-1	1	-1.732	1.732	0
X1	Centrose	71	129	50	150	100
X2	Cornstarch	11	39	0	50	25
X3	Pressure	92	208	50	250	150

Table 26b: **Simultaneous optimization of controlled release theophylline tablets with controse**

X:3	**Response > 1**
➢ Amount of Controse	Rate constant in the fast release function and slow release fraction
➢ Cornstarch	
➢ Compression pressure	
Mixture of hydroxy propyl methyl cellulose with lactose and cornstarch	

Table 26c: Prediction of dissolution profiles of matrix controlled release of theophylline

X :4	Response > 1
➢ MCC	▱ % of drug released at each sampling point
➢ GMS	Neural program LOO-CV Tr: CG, SAA Similarity factor >60
➢ Time of sampling	
➢ Difference between the release rates of preceding two time points	

X: 2	Response: 2
DEBC	TIS
SIA + IPA	Rp
2nd order polynomial RSM Ketoprotein : HPE : HEC = 3:1:1 % NN : SA AIC	

Table 26d: **Optimization of dichlofenac sodium sustained release matrix**

X:4	Response > 1
➢ Conc of cetyl alcohol	% of drug released at each sampling time
➢ polyvinylpyrrolidone K30	
➢ Magnesium stearate	
➢ Sampling time	
H# : 12	

%	NN	Polynomial
OEBC	1.15	0.610
DEA	1.15	0.923
IPA	31.1	36.7

Prediction of release patterns: Güres et al. [270] predicted the release patterns and solubility of differently sized extrudates containing diprophylline, tristearin and polyethylene glycol by a hybrid algorithm of NN and genetic programming (GP). The constants of Weibull equation are estimated with GP programming and the results are close agreement with experimentally monitored results.

Optimum experimental conditions of polymer composition: Gubskaya et al. [359] developed optimum experimental conditions for the polymer compositions of sustained (controlled) delivery drug (voclosporin) system using RSM. Fifteen polymers compositions were selected outside design space and drug release profiles were predicted with NNs. The hydrogen bonding characteristics and thermodynamic parameters for model complexes of drug and polymer are inferred from molecular dynamics (MD) calculations. These results are basis to probe into interactions in drug-release system. Gubskaya et al. [359] further probed into NN and MD modeling of polymeric drug delivery systems. RSM was used to arrive at optimum polymer compositions of tyrosine-derived polycarbonates for controlled delivery of voclosporin. It is a potent drug candidate for ocular diseases.

Chart 38: Controlled release tablets of metoprolol tartrate

X	y
Formulation composition Compression force Tablet Tensile strength Porosity	Drug release trend Matrix ▪ Polyethylene oxide polymer and glyceryl palmitostearate Drugs ▪ Diclofenac sodium and caffeine
Method	Task
Monte Carlo simulations or genetic algorithms optimizer	Drug release
Decision trees were constructed following.	Discretization of Data Knowledge discovery
Elman_NN	Drug release profile
Inference : Elman_NN >> MLP_NN	

Dissolution profiles: Petrović et al. [269] proposed Elman_NN to predict dissolution profiles of controlled release of tablets with hydrophilic and lipid matrix (chart 38)

Drug release profile: The co-axial electro spinning process is used to fabricate core-shell fibers of tetracycline hydrochloride. It is encapsulated by poly(L-lactide-co-glycolide) (PLGA) or polycaprolactone (PCL) in the sustained release drug. Maleki et al. [230] predicted Peppas constants (chart 39) with NN model to probe into drug release profile of this nano-fibrous pharmaceutical preparation. Akbar et al. [214] reported robust predictive NN models for release of drug from arabinoxylan matrix using molecular descriptors calculated from quantum chemical geometry optimization of sixteen drug molecules (chart 40).

Chart 39: prediction of Peppas constants for sustained release drugs

Objective
Drug release profile of nanofibrous drugs

NN model
- Input
  - shell polymers
    - Density
  - Hydrophilicity
  - Core and shell phases
    - Feed rates
    - concentrations
  - TCH Contribution
  - Electrical field
- Output
  - Peppas constants

Chart 40: NN prediction of release of drug from arabinoxylan matrix using molecular descriptors from optimized geometry by ab initio quantum chemical computations

structure optimization
neural networks

Mol Descriptors	Pruning methods
16 drugs → *ab initio* → *Optimized geometry*	
1685 Quantum mechanical, physico-chemical and structural descriptors	Heuristic rules Forward selection Unsupervised -------→
Drug matrix	Arabinoxylan matrix
ExplFac softness, lipophilicity, unsaturation, atomic polarization, cyclic topology geometry of the molecules	Release = Fn(ExplFac)
	Models
	MLR NN LOO-CV y-scrambling

Chart 41: Controlled release tablets of metoprolol tartrate

X	y
[Sucrose ester] Tablet volume tensile strength Porosity	HLB SOM_NN MLP_NN

Controlled release of water soluble drugs: Metoprolol tartrate is a highly water soluble drug. It's controlled release as direct compacted matrix tablets form was developed with sucrose esters (SEs). The tablet porosity at different values (0 to 16) of hydrophilic–lipophilic balance (HLB) increases the complexity of the system. The inter relation among explanatory factors are visualized in 3D- surfaces through SOM_NN. Chansanroj et al. [245] proposed a predictive model with MLP_NN (chart 41).

Chart 42: NN models for particle size and drug loading rates in controlled risperidone (drug) release formulations

Drug	NIR (Y)
Risperidone	
Drug carrier	
Poly(d,l-lactide-co-glycolide) microspheres	*Models- Calibration*
Particle size and drug loading rate	*Soft + Data driven*
Laser diffraction particle Size analyzer	*GA-NN*
HPLC	*PCA-NN*
	PLS-NN

Task	Models
Outlier detection Selection of calibration set	Monte Carlo algorithm + partial least squares
Calibration	Moving window PLS RBF_NN

Particle size and drug loading rates in controlled release tablets: Microspheres have been developed as drug carriers in controlled drug delivery systems for years. Song et al. [266] modeled particle size and drug loading rate of risperidone with poly(d,l-lactide-co-glycolide) as drug carrier with NN (chart 42). The variable space reduction is performed with PCA, PLS etc. The high correlation (0.935) for calibration samples and the accuracy for 15 samples outside training lot testifies the use of this approach in controlled drug release calibration.

16. Calibration of drugs

The accurate and precise estimation of the active constituent of a drug in the presence of excipients and preservatives is vital. British Pharmacopoeia and American pharmacopoeia update the assay procedures from time to time. The calibration involves developing a model for the response with the change in concentration of the analyte. Statistical experimental design is employed for choosing the concentrations of a sample in elite laboratories. The multi-component/ multi-variate analysis results in linear or non-linear models and now, NNs have been in extensive use.

Ni et al [188] showed that NN and PLS resolve the mixture of acetaminophen and phenobarbital (table 27) over a wide concentration ratios in synthetic mixtures (table 27a). The application to analgesic tablets using standard addition procedure indicates that PC-NN excels simple NN as well as a sought after PLS in multi-component and multi-response calibration. Dou et al [144] compared NN and PLS for the assay of bivalent mixtures containing Paracetamol and caffeine (table 28) using first derivative NIR spectroscopic data. In the simultaneous determination of vitamin K and 1, 4-napthaquinone (table 29), GA-PLS is better than PLS, ITTFA and PC-NN [180]. It is better due to covariance information of explanatory variables vs. absorbance in PLS, as well as selection of wavelengths by GA. PLS-NN is indispensable when absorbance is a non-linear function of PLSCs.

Table 27a: prediction of synthetic mixtures

Acetaminophen				Phenobarbital			
Expt	PC-NN	NN	PLS	Expt	PC-NN	NN	PLS
2.0	**2.01**	2.05	1.85	15.0	**14.73**	14.66	15.37
4.00	**4.06**	4.09	3.84	13.0	**12.83**	12.78	13.35
6.	**6.05**	6.1	.87	11.0	**10.49**	10.38	11.52
17.00	**16.39**	16.39	16.36	0.00	**-0.04**	-0.43	-0.01

Table 27b: prediction of drugs
Acetamino Phen and Pheno barbital

Tablet	Acetamino Phen (mg/g)		Pheno barbital (mg/g)	
	Expt.	PC-NN	Expt.	PC-NN
Analgic - 1	24.8	25.4	55.9	56.4
Analgic -2	277.2	275.0	116.4	117.1
Acetamino Phen	1521.8	1519.2	1251.4	1263.6

Table 28: Multi-component Multi-response model using first derivative spectra

Component	%RSE			
	Training		Testing	
	NN	PLS	NN	PLS
Paracetamol	1.285	1.309	1.645	1.701
Caffeine	2.932	3.127	3.038	3.407

Table 29a: Calibration and prediction of 1,4-naphthoquinone and Vitamin K3

1,4-naphthoquinone ($\mu g\ ml^{-1}$)			Vitamin K3 ($\mu g\ ml^{-1}$)	
Real	NN_predicted		Real	NN_predicted
2.50	2.29		1.00	1.28
5.0	5.29		8.00	7.98
6.0	6.05		10.0	10.58
3.00	3.16		16.00	15.73

Table 29b: Comparison of RMSEPs for different methods

Compound	NN	PLS	GA-PLS	ITTFA
1,4-naphthoquinone	7.44	11.45	5.84	12.94
Vitamin K3	4.55	7.96	3.35	6.71

Chart 43: Muli-component calibration of drugs spiked in food materials

Explanatory factors
- Drugs
  - Levofloxacin
  - Gatifloxacin
  - omefloxacin

Models
- CLS
- PLS
- PCR
- RBF_NN
- Best model
- PCR (RPE: 7.71%)

Insturment
- Differential pulse stripping voltammetry (DPSV)
- Exptal design – Opt conditions
- Deposition time : 80 s
- deposition potential : −1250 mv
- Scan rate : 25 mV/s

Detection limits	
Drug	ng/mL
Levofloxacin,	2.38
Gatifloxacin	3.20 and
Lomefloxacin,	1.60

- Linear range
- 0.010–0.080 µg/mL

Spiked drugs: Zhong et al. [227] estimated spiked drugs simultaneously in food materials by soft modeling (chart 43), data driven techniques using experimental design for optimum operating conditions adapting a comprehensive chemometric multi-component calibration. The antibacterial drugs are adsorbed on a hanging mercury dropping electrode and then reduced by DPSV in Britton–Robinson buffer (pH 7.96).

Ternary mixtures

Darwish et al. [375] performed a systematic multi-component calibration model for ternary mixtures of drugs viz. Amlodipine (AML), Valsartan (VAL) and Hydrochlorothiazide (HCT) (chart 44). The statistical experimental design is used to for variation of concentration of drugs in the mixture, PCA to orthogonalize the correlated variables, GA for the selection of optimum number of variables and soft models (PLS) and NN as a data driven calibration approach. The standard addition procedure is employed to validate the procedure for pharmaceutical preparations.

Chart 44: Hybrid NN model for multi-component calibration models

Ternary mixture of drugs (X)
- Amlodipine
- Valsartan
- Hydrochlorothiazide

UV response (Y)

Experimental Design
- 3- drugs (factors)- at- 5- conc. (level)
- 25 mixtures
- Different ratios of drugs
- Calib.Samples: 15
- Test.Samples : 10

Pre-Processing	
Dimension reduction of correlated variables	PCA
variable selection	GA

Models- Calibration
- *Soft*
  - *PLS-1, GA-PLS*
- *Data driven*
  - *ANN, GA-ANN*
  - *PCA-ANN*

Quaternary mixture

Elkhoudary et al. [374] estimated concentrations of quaternary mixture of pharmaceutical preparations containing the drug, metronidazole with NNs and variable selection by PC, PLS and GA from UV spectral analysis (chart 45).

Chart 45: Four component calibration models

4-componet mixture of drugs (X)

- Metronidazole
- Spiramycin (SPY),
- Diloxanide (DIX)
- Cliquinol (CLQ)

UV response (y)

Models- Calibration

- *Soft + Data driven*
- *GA-NN*
- *PCA-NN*
- *PLS-NN*

Chart 46: Goals of virtual library

- Identifying a small subset of virtual space with best fit design
- Developing a library around a lead
- Selecting compounds with drug like characteristics and in conformity with ADMET profiles

17. Pharmaco kinetics (PK) and Pharmacodynamics (PD)

It is suggested that NN is a useful analytical tool for pharmaco kinetic data analysis [159]. The failure of a compound which was initially selected for drug is due to solubility, pharmaco kinetics and toxic liabilities and virtual libraries (chart 46). It is emphasized NNs are superior computational techniques over conventional model independent PK/PD approaches. The total clearance and distribution volumes are crucial pharmaco-kinetic (PK) factors in humans. An NN model was developed with physico-chemical properties of the drugs and PK derived information on animal. Hussain et.al. in early 1990s, made a feasibility study of prediction of the human PK parameters from animal data. Based on the ratio of concentrations of barbituric acids between tissue and unbound plasma of rat, lipophilicity of the compounds was successfully predicted.

18. Performance

The NNs in the beginning were used for emulating the Boolean functions, storage/retrieval of binary strings and association between abbreviations and acronyms. Later, NNs were competitive to retrieve the correct sequence from distorted/corrupted input. Here, the performance was judged based on the crisp logic. After 1980s, pattern recognition and classification including pin code, signatures, alphabets etc., were tackled. Here, multitudes of answers were a reality rather than an exception. The degraded performance was the start to probe more into the task and arrive at a better solution. The correlation coefficient between two random variables gives the measure of the linear relationship between them [389].

Sensitivity analysis: The influence of input factors on the response is crucial in pruning uninfluential factors is the primary objective of sensitivity analysis (Formulae **1** and Formulae **2)** popular in statistical paradigm. Mendyk [257] reported the influence of input variables on the dissolution process of ketoprofen from solid dispersions. The output for a small change of one input variable within the best range is calculated. The ratio of the variation in output to the change in input variable is called sensitivity coefficient. The greater the value of the change in output, the more is the influence of ith variable (Alg. 4) on the performance of the model [389]. A large magnitude of the sensitivity coefficient reflects a high influence on the output.

Formulae 1: Diversity index and illustration

$$MSE_i = \frac{1}{NP} * \sum_{j=1}^{NP} ynn_j - ynnid_j \quad ^2$$

Ynn_i	:	Output with all input variables
$Ynnid_j$	:	Output when ith variable is deleted
NP	:	Number of patterns
MSE_i	:	Mean square error when ith variable is deleted

$$Num = \frac{\sum_{i=1}^{nsol} \| X_i - X_{best} \|}{nsol}$$

$$De = \| X_{best} - X_{worst} \|$$

Xi	:	Vector representing the ith solution
Xbest	:	X coordinates for best objfnValue
Xmin	:	Lower bound of X
Xmax	:	Upper bound of X

Formulae 2: Information gain

$$Inf\_gain = \sum_{j=1}^{Nclass} \left(\frac{l_j}{NP} * \log \frac{l_j}{nl} + \frac{r_j}{NP} * \log \frac{r_j}{nr} \right) - \sum_{j=1}^{Nclass} \left(\frac{l_j + r_j}{np} * \log \frac{l_j + r_j}{nl} \right)$$

Nclass	:	Total number of classes
NP	:	Total number of expression values
n_l	:	Total number of values left partition
n_r	:	Total number of values right partition
l_j	:	Number of values belonging to class i in the left partition
r_j	:	Number of values belonging to class i in the right partition

$$AIC = NP * \log SSR + 2 * nwts$$

SSR	:	Sum of squares of residuals
nwts	:	Number of weights in NN

$$Diff\_fact = \left\{ \frac{\sum_{j=1}^{Nclass} |R_i - T_i|}{\sum_{j=1}^{Nclass} R_i} \right\} * 100$$

R_i	:	%drug released from reference formation at time t
T_i	:	%drug released from formulation
W_i		Optimal weight factor

$$Similar\_fact = 50*\log\left\{\left[1+\frac{1}{n}*\sum_{i=1}^{NP} wi*\ R_i - T_i\ ^2\right]^{-0.5}\right\}*100$$

$$err\_app = \left(\frac{n_1}{n}\right)*ei + \left(\frac{n_c}{n}\right)*e_c + |e_1 - e_c|$$

$$\deg\_app = \left(\frac{c}{e_a}\right)$$

e_1	:	Relative standard error of training set
e_i	:	Relative standard error of monitoring set
n_l		Number of samples in training
N_c		Number of samples in monitoring
c		constant

If deg_app is large
Then more models approach real nature

$$\text{Rate\_corr\_pred} = \frac{TP+TN}{TP+TN+FP+FN}$$

sensitivity

$$\text{Rate\_corr\_pred\_all\_pos} = \frac{TP}{TP+FN}$$

Specificity

$$\text{Rate\_corr\_neg\_pred\_all\_}neg = \frac{TN}{TN+FP}$$

e_1	:	Relative standard error of training set
TP	:	True (correctly) classified as positive
TN	:	True (correctly) classified as negative
FP	:	False (incorrectly) classified as positive
FN	:	False (incorrectly) classified as negative

Alg. 4: Sensitivity with PCA [389]

```
Calculate PCs for the input matrix X
Train NN using PCs as input
For i = 1 to npc
        Perform sensitivity analysis
        Importance of x variables
        assessed from loading
        coefficients
End for
```

The selection of explanatory factors is performed with either or both supervised and unsupervised machine-learning algorithms. The order of addition of variables into the model also plays a critical role. The robust procedures include genetic-/ simulated annealing (SA) algorithms etc. Xiao [149] employed SA coupled with supervised SOM for prediction models for classification. The weight matrix of the refined NN is a good indicator to prune non-influential explanatory factors. But, other methods like forward selection, backward elimination and GA play a vital role. GA searches the solution space through the simulated evolution of random candidates following cross over and mutation. It becomes a matter of choice or voting with conscience in selecting the variables.

IV. Drug Discovery and Design (19-24)

The classical modus operandi of drug discovery was isolation of active ingredient/ partial or total synthesis, testing for biological activity through microbial studies and reinvestigating the rare hit compounds. The concerted efforts of pharmaceutical industry are to shorten the time period, improving the efficacy and success rate of the hits. Combinatorial synthesis and high- throughput screening (HTS) in the experimental front and virtual library of target drugs, computational quantum chemistry and quantitative structure biological response (SBiolR) models within the realm of existing theoretical postulates drastically reduced the gestation period of drug discovery. The earlier random search in limited chemical space with an average hit rate of less than 1% in [155] is now termed as irrational design (ID). In ligand based design, quantum chemical/theoretical models and structure activity relationships (SActivR) render the process more efficient on scientific ground rather than blindfold hit and trial approach [149], a first step moving away from this hurdle. Rational drug design (RDD) evolved through the culmination of synthetic procedures, heuristics, molecular docking, pharmaco kinetic principles, artificial intelligent tools etc. Karplus of Harward University adopted the bottom up approach where in computational techniques were used to understand the interaction of small molecules with protein. Lipinski rule of five is simple, well-accepted and considered as the best predictive method from the analysis of 2245 drugs from world drug index. However, it depends on the chemical structure to recognize the drug likeliness. Another limitation is that this rule could not discriminate compounds in MACCS-II drug data report (MDDR). Later, chemical space filter employing molecular saturation related descriptors and pharmacophore factors are used to analyse MDDR, CMC ACD and CNPP. Newer measures of similarity, dissimilarity and diversity of clusters of compounds, database of most probable fragments/functional groups, in-silico/in-vitro/in-vivo investigation of prospecting target/target like molecules have become indispensable. The promising molecules are tested on animals and finally go for clinical trials. Yuan et al. [281] brought out a new version (2.0) of LigBuilder (Chart 47) useful for the de novo drug design.

Failures in different phases of acceptance of bioactive molecule to a marked drug: At the core, discovery of a drug or in general preparation of a material with desired characteristics is an inverse problem. The solution is difficult and multiple answers are obtained in spite of using constrained framework. There is a considerable progress in tackling inverse problems and the information/knowledge generated even in other disciplines like information science brought renaissance in probing deep into the true/real process. Reutlinger and Schneideret al. [305] reviewed machine learning techniques and AI methods in extracting influential factors in medicinal chemistry phase of rational drug discovery.

Chart 47: Features of LigBuilder (v 2.0)

- Analysis of synthesis accessibility for designed compounds
- Cavity detection of the positions and shapes of the binding sites on the surface of a given protein structure
- Estimation of drugability
- Heuristic design to best fit the detected cavities
- **Drug**-like and privileged fragments option to template ligands using internal and external ADME(Tox) filter
- Drug-like moieties

The prediction of activity consists of making use of hither to available databases developing a database of structural features of known active compounds, arriving at a good similarity measure, classifying active and inactive moieties and assessing expected biological response with a SAR model [147]. A few typical reasons for failure of potential drug candidates reaching the patients are toxicity, lack of efficacy and pharmaco kinetic data. The properties like poor solubility; permeability, metabolic and excretion profile, adverse reactions influence of promiscuity are responsible for rejection in clinical development.

The failure of many compounds as drugs at the stage of clinical trials is attributed to the lack of pharmaco kinetic and absorption-distribution-metabolism-excretion-toxicity (ADME(Tox)) data [147]. In silico prediction is an alternate to reduce the large rejection rate and concentrating on most promising

compounds with drug likeliness. The diversity/similarity of chemical space of large number of molecules in virtual library is a preamble to comprehend pharmaceutical active region leading to therapeutic action. The impact of NNs, ligand-based selection, SXR landscape is detailed.

19. Drug likeliness

A good pharmacological activity of a compound is a necessity for further study as a prospective drug, but it is not a sufficient condition. The first phase is screening molecules against a disease target or particular pathogen followed by lead optimization for identified hits is a combination of laboratory and computational pursuit. Ramamoorti et al. reemphasized that time period for a new drug to be available as prescribed drug for patients is around fifteen years and costing more than a billion USD. A point of concern is more than 80% of lead molecules entering clinical trials slip off without reaching the FDA standards. The cumulative experiences of drug industry and academia have brought out drug likeliness indices to choose a lead compound and also to eliminate the clusters of molecules based antimodel (394b) for further study. A host of other physico chemical (stability/solubility), biochemical (bio-availability/ADMET) and non-toxicity parameters are a few typical measures of drug likeliness and its classification is reviewed extensively. The approach of drug likeliness is a result of screening of large number of compounds synthesized and from those in the virtual library, awaiting experimental preparation. Walters opines the molecules containing functional groups and/or with physical properties similar to the majority of the drugs is a measure of drug likeliness. The passage of oral drugs through gastrointestinal tract (GI), absorption in the intestine, BBB penetration, stability of metabolites and reaching the target are bioprocesses studied from pharmaco kinetic and pharmaco dynamic perspectives. The interactions of the drug with protein, DNA and biomolecules at the site are multitude of complicated processes ranging from covalent/hydrogen bond to hand shake and dispersive interactions. Some of the pragmatic approaches include functional group filters, evaluation of chemical space etc. The chances of success increase by eliminating unwanted molecules and picking up those with drug like moieties.

NN models for drug likeliness: Neural networks discriminate drug like molecules from non-drugs using 1D-, 2D-, pharmacophore /topological and molecular descriptors [154]. It is reported that NN is an efficient drug likeliness filter and useful to develop both focused and diverse libraries. Takaoka [147] modeled the drug likeliness score data from a panel of expert chemists with feed forward NN using BP training algorithm. In this study, six 2-D molecular topological descriptors are used and the classification success was around 73 to 76%. Retrospection revealed that the individual human experts have higher variability in assigning the drug likeliness score for the same/similar structures. Wan and Harrington studied 30,000 drug like compounds from 19 distinct synthetic libraries. Fatemi et al. [181] predicted bio concentration factor for 53 aromatic molecules based on 132 electronic/topological descriptors. GA and stepwise regression were used to prune molecular descriptor space (table 30) and the NN results excel those of MLR (table 31). The formation of large metal mesh of tin-organic complexes are good drug-like compounds in breast and colon cancer treatment [265].

$$1\,petabyte = 1Kterabytes\ or\ 2^{50}\,bytes\ or\ one\,quadrillion\ \ 1{,}125{,}899{,}906{,}842{,}624 \cong (1{,}000{,}000{,}000{,}000{,}000)\,bytes$$

Table 30 : Variables selected for prediction of bio-concentration factor

Stepwise-MLR	GA -MLR
Dipole moment	Dipole moment
Moment of inertia	Moment of inertia- C component
LUMO	Path-one connectivity index

Table 31: Comparison predicted bio-concentration factor with NN and MLR [181]

%	Stepwise-NN	GA-NN	Model	
			NN Architecture	
			I#-H#-O#	5-3-1

Electron density on most positive atom	Path-four connectivity index
Molecular mass	Molecular surface area

SEC	0.432	**0.259**	TF	sigmoid
SEP	0.573	**0.398**	Lr rate-bias	0.6
			Lr rate-weight	1.0
			Momentum	1.0

Drug target: Cytosolic phospholipase A2α is in arachidonate pathway and thus a good drug target. Indole derivatives inhibit the activity and were attributed to global charge transfers, geometrical distance distribution and type of linking of carbon atom to benzyl sulfonamide. Lu et al. [222] reported the performance of SVM was better than NN and PLS models (table 32).

Table 32: SActivR models of indole derivatives with molecular descriptors

Molecular descriptors	Pruning model	Select descriptors
1777 MolDesc (X) ▶ Topological charge index ▶ Sum of E-State of atom type ▶ Atomic ⌗Sanderson ALOGP ⌗Charge ⌗Polarizability	MLR --------→	5
49 indole derivatives SActivR_model SVM > NN > PLS		

Ligand (drug) interaction with biological site: In a biological system, both ligand (drug) and the target (biological site) are both flexible. They tend to alter their conformations and mode of binding to accommodate the partner. Thus, the energy surfaces of the interaction are multi-dimensional, complicated with several extrema/ flat surfaces. This makes the detection of biologically relevant conformer/interaction very difficult. Molecular mechanics, molecular dynamics and quantum chemistry are employed to study steric, electronic and hydrophobic interactions. Dipole-dipole/ dispersion forces, stacking interactions and H-bonding are important in the ligand-target interaction. Their magnitude is small compared to the covalent or electrostatic energy contribution. But, due to a very large number of them, its impact for biological interactions becomes significant. Yet, a complete study from first principles is impossible both from the existing scientific framework and computational time with the available hardware [148].

20. Virtual library & Virtual screening

The experiments with predicted set of compounds not yet synthesized showed promising results. It is not even an exotic brain wave to dream of synthesizing and measuring large number of properties [140] of compounds in today's chemical space. Instead of working with a handful compounds off the shelf, a new era of virtual libraries is on. It is a versatile, rapid and rational tool to explore thousands to millions of compounds. KINASE and GPCR targeted libraries were designed using NN. The large number of molecular descriptors proposed during the last three decades or a subset of them are instrumental in restricting the physicochemical search space, which changed the facet of early pre drug discovery paradigm. The new in silico paradigm and the choice of the compounds by combinatorial synthesis is based on structural features related to increased activity, selectivity, acceptable ADMET profile etc. Thus, the design of virtual library has become an integral part of drug discovery [147] with the diverse objectives. If 10^5 compounds are enumerated per second, three months of CPU processing time for 10^{12} compounds is required and this rate is possible only with 1D- and 2D- molecular descriptors. But, a knowledge of 3D-structure of receptor, conformational sampling, choice of scoring function, apart from a set of screened compounds result in a sure drug like compound. Virtual libraries of millions of compounds are common and it is now easy to think of a database with trillion compounds. In fact, it is a beneficial exercise to predict typical properties before using a screening library or attempting synthesis.

Virtual screening is to identify chemical compounds (in a database) with required functional groups/moieties and sorting them with increasing probability of biological activity. The highest ranked compounds are likely to exhibit the activity of the desired drug/medicine/lead/drug like moiety. Using this as the locus, prospecting hits are built up or synthesized for testing on animals, which constitutes the prime stage of the lead-discovery task. But, HTS is still expensive. This hampered the approval of new compounds for drugs. The computational filtering is crucial in combinatorial chemistry where billions of compounds can be generated from common reagents. NNs improved the quality and diversity of virtual screening. The data driven predictive modeling with intelligent computational models of nature mimics (E-man) have been unequivocally yielded reliable outcome.

21. Biochemistry and metabolism

Passage of drugs/molecules in the human body

The passive absorption and/or transfer of medicines/ small toxic molecules in the human body is complicated (chart 48), but this information is of primary concern to probe into drug action and side effects at molecular level. Further this knowledge is certainly required to implement nanotechnology and genomics in personalized medicine. Yet, it is difficult to probe even with current analytical and pharmaceutical technologies. Kouskoura et al. [311] modeled RP-HPLC profiles of 113 drugs/ analytes with molecular descriptors using PLS and NNs. The passage of drug in human body is modeled with correlation of descriptors with retention time of analytes eluted from C4 column with an aqueous phase. NNs predicted the behavior of a new drug in human body with high reliability.

Chart 48: Molecules into human body

- Food/water/air
- Pollutants
- Pathogens, viruses
- Mode of drugs administration for treatment
- Tobacco, beverages, drug abuse …

Drug concentration profile

The concentration of the drug in the blood stream is to be maintained to avoid risk in the case of patients with hypertension, diabetes etc. The passage of psychiatric drugs through blood brain barrier (BBB) is essential for the active transport while all non-psychiatric drugs and their metabolites should not cross the barrier. The drugs used by HIV patents pass to the infants through breast milk. The mechanisms are multifarious and thus understanding from first principles is not possible. Monitoring metal ions discriminates between cancerous patients and healthy individuals, but metabolism is not simple. The mechanistic approach in drug delivery systems, metabolism of a drug partitioning through BBB, classification of substrates and non-substrates are intricate. The mechanism of reversible inhibition of compounds on the enzyme H, K-Atpase is not completely elucidated and structure activity relationship (SActR) is a viable method to choose active compounds. The quantitative relationship between causal factors and response in vivo are multifaceted and non-linear. NNs are appropriate, as they do not involve any implicit assumptions. The goals of in vivo toxicity [183] are to find answers to queries viz. Is the drug toxic? Which organ is affected and to what extent? The next phase is to extrapolate the results to humans with an ultimate target of modification of the structure of the drugs. Tolle et al. [234] used SLP with 7-30-1 architecture to model the concentration of tobramycin in a drug to repress infectious deceases of the blood.

Molecular descriptors

- Physic-chemical properties
- Mobile phase mixture in different proportions
- Analytes
- Structural characteristics molecules

Residual drug analysis by IR-reflection absorption spectra. Infrared-reflection absorption spectroscopy (IR-RAS) [300] along PLS with different weighting schemes is used for rapid estimation of residual drug amounts without sampling techniques (table 33). The higher value of weight is adapted to sample nearer to query and it is better than locally weighted PLS scheme.

Table 33: IR-RAS estimation of drugs with PLS

Compound	RMSEP	
	PLS	LW-PLS
Ibuprofen	x+36	x+14
Magnesium stearate	y+39	y+24

NONMEM software: It is an intelligent tool of clinicians and industry standard taking into account of nonlinear mixed models practiced in pharmacokinetic and pharmacodynamic studies. NONMEM is implemented under UNIX OS. It is used to administer drugs to patients and also in analyzing the clinical data. The what-if-analysis interface provides answers to the potential blood concentration level of the drug in a patient's blood stream and drug application data. The variables are age, weight, illness etc. of the patient, interval of dose and initial (peak) and second (trough) concentration in the blood sample. It is used for (hematologic/oncologic/ disorder) cystic fibrosis. The peak and trough concentrations predicted with (8-23-25) SLP-NN trained using BP algorithm was better than NONMEM software. The prediction of drug (tobramycin) concentration in the blood for a data set with 622 points was superior with NNs compared to NONMEM. The study is centered on diagnosis of cystic fibrosis and hematologic-oncologic disorder. The concentration levels of tobramycin in blood plasma of pediatric patients were predicted by NNs and compared with the figures of industrial standard NONEM software.

Chart 49: Life cycle of malaria parasite

Life cycle	of Plasmodium parasite within its human host
	sporozoite form of malaria parasite enters human host
	Stage 1: liver-stage Migrates to the liver Matures into schizonts within the hepatocytes These schizonts burst -- release merozoites Merozoites infect circulating erythrocytes blood-stage of the malaria
	Stage 2: blood-stage
	cycle of asexual replication
	Within the erythrocytes, the merozoites undergo asexual replication, Merozoites transforming first into trophozoites → schizonts. Blood-stage schizonts burst → releasing additional merozoites into the bloodstream, These additional merozoites subsequently infect additional erythrocytes A small percentage of the merozoites will instead mature into gametocytes within the erythrocytes.
	continues
Completed	when the gametocyte-infected erythrocyte is ingested by a female mosquito during a bloodmeal

Drug metabolism and metabolites

In order to understand the fate of a compound in the human body, experimental as well as theoretical studies of solubility, permeability, stability etc., are performed. In this context, NNs play a vital role [147]. The metabolism of a drug of any form viz. oral, intravenous, dermal is not simple and the modeling and prediction are at an infant stage. The success of phase II metabolic study and their toxicological effects are pre requisite for the approval of the drugs. All these investigations are carried out experimentally and with theoretical calculations. Five models have more than 80% predictive accuracy and the remaining ones with >60% prediction. Winkler [148] states it to be the first report in using PR techniques to discriminate substrates and non-substrates of Phase-II human drug metabolizing enzymes. The modeling of phase-II metabolic process of glucuronidation with PLS-discriminant analysis, Bayesian regression NNs and SVM was performed. The objective was to classify substrates and non-substrates of 12-iso forms of human UDP-glucuronosyl transferase (UGT). It is an enzyme super family involved in the metabolism of drugs, non-drugs, xenobiotics and endogenous compounds. Here, 2D-descriptors were used which reflect on bond making and bond breaking processes. The objective of this study was classification rather than regression.

Life cycle of Plasmodium parasite within its human host: The entrance of malaria parasite into human being and its life cycle is depicted in chart 49.

NMR with quadrupolar Nuclei: The nitrogen plays a dominant role in biological, pharmaceutical and organic materials. Although ^{14}N is quadrupolar (I = 1) and 99.6% abundant isotope occurring naturally, earlier studies were only around ^{15}N (0.36%) due to then developed technology and methods. The magic-angle spinning (MAS) methods now available exploit the transfer of magnetization between ^{14}N and ^{1}H or ^{13}C with a half nucleus spin. This results in line shapes due second and third-order quadrupolar interactions. This probe outputs ^{14}N quadrupolar couplings, C−N internuclear distances/ dynamics in pharmaceutical compounds/ amino acids and small peptides (chart 50). The future is exciting eye to see beyond todays' intelligent and smart electronic eyes.

Chart 50: Applications of NMR of quadrupolar nuclei

Quadrupolar nuclei	Application fields
^{2}H, $^{6/7}Li$, ^{11}B,	Chemistry, physics, biology, materials
^{14}N, ^{17}O, ^{23}Na, ^{25}Mg	Science, and geology, functional materials ceramics, glasses and clays, polymers
^{27}Al, ^{35}Cl, ^{39}K,	Pharmaceuticals and biomaterials, energy materials, compounds
^{59}Co, $^{69/71}Ga$, ^{93}Nb	

MAS	Magic-angle spinning
DAS	Dynamic angle spinning
DOR	Double rotation
MQ_ MAS	Multiplequantum MAS
DNP	Dynamic nuclear polarization
AIRSS	Ab initio random structure searching

In-vivo and in-vitro procedures: The measurement of the fraction of the drug transported into the brain is the basis of all in-vivo methods. It is implemented by the direct determination of general methods like brain-plasma ratio ($log\ BB$) or permeability surface area product ($log\ P_s$). Its disadvantages are and low throughput laborious procedures. In in-vitro methods, the brain micro vessels are isolated [278] and seeded in the culture medium, circumventing the above difficulty. This results in the growth of endothelical cells to form monolayers suitable for experimental examination. The BBB partitioning permeability thus involves complex biological processes and it is difficult to model from first principles and even the available models are scarce. In 1988, Young et al. studied the influential physicochemical parameters for the brain penetration using MLR. The data obtained from different experimental protocols on BBB permeability is limited, uncertain and contradictory. It is also influenced by plasma/protein binding, active efflux from CNS by transporters such as P-glycoprotein and metabolism. Several others reported MLR models for the passive transport of few (less than 50) compounds. Recently, PCA and PLS models using molecular descriptors were also proposed. Thus, MLR and other linear methods are inadequate as the relationship between BBB penetration of compounds and their physical properties are complex and non-linear [278].

Prediction of MHC-class II binding peptides: Major histocompatibility complexes (MHCs) are cell surface glyco proteins present on antigen-presenting cells. MHCs and proteins play a crucial role in initiating and regulating immune response. Winkler [148] modeled 9-mer-peptide motifs with regularized Bayesian NNs. The assumption of the model is MHC class II binding activity depends only on the highest ranked embedded 9-mer and that reverse sequence of active 9-mers is inactive. The prediction of test data not containing 9-mer motifs also is excellent. It endorses the predictive capability of the model for a difficult task with truly unknown patterns in the test data.

ॐ Intestinal absorption

The intestinal permeability is a vital parameter for the efficacy of oral drugs. Winkler and Burden [148] applied Bayesian NNs with 2 to 5 hidden neurons to model logarithm of the logit transformed percentage intestinal absorption of 169 drugs with molecular descriptors (table 34). The model explained 85% of the variance with 6 to 11.9% of standard error of prediction (SEP).

Table 34: Modeling intestinal absorption using molecular descriptors

Descriptor	H1#	SEC	SEP
Topological	2	5.6	11.9
CIM/bc	5	2.5	6.7
Property	2	5.2	0.92
Abraham	4	7.1	8.4

ॐ Blood brain barrier (BBB)

The Blood brain barrier **(BBB)** is a physical barrier with a large surface area in the circulatory system. It controls the penetration of drugs and many other toxic substances into the brain. Central nervous system (CNS) drugs cross the BBB by different mechanisms. The CNS inactive medicines exhibit more complicated behavior. Some compounds do not penetrate at all, while others are rapidly metabolized or expelled by active efflux processes [144]. Hitherto only passive diffusion is considered in BBB models. The BBB permeability is expressed as the ratio of the steady state concentration of the drug molecule in the brain and in the blood $Log\left(\frac{C_{brain}}{C_{blood}}\right)$. Another way of quantification is in terms permeability surface area [278]. The permeability of BBB is determined both by experimental and computational procedures. The two categories under the experimental procedure are in-vivo and in-vitro processes.

The standard deviation for MLR model with 328 BBB compounds is around 0.3 log units which is nearer to experimental accuracy. But, if it comes to prediction, it is a challenge with hard modeling techniques. The complex models with molecular descriptors will predict better only by improving the accuracy of experimental measurements of training data set. Garg and Verma [278] compared various models to predict the ratio of steady state concentration of drugs between brain and blood plasma from seven molecular descriptors (table 35).

Table 35: Statistical parameters of models for logBB [278]

	7-5-2-1	Cerius	CSBBB	Pre-ADME
Tr set	132	120	103	88
Te	50	---	74	42
R^2	0.81	0.44	0.57	0.58
SE	0.30	0.52	0.43	0.54

BB : ratio of concentration of drug in brain and plasma
SE : standard error

Drug activity

The biochemical pathways or responses of whole organisms are complicate network of multiple processes and they are reviewed in detail. The complexity is multifold in reactions, properties, relationship and propagation. The non-linear dynamic behavior, chaotic transitions between different states and responses of interaction of elements, groups, moieties, molecules etc., render the system not amenable for predictive modeling in the classical framework. Top-down approach with model driven and data driven paradigms is an alternative method to bottom-up procedure to study protein targets, cells and organisms. The emergent, over all parameters are modeled within mathematical framework. Here, statistical, empirical, AI, soft and natural computational methods are employed phase wise depending upon the relevance and cost to benefit ratio.

The location of eukaryotic promoter regions in gene sequence is vital to understand many biological processes and drug action. But, the prediction of these locations depends on different recognition motifs. Further, many enhancer and repressor molecules influence the region. Winkler [148] modeled 785 promoters and 785 random sequences to distinguish with and without promoters.

Drug-protein-interactions

Prado-Pradoet al. [243] proposed multi-target SXR to account for possible drug-protein-interactions (DPIs) and drug-protein-no-interaction (nDPIs). An exhaustive study in the traditional mode of single target interaction for a set of molecules is not feasible from CPU time point of view. A two phase modeling

(chart 51) successfully paved way to arrive at OXO5 (with IC50 = 0.00083 µM), which is more active compared to drugs pargyline/clorgyline.

Chart 51: Complex network for multi-target drug-protein interactions

Database

⇨ US FDA benchmark dataset

DPIs

Software	Descriptors
DRAGON	2D molecular
MARCH-INSIDE	3D structural

Models

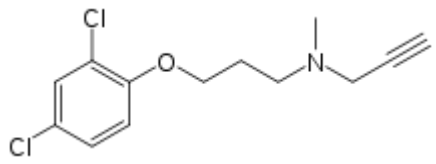
⇨ SLP_NN (21-31-1 : I#-H#-O#)

⇨ Complex Networks with 855 nodes

519 drugs + 336 targets

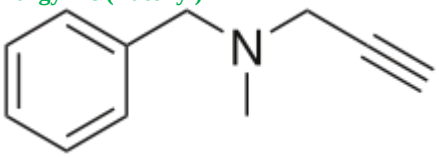
Dataset	Correct classification SLP_NN	
	DPIs	nDPIs
Trn	303 out of 339	480 out of 510
Test	625out of /678	730 out of 780

Clorgyline



N-[3-(2,4-dichlorophenoxy)propyl]-*N*-methyl-prop-2-yn-1-amine

Pargyline (Eutonyl)



Generic name : isocarboxazid
IUPAC :
N′-benzyl-5-methylisoxazole-3-carbohydrazide
Metabolism Liver
Excretion Urine
Trade Name Marplan

Binding activity of drugs with small molecules/active site/DNA

The correlation between (micro) modules of brain and aberrant neuro behavior is strikingly inconsistent. It is due to differences in methodology to find true neuro-anatomical configurations underlying the disorders. Further, no single brain volumetric profile satisfactorily correlates neuro behavioral disorders. Thus, the directly observable abnormal behaviors are an artifact of final, common pathway eventuating from multiple different brain abnormalities. It is almost impossible to pinpoint a specific brain abnormality responsible for a particular behavior. The vulnerable model is to relate multiple neuro anatomic perturbations leading to the same cluster of atypical behaviors.

The location of eukaryotic promoter regions in gene sequence is vital to understand many biological processes and drug action. The recognition motifs, enhancers and repressor molecules influence the prediction of the location. Winkler [148] modeled 785 promoters and 785 random sequences to distinguish the sequences with and without promoters. They used a sliding window of 50 bases to scan the promoter and nonpromotor sequences with Bayesian NNs. The ratio of true positive predictions to the total number was 3.6, which is comparable with Dragon, a literature reported procedure. The authors contemplate to reduce the false positives as well as false negatives using consensus method. The adverse effects of the drugs were successfully predicted with NNs. The accuracy of prediction of adverse outcomes in pediatric meningococcal disease was comparable with the results of multivariate logistic regression [159].

Gene expression

The human HIV-1 Vpr mutant cell is an infected dendritic cell. Thus the gene expression microarray time series is a difficult classification task. Barman and Mukhopadhyay et al. [360] used intelligent soft modeling techniques to find out significant gene, which will be base for future drug target. Streptococci, a group of Gram-positive bacteria, also developed resistance to many current antibacterial drugs [203]. This warrants a rapid search for design of molecules with high activity, low EC50 and low toxicity to humans and animals. Speck-Planche et al. [203] resorted to multi-target SActR to combat with the resistance of

bacteria to current drugs and limitation of single target models. A multi-tasking approach with simultaneous prediction of anti-streptococci activity and toxic effects against *Mus musculus* and *Rattus norvegicus* is reported *using* NN classification (chart 52).

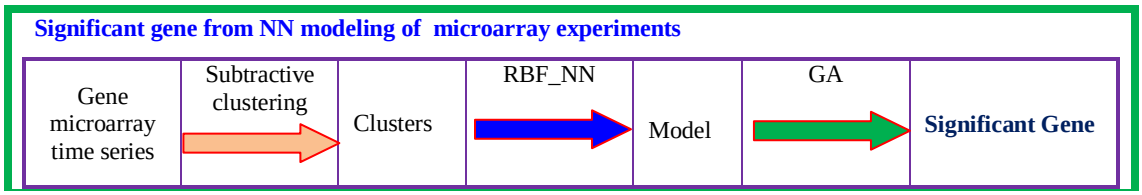


Chart 52:NN classification into high biological activity and/or low toxicity compounds	
database	> 11500 records
NN Classification	97%

Molecular descriptor	Calculated from
Topological	Connectivity paths in the chemical graph
CIMI	Eigen values of the molecular adjacency matrices atom charges binned into categories based size
Property	Number of hydrogen bonding groups in the molecule log $P_{oc/wa}$
Abraham	Free energies of interaction of molecules with biological systems

Pre-clinical and clinical trials in drug approval

The general protocols in drug approval and post approval monitoring when the drug is in use are briefed in chart 53.

Chart 53: Broad protocols of preclinical, clinical and post-clinical studies			
Preclinical			Non-human subjects, Gathers efficacy, toxicity, pharmaco-kinetic information
Phase	**0**		Exploratory, first-in-human trials Human microdosing studies Go/no-go decisions
Clinical trials & Approval [FDA (USA); EMA (European Union)]	**I**	Healthy human volunteers	20–100 healthy volunteers Safety (pharmacovigilance), tolerability, pharmacokinetics, pharmacodynamics
	II	Patients + volunteers	Larger groups (100-300) Continuation of Phase I safety assessments
	Patients III	Patients	Randomized controlled multicenter trials 300–3,000 patients
Post-approval monitoring Detection of harmful effects	**IV**		Restricted to certain uses Drug being no longer sold
Translational research	**V**		Comparative effectiveness Research & integration of clinical treatment

Knowledge extraction

Zhang,et al. [271] brought out a knowledge base by the predictive modeling of hundreds of push–pull osmotic pump (PPOP) data of famotidine tablets and human experience of inferences (chart 54). The nucleus of the inference engine is the data driven predictive model of poorly water-soluble drugs and popular excipients. Osmotic pump technology (OPT) is gaining importance all over the world day by day.

22. Structure X (activity/property/toxicity …) Relationships (SXR)

The size and content of data/ information/ knowledge/ intelligence and something beyond is as small/as large as nature itself. The instruments, perceiver and analyst are all the same (if they exist) i.e., nature itself. In the human framework the magnitude of the data can now be considered as a galaxy and the knowledge extracted with scientific/intuitive/professionals with formal education is a speck in an ocean.

The efforts of artificial intelligence scientists over half a century and the natural intelligence ever since the origin of life including *homosepians* need a new dimension to extract and formalize intelligence and meta intelligence bits. The predictive modeling was not respected even in 1980s and it was deemed as a vulnerable mental exercise. Even now, the heuristic is that one should resort to the prediction of activity, response, property etc., iff (if and only if) the value is indispensable for further study and its experimental determination is difficult or not cost effective. The activity of a chemical moiety in isolation/presence of a matrix in biota/human beings is of utmost interest. LD_{50} (50% of lethal dose), ED_{50} (minimum effective dose for 50% curing a disease) and ID_{50} (50% inhibitory dose) are a few popular measures of activities in vogue. The premise is that the activity/characteristics of a chemical are implicit or encoded in the molecular structure. The physico-chemical characteristics and biological activity of any two chemicals are not identical quantitatively, although similar from a qualitative standpoint of view. During mid twentieth century, Hammett proposed linear free energy relationships (LFER) in physical/organic chemistry and Hansch [390] put forward models for compounds of interest in pharmaceutical chemistry, agriculture and toxicology. The explanatory (causative) factors considered were the donor characteristics of the substituents and hydrophobic parameters. The linear models in one or more explanatory variables were analysed with multi-linear regression (MLR). As the biological activity was mostly considered in yester years, the term quantitative structure activity relationships (QSAR) became popular and this was the start of today's major discipline occupying a niche in computational chemistry. SXR (Structure [X: activity/ property/ response/ sequence/ …] relationships) is now the generic term in the interdisciplinary research with synergistic benefits from information/technology integrated with domain specific knowledge. SXRs (where X:activity) (Chart 55**)** are credible tools in this decade emanating complementary, supplementary and otherwise-not-obtainable information to experimental scientists involved in drug discovery, pharmaceutical chemistry, toxicology and materials synthesis.

Chart 54: Expert system for push–pull osmotic pump tablets

Drug	Famotidine
Database	Hundreds of PPOP formulations of poorly water-soluble drugs/ pharmaceutical excipients
Information technology	VB.NET SQL Server
Prediction model	MLP_NN BP
Knowledge base	Rule base Experience prediction model

Chart 55a: General algorithm of SXR

Iterate

Measurements (y)

Direct or indirect response from in vitro (ex-vivo)/in vivo/in silico from animals, human volunteers, patients and simulated data from hitherto available best set of empirical/theoretical/computational models

Chart 55b: Structure X relationships (SXR) ; y = Fn(X,[par; Wt; const])

X
Activity
property

y	
Inhibitory conc.	IC_{50}, IC_{75}
Effective conc.	EC_{50}, EC_{75}
Lethal dose	LD_{50}, LD_{99}

- **Explanatory factors (X)**
- Explanatory factors/feature variables from macroscopic/microscopic physiochemical properties, molecular descriptors and heuristic parameters
- **ObjFns**
- Single/multiple objectives functions
- **Pruning X**
- Selection of similarity/dissimilarity/diversity measures in Euclidean/ Mahalanobis/Manhotton spaces

- **Models y = fn(X;freePar)**
- Multiple convergence criteria, stopping rules, measures to enhance generalizability and robustness of the model
- Model/ Data driven relations

- Pruning/growing architecture

- **Analysis of Model(s)**
- Fitness/ Residual analysis and statistics influence
- Best set of models
- Ensembles, Forests
- Pareto optimals
- **Knowledge Extraction, critical information, Intelligence bits**
- Knowledge extraction tools in model driven (C52, FIS) and
- data driven (NNs, evolutionary algorithms) paradigms

- Comparison with achieves
- Comparison with the experimental data, case histories and other models
- Reorganization, reorientation, targeting at unachieved goals and gaps in the targets

End iterate

- response
- sequence

PCA
PLSR
SVM

NNs	
-supervised	
FF	SLP
	MLP
Recurrent	
Unsupervised	
SOM	Kohonen
ARTx	
supervised	Neural gas
	LVQ
	$ARTMAP#
Counter propagation NN	

- Linear
- Non-linear
- Parametric
- Non-parametric
- Non-normal
- Distribution free
- Data driven

- Mathematical
- Statistical
- Distribution
- Distribution free
- Stochastic
- Chaotic
- Fuzzy
- Nature inspired
- Soft
- NNs
- Hybrid
- [Statistics soft NNs Nature inspired]
- [binary, ternary, quaternary, …]

SXRs are complex mathematical relationships between biological activity and chemical structure. The axioms of SXR are that structural descriptors are the basis of observed properties, and the structure is transformable to numerical descriptors. SXRs evolved over the last half a century from a simple linear regression model with one or two variables to ensemble of complex non-linear models using hundreds to thousands of experimental/theoretical/computational descriptors. The algorithms for SXR (Chart 55) consist of training, model validation, prediction and iterative development of selection/improvement of the candidates from limited number of designed experiments. The corporate databases contain more than 10^6 small organic molecules and the theoretically possible number is up to 10^{100} [155]. The investigations over years ranged from 20 to more than 30,000 compounds. These studies stem from academic institutes

to small/large pharma industries through governmental/non-governmental laboratories. Many tools of orthogonalisation, experimental design and variable selection have become integral part of this activity. SXR finds promising candidates faster and also surges potential failures before they are pumped into later stages of drug development process [149]. Yet, the lacuna of SXR paradigm is in the visualization of molecular structure; even quantum chemically (abinitio/DFT) optimized molecule is limited to the gas phase only. Although, the dielectric constant and non-covalent descriptors are used, the changes in structure with properties are not fully modeled [149].

But the advances in modeling techniques and realizing the impossibility of computations from first principles, predictions from models were taken into confidence as complimentary information for synthetic compounds, naturally occurring moieties and even those from the virtual libraries (awaiting isolation/synthesis). Later 3D-, 4D-, and 5D- SXR joined the bandwagon of predictive tools opening new vistas in pharmaceutical/ biochemical/ toxicological studies.

The focus is to build more number of intelligence bits (light houses) in the ocean of knowledge and lay virtual highways/express ways/short-cuts to reach as nearer as possible to the unknown solution of the inverse problem in the shortest possible time scale. Of course, it is like searching for a needle in a haystack. In this decade, pursuing for Pareto solutions is preferred on realistic grounds. The transformation of data to intelligence is beyond dimension reduction, viewing/ comprehending in chemical/ biological/ pharmacological or brain space. The solution of an inverse problem is tiny compared to the definition, boundaries and knowing everything about nature and consequences over time and space in dynamic environment.

ॐ Multi-dimensional (m-D) SXR

mD-SXR encompasses 3D-geometric structures, conformers, receptors and solvent molecules. It is thus, a new instrument in the arsenal of computational models generating tidbits of information indispensable in traversing through the dark regions of experimentation, theories and even heuristics. It ranges from 1D- to 3D- description of a chemical compound [288]. 2D-SXR was an extensively investigated model for in vivo and in vitro experimental data in animals. The computable characteristics (from quantum chemistry, statistical thermodynamics, electro-statics, geometric measures, data driven models etc.) of a compound from 3D-optimized geometry now called molecular descriptors exceed 3500 in number.

3D-SXR: The geometric structure of chemical compound/species is optimized by computational quantum chemical calculations. The accuracy increases with level of theory (SEMO, ab-intio, DFT) and basis sets and so on. The consequently derived molecular descriptors obviously are nearer to true values only at the highest possible computational methods. But, the pragmatic approach is based on size of molecule, number of compounds considered in a study and available cost-effective hardware. SOM-NN is used to predict the activity employing 3D-QSAR. But, the failure in scaling up for virtual screening of large combinatorial libraries is attributed to the lack of software in yester years.

4D-SXR: The objective of 4-D SXR is to explore the conformational space freedom of a compound in 3D-SXR. Here, a number of conformational states of a ligand are considered and applied successfully to conformational flexible and receptor dependent molecules. It is the central theme of pharmacophore mapping where a spatial rectangular grid is constructed over molecular configurations [139]. It defines the cubes used to calculate a basic descriptor characterizing each molecule i.e. grid cell occupancy descriptor. It characterizes the pattern of occupancy of each cubic cell by atoms of the molecule during molecular dynamic simulations. Bak et al. [273] put forward a SOM version and recently the same authors extended it to receptor independent interactions. Thus, 1D- to 4D- is concerned with molecule on hand and does not require even the cognizance of the target/receptor.

5D-SXR: It is an extension of 4D-SXR to obtain realistic predictions of ligand receptor interaction.

6D-SXR: The inclusion of a set of solvent models to incorporate the effect solvent constitutes 6D-SXR, the current fertile area of investigation.

- Data driven models

NNs are potential tools in developing predictive models for the correlation of in vivo and in vitro processes with in-silico libraries. The very large literature on SXR unequivocally emphasizes the role of NNs, which surpass traditional classification and prediction techniques due to their capacity to imbibe non-linear relationships more efficiently. This reduced animal testing and laboratory experiment in the preliminary screening from thousands of compounds.

SXR is nearly half a century active research area and regulatory stipulations for acceptance of results started two decades ago. The guidelines of Organization for Economic Cooperation and Development (OECD) for rationale are briefed in chart 56 and chart 57.

Chart 56: OECD guidelines for applicability in predicting metabolism and toxicity

- Defined end point
- Unambiguous algorithm
- Defined application domain
- Measures of goodness-of-fit
  - Robustness
  - Predictivity
- Mechanistic interpretation if possible

Elton Zvinavashe, Albertinka J. Murk, Ivonne M. C. M. Rietjens, *Chem. Res. Toxicol.* 2008, *21*, 2229–2236, Promises and Pitfalls of Quantitative Structure-Activity Relationship Approaches for Predicting Metabolism and Toxicity

Chart 57: Output of om_ref_JAVATYP.m

Pitfalls of SXR

Dearden, J. C.; Cronin, M. T. D.; Kaiser, K. L. E. How Not to Develop a Quantitative Structure–activity or Structure–property Relationship (QSAR/QSPR).	SAR QSAR Env. Res. 20, 2009, 241-266.
Doweyko, A. Is QSAR Relevant to Drug Discovery?	IDrugs 11, 2008, 894-899
Doweyko, A. QSAR: Dead or Alive?	J. Comput.-Aided Mol. Des. 22, 2008, 81-89
Golbraikh, A.; Tropsha, A. Beware of q^2!	J. Mol. Graphics Modell. 20, 2002,269-276

Chart 58: NN model for SActivR of stannoxanes and ID50

Compounds

2,6-pyridine-dicarboxylates [C5H3N(COO)2SnRR′] (R, R′ = alkyl, aryl)

di-*n*-butyltinbis-benzoates [(C6H5COO)2SnBu2]

Method	Function
PM3	Geometry opt
Molecular descriptors	Thermodynamic Structural
GA MLR	**Pruning →** Molecular area/volume Lipophilicity Molecular dipole polarizability(X)
NN_BP	**SActivR** ID50 = NLFn(X)

Johnson, S. R. The Trouble with QSAR (or How I Learned To Stop Worrying and Embrace Fallacy). J. Chem. Inf. Model. 48, 2007, 25-26.

Scior, T.; Medina-Franco, J. L.; Do, Q. T.; Martinez-Mayorga, K.; Yunes Rojas, J. A.;Bernard, P. How to Recognize and Workaround Pitfalls in QSAR Studies: a Critical Review. Curr. Med. Chem. 16, 2009, 4297-4313.

Tropsha, A. Best Practices for QSAR Model Development, Validation, and Exploitation. Mol. Inf. 29, 2010, 476-488.

Tropsha, A.; Gramatica, P.; Gombar, V. K. The Importance of Being Earnest: Validation is the Absolute Essential for Successful Application and Interpretation of QSPR Models. QSAR Comb. Sci. 22, 2003, 69-77.

Structure activity Realationships (SActivityR, SActR)

Xiao et al. [149] classified a large set of compounds into low, moderate and high biological active categories by supervised SOM. The multidimensional molecular descriptors are selected using SAA, PLS, k-NN, NNs etc. The accuracy in classification by a few typical models indicates the superiority of a hybrid approach viz. simulated annealing algorithm coupled with supervised SOM. Tomas-Vert [293] developed a SActR_NN model to discriminate the active and inactive molecules for antibacterial activity using topological molecular descriptors. Fernandez [201] reported a SActR between IC_{50} (inhibitory action) of aldose reductase enzyme with descriptors from Dragon software for 75 flavonoid compounds. Genetic algorithms are used to select influential descriptors. The NN model is superior to an earlier MLR model using classical and quantum chemical descriptors. Borges [291] arrived at molecular descriptors with reasonable correlation between experimental values of IC_{50} of the enzyme. Valcarcel et al. [265] reported SActR models of substituted 2, 6-pyridine-dicarboxylates with molecular descriptors pruned with GA and MLR (Chart 58). The NN model of ID_{50} showed higher anti-tubercular activity with prospects in breast and colon cancer therapy. Segala [290] developed a NN correlation model between chemical structure and biological activity for a series of compounds having antispermatogenic activity. The results are superior to those with PCA and k-nearest neighbors. Szaleniec et al. [353] found NNs predict enzyme activity of ethyl benzene dehydrogenase (EBDH) with $R^2 > 0.9$ using electronic and geometrical molecular descriptors. The algorithms for input selection, network structure, weight optimizations and data division into training/validation/testing are reviewed.

Inhibitors of ACE: Carli et al. [219] employed tiling-contextual neural network for structures(TC-NNfS) to model inhibitors of angiotensin converting enzyme (ACE) using a small set (forty five) molecules of therapeutic action. The comparison of results with other SXR models (chart 59) showed better performance of NNs.

Mycobacterium tuberclulosis (M. tuberclulosis): Kovalishyn et al. [224] explored SXR models for diverse compounds using molecular descriptors calculated from Dragon software (chart 60) and ADRIANA.Code. These models are of interest in the early phase of choosing set of prospective drug like molecules for M.tuberclulosis. Ventura et al. [242] synthesized two new compounds and tested against *M. tuberculosis* based on SXR models of hydrazides. The activity predicted by NN models (chart 61) is close to the observed value endorsing the efforts in rational drug design protocols are worth pursuing in right perspective. Sardari et al. [217] employed chemoinformatic output (molecular descriptor values) in developing structure-minium_inhibiroty_concentration relationship (S.Inh.Conc.R) model for 400 compounds (chart 62) using NNs and PLS with an objective of designing a better drug-like molecule for Mycobacterium tuberculosis.

Chart 59: SXR models for ACE inhibitors

- MLP-CS,
- MLP
- RBF_NN
- GaussianProcesses
- LeastMedSq
- M5P
- LWL
- LinReg

Chart 60: Dragon output of molecular descriptors

Constitutional descriptors (48)	Topological descriptors (119)
Connectivity indices (33)	Information indices (47)
Edge adjacency indices (107)	Burden's Eigen value descriptors (64)
Topological charge indices (21)	Eigen value-based indices (44)
Randič molecular profiles (41)	Geometrical descriptors (74)
RDF descriptors (150) radial distribution function	Walk and path counts (47)
3D-MoRSE descriptors (160)	WHIM descriptors (99)
Functional group counts (154)	Atom-centered fragments (120)
Charge descriptors (14)	Molecular properties (29)
2D binary fingerprints (780)	GETAWAY descriptors (197)
2D autocorrelations (96)	2D frequency fingerprints (780)

Chart 61: Predictive NN models against *Mycobacterium tuberculosis*

Compound bases
- Hydrazides (173)
- Mol Descriptors (96)

Models
- MLR
- FF_NNs
- Associative NN
- Ensemble of NNs
- Counter propagation NN

- Trn : 94
- Test: 18
- Mol Desc : 7

Prediction	R^2	RMSE
Associative NNs	0.874	0.437
MLR	0.845	0.472

238 Compound bases
- PubChem

Models
- Random Forests
- Associative NN

Prediction	active	inactive
Accuracy classification	0.76–	0.88
Q^2 regression	0.66–	0.89

Chart 62: Chemoinformatic modeling of antimcobatcterial compounds

Compound base
- 400 Antimycobacterial

DRAGON software
- 1400 Descriptors/compound (X)

Response
- Min(inhibitory conc.) (y)

Models

kNN, k-means	Clustering
PLS +NN	SXR

R^2	MSE
0.98	0.0002

Table 36: SLP-NN for antitumor activity vs molecular descriptors

SXR_model	R^2
MLR	0.506
SLP_NN (5-8-1)	0.983

Antitumor activity: Qin et al. [307] reported the success of SLP_NN in modeling antitumor activities of substituted chloroethylnitrosoureas with molecular descriptors (table 36).

Narcotic activity: At the beginning of 20th century, the potency of narcotics was correlated to lipophilicity [288]. The prediction of adverse effects of xenobiotics in risk assessments through SXR is an acceptable paradigm [288]. Zheng, et al. [202] developed butyrylcholinesterase (BChE) mutants with ~2000-fold improved catalytic efficiency against cocaine earlier (chart 63). Later these authors [198] reported a NN model for SActR between pIC_{50} of 53 BChE inhibitors descriptors which is superior to molecular docking and MLR. This computational paradigm has prospects in discovery of novel effective inhibitors of BChE in the future ventures.

Chart 63: Prediction of molecular inhibitory activity vs. BChE (Anti-cocaine drugs)

- y : *pIC*50 of Butyrylcholinesterase (BChE) inhibitors
- Compounds : 93 small molecules
- X : docking generated energy descriptors

Model	r^2	rmsd	q^2	Loo_ rmsd
MLR	0.89	0.51	0.85	0.58
NN	**0.95**	**0.33**	**0.90**	**0.48**

Structure cancer Cell relationships (SCancR): Nakagawa [136] et al. reported the hybridization of two paradigms to open new vistas in SActR. ESPs of a chemical model from ab initio calculations (RHF) were the input to NN and outcome revealed that negative potential localized at 10 and 11 position of ring A (of lactone) is recognized by ABCG2, whose over expression confers cancer cells resistance to SN 3814 camptothecin analogues were investigated in regard to substrate specificity of ABCG2. The compounds with a hydroxyl group in 10 or 11 position of ring A, are recognized by ABCG2 and thus effectively extruded from cancer cells.

Structure Biodegradability Relationship (SBiodegradR): The number of organic compounds is very large (greater than 10^8) and the time for experimental determination of biodegradability is very high. As emphasized earlier, the prediction from the first principles of chemistry and biology is also impossible at the moment. The alternative left is to exploit the experimental data using modeling paradigms. The primary aim of QSBiodegradR (quantitative structure biodegradability relationship) is to predict anaerobic biodegradability of organic compounds, their mechanism and classification of chemicals into poorly/ partially biodegradable.

Structure Toxicity relationships (SToxR)

The term toxicity is just a biological end point. At the molecular level a large number of reactions are involved in different processes. Although, more than 82,000 substances are in current list of US-commerce, toxicity and hazardous profile of many of these chemicals are not yet completely known. Further there is an increase of 2000 to 3000 chemicals or their derivatives every year. A maximum of 15% of the inventory of toxic substances control act (TSCA) have mutagenicity information. In European community also the number of chemicals in the market place is exponentially increasing [239].

Chart 64: Cardio_toxicity risk potential and lipophilicity of a drug described as the log *P* value.

- Drug (447 records)
- Chemical structure (175)
- Physico-chemical parameters

TFs

- Hyperbolic tangent
- Sigma
- FSR function Test set : 45 records

- MLP (I#-3-2-O#)
- Neuro_FIS-Mamdani MISO
- 10-fold CV

Cardio-toxic effects: Some drugs inhibit fast potassium channels [190] encoded in human ERG gene, reflected in EEG interferences. The consequences of this drug acquired (DA) long QT syndrome (LQTS) is ventricular arrhythmia. This forced the withdrawal of currently used marked drugs. This scenario now focused attention towards pharmacological safety in early prediction of hERG channel–drug interaction potential. Polak et al [190] studied structure–cardio toxicity empirical relationship using publicly available drug databases and data from publications with NNs (chart 64).

S.antiColorectalCancer.R: Speck-Planche et al. [205] developed for the first time a modeling approach for multi-(ten cell lines) target in predicting anti-colorectal cancer compounds making use of in-silico library and virtual screening leading to rational drug discovery. Two models are found to be trust worthy correctly discriminating active and inactive compounds to more than 90% both in training and prediction phases.

Descriptors	Model
Fragment	LDA
2D-global	NN

Cytotoxicity-multiplexed biological assays: Now, multiple measurements of cellular parameters are made in the same test. Tenorio-Borroto et al. [206] combined measuring cytotoxicity of an anti-microbial drug G1 in spleen of two organisms (human being and mouse) and NN modeling of molecular descriptors of a larger set of drugs (chart 65). It correctly classified 8258 out of 9000 i.e. with an accuracy of 93.0%. For the first time EC50 (11.41 μg/mL) and Cytotoxicity (27.1%) resulting from over usage of drug G1 are experimentally determined.

Chart 65: NN models of cytotoxicity

#Drugs 7903 Organisms Human Mouse	Endpoint One out of 1418 assays 36 Molecular/ cellular targets 46 Standard type measures
Molecular descriptors TOPA-MODE STATISTICA	Models Linear_NN RBF_NN Probabilistic_PNN MLP_NN

Toxico-genomics: Probabilistic_NN is used to predict toxin-affected organs in rat strains with a success rate of 99%. The samples were predicted into five classes-liver, kidney, liver and kidney, mitochondrial toxins and controls- for each strain. In the case of multiple organ (liver and kidney) toxicity, the success rate of Prob_NNs is low (77%). CLOUDS, derived from Prob_NN gave similar results as k-NN (robust classification method). The NMR analysis of urine samples and modeling with NN is less expensive compared to toxico-genomics and proteomics. Good prediction of toxicity in liver and kidney is observed with NN [183]. The current interest is in classification based on sub-organ-sites or mechanism of toxicity. The mechanism and causes of onset and development of cancer is identified. But, the whole picture still remains obscure and unclear. It levies a negative toll in effective treatment and definite and promising cure. Thus, prevention and early confirmative diagnosis are the weapons at disposal to fight against terrible malignancies.

Measurement of toxicity: The measurements of toxicity of a compound, in general, are carried out by traditional histopathalogical screening examination. But, it is slow and expensive. In the metabonic screening of biofluids, NMR spectroscopy is used to detect the toxicological effects on animals subjected to model toxic compounds. In recent years, statistical gene transcription and protein expression have supplementary/complimentary information for the experimental results. Non-receptor mediated acute toxicity is most often quantified in individual lethality. It also results in change in growth or reproduction or biochemical/physiological changes. These effects are further classified into non-covalent and covalent modes. Covalent toxicity includes the effect of irreversible chemical reactivity of electrophilic/nucleophilic group and the non-covalent toxicity includes reversible narcosis. Receptor mediated toxic effects such as endocrine disruption fall into predictive toxicology. These effects assume a ligand-receptor interaction of the ligand (xenobiotic) when the receptor is non-covalent with a lock-key mechanism. Binding and activation require specific 3D-conformations. The interactions include molecular packing, ionic and hydrophobic interactions and hydrogen bonding. Exitotoxicity is a phenomenon observed in neurons or myocytes. When the excitatory molecule exceeds the physiological range in intensity or duration, stimulation occurs leading to toxic effect. The typical examples of excite-toxins are capsaicin, acetylcholine and glutamate. The last compound is the most important in CNS and it is rapidly released at synapses during stroke. Gasic and Nicotera [387] reported the consequences of acute injury of neurons in excite-

- Hepatotoxicity
- Cardiotoxicity
- Genotoxicity

Chart 66: Psycho-diagnostic instruments (probes)

LIPS	:	Leiter international performance scale
CPM	:	Coloured progressive matrices test
MDS	:	The mental development scale
PEP	:	The psycho educational profile

toxicity and brain ischemia. The concepts like 'die hard', or 'to sleep or dream' are elaborated in patients affected by age related neuro degenerative disorders including Alzheimer's and Parkinson's disease. Di Nuovo et al. [17] applied polynomial regression, MARS, geralized regression and ANFIS with subtractive clustering/ fuzzy-C-means clustering model to arrive at intelligent quotient estimation of mentally retarded patients suffering with various pathologies from psychometric test (chart 66) results.

Toxicity models: The limitations of the models are primarily due to the plethora of mechanisms involved [288]. Thus, in spite of advances both in biology and modeling, prediction is prone to be erroneous. The modeling of toxicity on human health are based on receptor, non-receptor and mediated toxicities. Ekins [313] reviewed application of SVM and Bayesian models for toxicological (SXR) models. The future course will be in using nature inspired-hierarchical-machine-learning algorithms for hundreds of thousands of compounds, thousands of molecular descriptors in diverse bio-chemical, pharmaceutical-, and chemical-spaces. A few typical studies in toxicology using NNs in developing SXR models include pneumoconiosis in foundry workers, cancer detection [179], activity of anticancer reagents [138], toxic effect of PAHs on fish [181] etc. The prediction of toxicity at molecular level by FAM_NN, Kohonen_NN and Bayesian_NNs is superior to MLR.

Toxicity of breast milk vs drugs/medicines: The prediction of M/P (milk to plasma) ratios is overestimated for acidic drugs, while underestimated for basic/neutral drugs. Agatonovic-Kustrin [145] proposed a genetic NN for prediction of degree of transfer of the drug into the breast milk employing molecular descriptors. From a detailed study of the effect of number of hidden layers (table 37a), neurons, size of training set (table 37b) and sensitivity analysis (table 37c), a four layer MLP_NN (26-5-5-1) trained with back propagation is adequate in explaining M/P values. As this approach does not require experimental parameters, M/P ratios of even not yet synthesized new drugs/drug like compounds/moieties from virtual libraries can be estimated for intelligent pruning. Fatemi and Ghorbanzad'e [244] discriminated high (M/P > 1) and low (M/P < 1) risk of 154 drugs for infants from measured ratio of concentrations of drugs in milk and plasma of lactating women (chart 67). The counter propagation_NN reached 90% accuracy for external test dataset. The most/least toxic compounds (12,998) out of 30,000 compounds in a database with SLP (164-13-1) using SNNS software are analysed. The input is fragment descriptors and the output range is divided into toxic, nontoxic and uncertain. The confusion matrix (table 38) for a typical run shows that NN model misclassified less than 5% of non-toxic compounds and 9% of toxic compounds. This is a promising tool to filter potentially cytotoxic moieties in drug development cycle before synthesis or during lead optimization.

Table 37a: Best model for prediction of M/P values of some typical drugs by NN-GA

Drug	Expt	NN		Log (phase Distribution) Model
		26-5-5-1	18-6-1	
Aminoprylline	0.830	0.88	0.78	0.96
Atenolol	2.100	2.10	1.95	2.83
Metoprolol	2.600	2.61	2.58	2.57
Nadolol	4.600	4.61	4.60	2.39
Procainamide	3.20	2.91	3.18	2.50
Temazepam	0.14	0.02	0.06	0.05
R^2 of		0.962	0.910	0.805
$y = a1 * ycal + a0$				

Table 37b: Performance of NNs with architecture

I#	H1#	H2#	O#	RMS	
				Tr	Te
61	12	--	1	0.824	1.814
61	***5***	***5***	***1***	***0.825***	***1.608***
31	13	---	1	0.819	1.850
31	**5**	**2**	**1**	**0.817**	**1.670**
26	8		1	0.844	1.507
26	**5**	**5**	**1**	**0.590**	**0.425**
12	4		1	0.904	1.440
12	4	4	1	1.001	1.227

Table 37c: Sensitivity of input variables

Variable	Sensitivity
κ_1	0.13291
κ_1	0.009811
Log P	0.06236
MW	0.00479
….	
$-NH_2$	0.00909

Table 38: Confusion matrix for cytotoxicity prediction

Training set			
	Toxic	**Non-toxic**	**Unknown**
Toxic	2400	211	725
Non-toxic	162	4044	756
Unknown	2886	10112	4704
Test set			
	Toxic	**Non-toxic**	**Unknown**
Toxic	556	72	195
Non-toxic	52	912	213

Toxicity to Skin: The skin is the principal barrier against environmental insult preventing health hazards. According to EC stipulation [386], the extent of corrosivity of chemicals (chart 68) is measured by the development of necrosis (irreversible damage to the skin tissues) when a chemical (500mg of a solid or 500ml of a liquid) is applied to the skin of a rabbit for a period of 4hrs. The other measures of severity are causing burns within three minutes or severe burns instantaneously. The permeation/transportation of the chemical from the site of administration/exposure/contact to the site of attack is the prerequisite for either biological/drug/toxic action. This is beyond well explored physical, chemical and biological forces, many being non-linear [141]. The binding or reaction with the receptor or target is responsible for the reaction. Barratt et al. [385] predicted the skin permeability coefficients, skin corrosivity of organic acids, bases and phenols with NNs. The explanatory factors are molecular volume, melting point, log (partition coefficient) and in vitro cytotoxicity parameters [386] like pKas. A list of typical organic compounds which are skin irritants are presented in table 38. They [382] extended the size of the data set to cover the boundary region and the model increased confidence in predicting the classes. It is found that the mixtures of surfactants exhibit lower irritation of the skin compared to the summation of the individual irritation potentials. The reduction in critical micelle concentration (CMC) of the mixtures is thought as the critical parameter, but the results are criticized as the experiments were conducted below cmc. Handels [111] reported NNs with B.P in the diagnosis of malignant melanomas and neurotic nerve automatically. Features are obtained from 2D image analysis of skin surface profile. The classification accuracy is around 97.0%. Infrared imaging of rat skin could discriminate cancer caused from inflammation and hematoma. IR camera with a resolution of 76,800 pixels in the spectral range 8-14 and temperature resolution of 0.07^oC is used to detect thermo-graphic changes during walker_256_ carcinoma development.

Chart 67: Models of M to P ratios of drugs in breast milk

- ⇨ LDA
- ⇨ QDA
- ⇨ SVM
- ⇨ Counter-propagation NN

Eye irritation by organic compounds: A substance is classified as irritant to eyes if it causes a particular level of trauma in the Draize rabbit eye test i.e., if the mean scores at 24hr, 48hr and 72 hour exceed any of the symptoms cited in Chart 69. These authors [382] extended the size of the data set to cover the boundary region which increased model confidence level in predicting the classes. Barratt [385] employed 34 alcohols (Table 39) in the model with PCA and NNs. The classification into irritant and non-irritant are assigned the values of 1 and 0. The descriptors employed are dielectric constant, logP, dipole moment, R_Y and R_Z. The NN is accurate to an extent of 97.27% in training, but the predicted values are widely different especially in the middle of the range, 0-10.

Mechanism of eye irritants: The irritant compound partitions into membranes. Thus, a chemical with high dipole moment has lower hydrophobicity (logP) and so cannot pass through the membranes [384]. However, a small dipole moment is necessary for the passage. The chemicals perturb the transport of ions across the cell membrane

Table 39: Misclassification of Toxicity mechanisms [185]

Two classes	RBFNN	SVM	LDA
1,3/2,4	3	1	6
1/3	**11**	13	10
2/4	**2**	3	5

in the eye by changing the electrical property. It is the cause of eye irritation when exposed to neutral organic compounds.

Structure-Mutagenicity-relationships (SMutagenicityR): Mutagenicity is utmost critical toxicity expression associated with the chronic exposure to various categories of chemicals including environmental pollutants, potential therapeutic agents and those in toxic material manufacturing units. It is a toxicity end point [239] and has similarity with carcinogenicity mechanisms. Thus, the prediction of mutagenicity for chemicals without biological data is of current interest. Valkova [186] studied 95 aromatic and hetero aromatic amines with MLR, PCR, PLS, ridge regression and NN models using log P, EHOMO, ELUMO, topological, geometrical and quantum chemical descriptors. A minimal training set selected covering the information space efficiently. Six parameters are used in the linear model and back propagation NNs. Vracko et al. [239] employed counter propagation NNs, which is generalization of SOM, with different combination of topological, geometric and quantum chemical descriptors.

Genotoxicity: Genotoxic carcinogens themselves may be mutagenic or become mutagenic after metabolic activated alkylate DNA. Although, experimental methods are available to determine the mutagenicity of the chemicals, they are expensive and time consuming. Thus, prediction from the structure is another root especially when large set of compounds is to be tested. The predicted genotoxins are rigorously studied to invoke governmental laws [147]. Yao et al. [185] classified three narcosis mechanisms of 194 organic compounds and reaction four modes of 221 phenols with LDA, QDA, SVM with RBF kernel and RBF_NN, (Table 39).

Chart 68: Skin corrosivity of chemicals

Compound
Acetic acid
Hexanoic acid
Dichloroacetic acid
Bromoacetic acid
Mercaptoacetic acid
Formic acid
Acrylic acid
Caprylic acid
Lactic acid
Oxalic acid
Phosphoric acid
Sulfuric acid
Iodoacetic acid
Chloroacetic acid
Trichloroacetic acid
Cyanoacetic acid
Glyoxylic acid
Methoxyacetic acid
2-Mercaptopropionic acid
Pyruvic acid
Butyric acid
Isobutyric acid
Propionic acid
Nitric acid
Hydrofluoric acid
Trifluoroacetic acid
2-Chloropropionic acid
EC_{50} : Effective concentration causing a 50% reduction in neutral red uptake from control cell level

Chart 69a : Predicted Eye irritation classification of chemicals

Chemical	Eye score	Class
Methanol	3	IRR
Ethanol	3	IRR
n-Propanol	5	IRR
n-Butanol	7	IRR
n-Undecanol	3	NI
9-iso-Butanol	5	IRR
2,2-Dimethylbutan- l-ol	7	IRR
4-Methylpentan-l-01	5	IRR
Heptan-3-ol	5	IRR
2,2,4-Trimethylpentan-l-ol	7	IRR
2-Ethyl-4-methylpentan-l-ol	5	IRR
2-Ethylhexan-l-ol	5	IRR
2-Propylheptan-l-ol	2	N1
iso-Propanol	4	IRR
Butan-2-ol	4	IRR
Pentan-3-ol	5	IRR
Cyclohexanol	7.7	IRR
2,6-Dimethylheptan-4-ol	2	IRR
Di-iso-butylcarbinol	2	IRR

NI : non-irritant : 1
IRR : irritant : >3
Boundary : 2 to 3

Chart 69b: Symptoms for classification eye irritants

	Eye irritant score
Corneal opacity	2
Iris lesion	1
Conjunctural redness	2.5
Chemosis	2

Structure Property Relationships (SPropR)

The major chunk of last century's focus in classical chemistry was to synthesize exponential number of similar as well as diverse compounds and to explore their material properties. Recent interest is around probing into inverse problem, which resulted in environmentally safe, less toxic and smart materials with properties within in the desired range. There is a renaissance in perception of looking at chemistry and now, the center of attraction is properties of materials and ironically not the compound [273]. The physico-chemical properties of drugs, lead compounds, excipients, solvents,

preservatives, drug releasing matrix etc. are an integral part of health sciences. Now, there is a substantial evidence for the role of physico-chemical parameters in various phases of health programs, but still it is a cluttered scenario. The biological-/ chemical-/ physical- parameters (Chart 70) modeled are of wide range bulk characteristics, now running into thousands of molecular descriptors.

BBB and skin permeability: Guha, Stanton and Jurs [279], in continuation of innovative SPropR studies, used counter propagation NN (with 7-5-1 architecture) (Table 40) for prediction of boiling point, BBB and skin permeability using molecular descriptors.

Henry's law constants: Out of 70,000 compounds in use, Henry's law constants are available only for 1200. It is true with many toxic compounds, pollutants, metabolites, and drug likely ones. Henry's constant was modeled with RBF_NN and MLR with different molecular descriptors calculated from CODESSA, Tsar, Dragon and HYBOT software packages. The Co-ordinates of centers of RBF are the molecular descriptors of chosen compounds (Table 41) by GA and weight vector from RBL to output is used to predict Henry's constant. RBF-GA (Table 42) is superior to MLR-GA and exclusive MLR models.

Solubility: The theoretical calculations of aqueous solubility of organic molecules are not at a stage of maturity. The empirical MLR models employing structural parameters are inadequate in prediction of solubility of pharmaceutical moieties. In 1991, aqueous solubility was modeled with NNs, which is the earliest report. Bayesian, RBF_NN, GR, FAM_NN and Kohonen-SOM

Chart 70: Phyico-chemical and Biological properties

- Log P
- Solubility
- Boiling point
- Heat capacity
- Viscosity
- Surface tension
- Thermal conductivity
- Auto ignition Temp
- Flash point
- Dielectric constant
- Density
- Absorption
- Classification of crystals
- Henry's constant
- Pk_a
- Diffusion coefficients
- VP
- Henry' constant
- Critical temperature
- Critical pressure
- Kirkwood function
- Flash point
- Auto ingnition temperatu re
- Viscosity
- Surface tenstion

J. Taskinen, J. Yliruusi, Adv. Drug Delivery Rev., 55, (2003), 1163-1183.

Table 40: Performance of CNN for typical databases

Database	Response	Architecture I#-H#-O#	RMSE		R^2	
			Tr	Te	Tr	Te
DIPPR	Boiling point	7-4-1	15.21	15.07	0.91	0.94
BBB	Blood brain barrier	4-4-1	0.25	0.47	0.88	0.74
Skin	Permeability	7-5-1	0.27	0.31	0.94	0.91
DIPPR : Design institute for physical property data						

Table 41 : Co-ordinates of centers of RBF and weight vector from RBL to output

Tetrafluoro methane	Trifluoroacetic acid	HCN	N-nitroso-morpholine	2-pentanone	Nitromethane
1.286	-15.692	13.999	-7.915	-26.422	7.033
Chlorfluzuron	3-pentanone	1,1,1,3,3,3-hexafluoro-propan-2-ol	Tripropylamine	2,4dinitrophenol	Trifluralin
-2.468	4.752	9.697	15.353	-3.103	2.935

NNs have been extensively applied with commendable success in addition to simple SLP_NN [140]. The performance of MLR was comparable to NN, especially when the relationship is linear. However, with a seventeen term regression equation the boiling point of 150 alkanes has lower CV-SD (2.88° K) compared to SLP (10-6-1) NN (3.6° K). A point here, worth to mention, is inclusion of higher order terms, although decreases the training error; it results in increase of correlation among explanatory variables. Consequently, regression coefficients are inflated and their SD is high resulting in unreliable model and obviously ending inappropriate prediction. Except in cases of preprocessing of variables in PC or PLS space, many of X-variables are correlated and the better option would be using a hidden layer like in SLP whereby the variables are automatically uncorrelated with sigmoid TF. NNs mimic most of the non-linear models and function better in several instances after few hundreds of epochs. Thus, one should be cautious about inclusion of cross product and higher order terms. Taskinen [140] reported that MLR with higher order terms is comparable to NN. Huuskonen [151] proposed NN model (Table 43) for aqueous solubility of 211 drugs with topological and electro-topological indices as explanatory variables. Eric et al. [268] developed counter propagation neural network predictive model for aqueous solubility of drug like molecules using pruned molecular descriptors (table 44). This is another tool in arsenal of DDD by non-experimental approaches to think of solubility enhancing structural modifications in the exploratory stage of development of drug-like template molecules.

Table 42: Comparison of NN with MLR models for Henry's constant

Model	Descriptors	r^2		RMSE	
		Training	Test	Training	Test
MLR	CODESSA	0.854	0.798	0.811	0.829
	Dragon	0.83	0.781	0.873	0.856
	Tsar	0.831	0.80	0.872	0.800
	HYBOT	0.925	0.875	0.582	0.645
MLR-GA	All	0.928	0.900	0.570	0.574
RBF-GA	All	0.929	0.984	0.564	0.520

RBF architecture	10-12-1
Width-RBF neuron	6.8

	Compounds
Tr	770
Ve	110
Te	60

Table 43: Prediction of aqueous solubilities of typical drugs

Drug	$\log Solu_{expt}$	$\log Solu_{expt} - \log Solu_{NN}$
Aspirin	-1.610	0.125
Benzocain	-2.320	0.247
Phenytoin	-3.990	-0.147
Testosterone	-4.070	-0.020
Diuron	-3.760	-0.032

Table 44: Prediction of aqueous solubility using counter propagation NN

Method	Function	
SOM	Compounds selection for Trn and Test	Tr: RMSEP 280; Test: RMSEP 94
Heuristic	Pruning molecular descriptors	7
Counter propagation_NN + automatic adjustment of descriptor's relative importance (AARI)	Predictive model	Tr: RMSEP 0.668; Test: RMSEP 0.679

Hansen solubility parameters: Járvás et al. [258] used COSMO-RS sigma moments calculated from state-of-the-art-continuum solvation model of computational quantum chemistry. The statistical decomposition of moments output polarization charge densities. These are high informative molecular descriptors. The predictive models are developed for components of 3D- Hansen solubility parameters of organic compounds of diverse functional groups and physico-chemical/quantum-level characteristics (chart 71). These multi-variate-non_linear-structure-property-relationship-NN_models (MV_NL-NN_SPR) have not

only high predictive ability for compounds with varying dispersion/ hydrogen bonding / polarity, but also possess transparent physico-chemical meaning.

Chart 71-Prediction of Hansen solubility parameters

Compounds
- Alkanes, alkenes, haloalkanes, nitroalkanes aromatics
- Amines, amides, amine/acid associates
- Alcohols, ketones, ethers, esters, acids
- Ion-pairs, ionic liquids

Trn	128
test	17

Software	Function
COSMO	QC Solvent model
NN	Data driven non-linear model

Molecular descriptors (X)
- Five basic sigma-moments

Response (y)
- Hansen solubility

Performance for test set

Correlation coef		Mean absolute deviation	
*R*2d	0.85	$\Delta\delta$d	1.37 MPa1/2
*R*2p	0.91	$\Delta\delta$p	1.85 MPa1/2
*R*2h	0.92	$\Delta\delta$h	2.58 MPa1/2

Permeability: Ghorbanzade et al. [378] reported a predictive NN model for corneal permeability of drug like organic compounds using molecular descriptor as explanatory factors (Table 45) using statistical performance measures.

Table 45: Prediction of corneal permeability of drug like molecules

MLR
MLP_NN

SPR
X: 7molecular descriptors
y : corneal permeability

Models	Purpose
PCA HCA	Two groups-exploratory analysis
Counter propagation NN	Classification of low permeable (LP) and very low permeable compounds (VLA)

Leave-many-out (LMO)-CV

Performance	MLR	MLP-NN
Q^2	0.584	0.774
SPRESS	0.378	0.087

Performance	%Classification accuracy
LP	95.7
VLA	95.4

Table 46: Predictive SPropR models for diffusion coefficients of drug from polymer matrix

Log P by piezoelectric acoustic sensor: The experimental determination of partition coefficient of a compound between n-octanol and water is a coveted and time tested procedure in calculation of hydrophobicity of drugs. Li and Cooper et al. [171] proposed an alternate method for lipophilicity of drug molecules. On a gold electrode of a piezoelectric acoustic sensor, a self-assembled monolayer of HSC10(CH2CH2O)6C18 was formed. When the drug compound of interest is partitioned in the interfacial layer, there is a change in sensor resonant frequency which is measured. The log D and also pK of molecules quinine (pKa = 7.95) and naproxen (pKa = 4.15) are determined.

- MLR
- MLP_NN + Bayesian regularization

Models	Purpose
Polymer–solvent systems	Three polymer–drug systems
(polystyrene–toluene, polyvinylacetate–toluene, polystyrene–ethylbenzene and polystyrene–tetrahydrofuran)	(paclitaxel–polycaprolactone, hydrocortisone–polyvinylacetate and procaine–polyvinylacetate).

Diffusion coefficients: Kale and Sanjeev [232] developed structure-property-relationships between diffusion coefficients of drug molecules in polymers based on modified free volume theory of diffusion (Table 46). The predictive model was applied to release of paclitaxel from polycaprolactone and future prospectives of the study are in the exploration of reverse engineering of designing optimally controlled drug release systems.

Osmotic second virial coefficients: Johnson et al. [302] predicted osmotic second virial coefficients for a large number of additives and also for IgG protein from NN modeling preceded by fractional factorial design (chart 72) with a goal of increasing protein solubility without any detrimental effect on its stability.

Chart 72: Selection of additives for solubilization of protein

Data driven modeling

Obj: **Increase** (protein solubility)
Constraint: **No reduction ([**stability of protein (thermal; aggregation)])

Phase 1: Identification of individual additives which reduce protein interactions
Phase 2: Fractional factorial design (Fr.Fact.Des) for different combinations of additives from phase 1.
B-values are measured
Phase 3: NN model for B-values = Fn(additives composition)
Prediction from trained-NN model
Phase 4: Prediction of B-values for 4000 formulations not used in Phases 1 to 3
IgG protein from Minerva Biotechnologies

ॐ Structure response relationships (SRespR)

Durcekova et al. [312] reported NN models for structure HPLC retention relationships (SRetentR) for 59 esters of alkoxyphenyl carbamic acid which possess local anesthetic activity. The simulated distribution, solubility and NMR parameters are in the predictive model (Table 47).

Table 47: Structure (HPLC) retention relationships of compounds with local anesthetic activity

59 Esters of alkoxyphenylcarbamic acid

Molecular descriptors(X)

Response: surface and/or infiltration anaesthetic activity

Simulation parameters

Separation systems	
Columns	**Mobile phases**
Phenyl	Acetonitrile/water
C18	Methanol/water

Models	
PCA Cluster analysis	Closeness
NN	Predictive model retention factor of

(y)		compounds
log *P* log *S* and NMR chemical shifts 13C and 1H	Performance	
	Linear model (k_predicted vs. k_expt)	Intercept approximately= 0 Slope =1

Structure parameter relationships (SParR)

Binding constants: Wen et al. [304] predicted binding constants of isoimperatorin and chrysophanol with SXRs using RBF_NN. They are comparable with experimental values (Table 48). These molecules are bioactive components in traditional Chinese medicines.

Table 48: RBF-NN SXR model for prediction of binding constants

SXR_ model	R2	RMS
MLR	0.8521	0.2678
RBF_NN	**0.9245**	**0.1736**

pK values: Gobburu [1995] proposed NN based S(pK)R for beta blockers. The model successfully predicted in vivo processes from in vitro experiments. Fraczkiewicz et al. in an collaboration project between pharmaceutical and software companies developed prediction of pKa of drug like molecules in silico (chart 73). The experimental pKa values at Bayer pharma were measured with Sirus T3 pH/EMF instrument. It collects 50 data points in 4 minutes in the pH range of 2.0 to 12.0 using 5 µl of 10 mM DMSO stock solution.

Protein-ligand complexes: Fourteen scoring functions are tested for 800 diverse protein-ligand complexes [296]. The scoring function calculates the fitness goal of a ligand molecule to its target protein. Empirical scoring functions do not require extensive conformational sampling. Thus, they are fast in computation and are used in HTS.

23. State-of-knowledge-of-medicinometrics and pharmacometrics

Diagnosis, treatment, pharmaceutical preparation, drug discovery, fine tuning of each of these sub disciplines appear to be simple for a naked eye, but at molecular level more complicated interwoven network like outside universe. Here, the complexity of task, current-state-of-science, limitations and future scope are briefed.

Chart 73: Prediction of pKa by NNs

	Chemicalspace_	
	Literature	industry
Compounds	~11000	~16000
pKa	~14000 literature	~19500 Expt_Bayer Pharma

pKa methods
- NN
- Microstates analysis

test sets	
~31000	New pKa values measured at Bayer
>16000	Most difficult equilibria

Performance		
Stastistic	Trn	Test
MAE	of 0.72	0.50
RMSE	0.94	0.67
R^2	of 0.87	0.93

Medical diagnosis

The clinical/ chemical/ biological (including viral) data, gold-standard tests, instrumental (X-ray, MSI, MRI, EEG, PET, ultra-sonic) procedures, biopsies, exploratory surgical probes diminished both false-positives and false-negatives in diagnosis. Magnetic Source Imaging (MSI, used in magnetoencephalography) is complimentary to fMRI, PET, EEG, SPET and offers information on spacio-temporal dynamics of activity of brain. Laser technology, robotic-surgery paved way nearing to blood-less-surgery dreamt in nineteen eighties. Intervention (electro-physical) operations enhanced the benefits of routine practices. There are consistent reports endorsing the positive benefits of NNs in medical care with implicit predictive information in diagnosis/prognosis and survival data analysis. The prediction of diseases and health perturbations in advance from analysis of genome of individual with upgraded

knowledge base of UK and US large ventures will be a new facet in the next decade health monitoring programs.

Evolutionary Confirmatory diagnostic tools: Gold standards (angiography for coronary artery disease, mammogram for breast cancer) at 6-sigma level repeatability drastically reduced false-positives_false-negatives for classification.

Analysis of biological and Clinical samples (ABCs): The chemical interactions — thermodynamics, kinetics, solute-solvent interactions — were primarily confined to analytical grade chemicals in chemical labs (table 49). Later the applications to biomaterials, pharmaceuticals in presence of excipients, industrial products, minerals/ores and were of utmost importance. The in vitro studies in probing into drug-/bio compound- interactions were means of understanding in-vivo interactions by logical extrapolations and indirect evidences. Recent advances in instrumentation, software/hardware made it possible not only to get direct evidences of single molecule, a cell and binary interactions in a living cell (i.e. in vivo) but to probe in time and space (volume).

Complexity of biological processes: Many biological processes are chaotic which have been modeled with NL methods [134]. NNs are promising instrument for even in solution of inverse tasks.

Solution approaches: There are a number of different quantitative models that can be used in a medical diagnostic decision support system including parametric methods, non-parametric procedures and several neural network models. Unfortunately, there is no theory available to guide model selection. There are consistent reports endorsing the positive benefits in medical diagnosis, prognosis and clinical/chemical survival analysis from NN' predictive information [159]. Innocent [91] et al. summarized the AI projects applied to medicine high lighting the impact of NNs and Fuzzy logic in diagnosis. Type 2 fuzzy sets deal with vagueness in the measurement. The predictive modelling is an important/indispensable component of medical care. It is already in vogue in medical instruments and robotic surgical adoptions.

Current practices medical treatment

The pharmaceutical drugs are administered through oral (tablets, syrup and patches), intra-muscular/intra-venous injections, drug-releasing implants and dermis route. The sustained release drugs even in nano form impregnated in drug carriers, multiple-drugs-in-a-single dose brought pharmaco kinetics to the desired range and increased psychological pleasure of a common patient. Anywhere in the world, even today only the (human) surgeon performs surgery on a patient. But, there is no robotic_surgeon in totality for surgical cure of a human patient. In yester years, the doctor was using surgical knives, scissors etc., and now, in robotic/tele-robotic surgery, robot – (crawling (snake), swimming) is a tool and it meticulously replicates on the patient the surgeon's finger movements and all micro details of operation at the console.

Table 49: Ultimate limits of detection and sensitivity in analysis

Period	Name	Metric unit (g)		
1960–1970	Nanogram	(ng)	10^{-9}	ppb
1970–1979	Picogram	(pg)	10^{-12}	ppt
1980–1989	Femtogram	(fg)	10^{-15}	ppq
1990–1999	Attogram	(ag)	10^{-18}	
2000–2009	Zeptogram	(zg)	10^{-21}	1000 Da molecule
2010–2019	Yoctogram	(yg)	10^{-24}	1 Da 1.7 H-atom
	Da: Dalton			

F. Adams, Talanta 85 (2011) 1230–1232

Pharma industry

Structure_expression into numerical descriptors: Hammett laid foundation stone for structure activity relationships (SAR) in 1950s for explaining rate or equilibrium constants of substituted benzoic acids. In 1970's, Hansch extensively applied SAR for compounds of biological-/ agricultural-/ medicinal importance with a few number of physic-chemical and structural features viz. substituent constants, MR,

log P etc. The molecular descriptors now running into four thousand changed the very frame of SActR into SXR.

Drug discovery

Although, modeling alone did not bring out a new drug altogether, it is accepted to be indispensable in all phases of research, product development and analyzing the benefits as well as ill effects. Statistical techniques were the integrated part of studies in drug design and pharmacy. However, small sample size, probability distribution function characteristics of input, their errors and parameters of the model limit the applicability. In pharmaceutical chemistry, the front-end activity viz. data collection with experimental design is time consuming. Yet, the overweighing benefit is high information content compared to that generated through OVAT (one variable at a time, a trodden and long nurtured practice) or work plan of the expert pharmaceutical scientist. Structure based approach is viable if biological target protein is available. On the other hand, one resorts to ligand based approach employing similarity search in case of no idea of site. High throughput search, chemoinformatics, bio-informatics and combinatorial chemistry generate a large number of compounds with therapeutic activity [153]. SXR is in silico screening procedure ensuring 'fail fast, fail cheap' and thus an affordable business model in drug discovery cycle.

Success story of in silico discovery: The discovery of novel nonsteroidal ligands for human sex hormone binding globulin with in silico route is a noteworthy incident. CoMFA/CoMSIA, NN based detailed and accurate QC-generated 3D-surfaces of electron density and ESP will reduce the lead optimization time schedule.

Databases

ADMET databases: Experimental ADMET data are scarce and even most of the acquired information is proprietary. When the data is available in the open sources, the experimental errors and variations between different reports are large. This hampers training NNs with large number of patterns, although this data driven paradigm is ideal to model complex relationships between chemical structure and ADME(Tox) responses [147].

Chemical, biochemical-, pharmaceutical databases: The printed/ electronic and online databases from commercial organizations, academia and proprietary drug researchers crossed petabyte of numerical and categorical data. We reviewed typical ones earlier in the year 2000 and an updated version will be separately published. Table 50 describes a few pertinent databases in pharmaceutical study for ready reference.

Table 50: Comparison of classification of compounds of pharmacological

NP		Data structure	Training	Testing	External validation
169	DB1	3-way	99	60.9	62.1
207	DB2	3-way	94	84.8	63.4
135	DB3	3-way	100	71.4	70.4
272	DB4	4-way	96.6	55.8	46.3
2400	DB5	3-way	85.5	57	60.6
SA-SOM >> PLS > [,SOM,] < [MC-SA_SOM]					

Data bases	
DB1	α4- β2 Neuronal nicotinic receptor
DB2	Dopamine receptors
DB3	Topliss oral bioavailability
DB4	Dihydro folate reductase (DHFR) inhibition
DB5	Growth inhibition (National cancSer institute -Anti-cancer data base)

Chart 76a: Outcome of quality of data and methodology

Data	Method	Result
Good	Good	Good
Good	Bad	Wrong
Bad	Good	Wrong
Bad	Bad	!!!!!

Typical Databases relevant to pharmaceutical science

Abbreviation	Acronym
ACD	Available Chemical Directory
CMC	Comprehensive Medical Chemistry
CNPD	Chinese Natural Product Database
WOMBAT	World Of Molecular BioAcTivity

Data for typical case studies

Duke University Medical center, Durham, NC	1991 Jan to 1992 May
Regional Thoracic surgery unit, Mersey, UK	1987 to 1902
University Hospital Charite Berlin (Germany)	1998-2002

WOMBAT

WOMBAT (World Of Molecular BioAcTivity) database,26 version 2006.1.

- WOMBAT is a target-annotated database available from Sunset Molecular Discovery (Santa Fe, NM).
- Version 2006.1 contains 154 236 compounds, collected from articles in medicinal chemistry journals published between 1975 and 2006.
- A reduced set of 135 877 unique chemical structures resulted after removing duplicate structures as well as those, for which some of the used physicochemical properties could not be calculated.
- contains the reported activity values, expressed as p*K*i value, information about the species in which the tests were performed, and the biological role of the structure (inhibitor, antagonist, etc.) as well as additional properties of interest.

Data sets from WOMBAT

568	Acetylcholinesterase (AchE)
999	Cyclooxygenase 2 (COX-2)
457	3',5'-cyclic-nucleotide phosphor-diesterase IV (PDE4)
2105	Thrombin
199	u-plasminogen activator (uPA) inhibitors

Chart 74: Neurofuzzy models for relationship between pharmaceutical preparations and pellet properties

227 Pellet formulations Extrusion/spheronization method	3000 Variables → sensitivity analysis (0.40)
Fuzzy NN	Ouptut Process knowledge if-then-else rules

Knowledge bases: Mendyk et al. [246] developed a neuro fuzzy model and extracted enhanced transparent knowledge in logical rule format for drug preparations as tablets using characteristics of pellets (chart 74). It throws light on future computer-guided optimum pharma products. The rule extraction algorithm becomes more concise and accurate by preprocessing of the data, pruning records with missing values and selecting relevant variables. A new paradigm [74] is proposed where in the prior knowledge can be used to determine the architecture of NN and to program a subset of weights to induce a learning bias. The latter is useful in training. Further extraction of knowledge from trained NNs opens new vistas in knowledge refinement. Obviously it paves way to surmount the uncertainty in the prior knowledge. Yamamura [159] proposed the development of suitable designs and performance measures conforming to

the well-established medical data framework. The discovery of even obvious rules by NNs without a priori information is the confirmation of their implicit computational intelligence, which can be a new dimension in data-information-knowledge-intelligence extraction/development. Fuzzy information systems (FISs), novelty detection, rule extraction features are now integral part of recent algorithms of many NN architectures.

Template typical drug molecules: Nantasenamat et al. [221] brought out a novel NN method of extracting template molecules from 3020 titles of published papers in text format (chart 75). The words culminating to recognition of template molecules from textual information are upgraded in the dynamic database. Most of 776 template compounds resulted are therapeutic drugs. Computational quantum chemistry is used for physico-chemical properties and classification procedures are employed for confirmatory information. This is claimed to be first of its kind in field of molecular imprinting discipline.

Chart 75: Extraction of template molecules from titles of literature

Methods
- NNs
- Simple dictionary
- Rule-based search
- Dynamic updating database

Data analysis and modeling
Exploratory and confirmative Data Analysis

Good data: Over years, there is resurge of emphasis of good primary data for valid information and consequent hypothesis, theories, models and most coveted predictions. The precision and accuracy of data increased with electronics, computer chips and preprocessing software. In this context, it is apt to remember the solution phase equilibrium measures Bjerrum, purity of benzene samples of Faraday meet today's standards. Bayer Inc. includes the experimentally designed chemical space also as a criterion of good data. Further, it showed the quality of SXR predictions in drug research by including small molecules from drug discovery programs. It advocates the philosophy of sharing internal data at global chemical/pharma companies with external collaborators will benefit all.

Good methodology: Apart from state-of-art-optimization procedures, physico-chemical scheme should be as nearer to the phenomenon as possible. In the case of acido-basic equilibrium constants, consideration of micro-states (which were neglected in yesteryears' compilations) raises the status of methodology.

The database with larger number of compounds covering required chemical space with sufficient number of data points developed from pKa values of good methodology operated on good data is an optimum takes off point for prediction for compounds not yet synthesized or those in virtual library. The wide spread negative shade of SXR does not vitiate the predictions from good_methodology good_data pair (chart 76).

The traditional methodologies started with scatter diagrams, frequency tables, distribution profiles, point estimates, t- F-, chi-square test, ANOVA and regression. Later, three-sigma limits, outliers, robust statistics, Bayesian statistics, robust regression, 2D-plots and MANOVA have been widely used. Recently, interval estimates, extreme statistics, extreme learning machines, fuzzy-, possibility measures, soft models, distribution free methods, nature inspired algorithms, hybrids of classical statistics with advanced statistics and Eman are in practice in advanced studies. In this evolutionary development, yester year's confirmatory protocols slip down to low level exploratory tools. Thus, a tool does not extinct altogether. Its adapted/ new/evolved forms are to be kept abreast and used to be on frontline in progressed_science to get together with the then perceived/ conceived / projected truth.

AI a complimentary tool and not a substitute to medical protocol

Artificial Intelligence or statistical/mathematical techniques cannot be dreamt to substitute/ alleviate clinical tests/ biopsy / expert opinion for dreaded diseases and for further intervention/ medication/ surgery [123]. But, the state-of-the-art-of-AI in medicine as second opinion machinery and obedient/ lapse free servant in prognosis, diagnosis, treatment, surgery, ICU deserves ovation. It increases the chances of accuracy of diagnosis prior to referring to expert (say oncologist/ cardiologist/ urologist/ Andrologist)

among experts especially when patient to doctor ratio is very high. For instance, specialized neurosurgeons are around 300, and another 3500 belong general neurosurgeons category in US. Computer aided designs compliment transfer of knowledge/skills and avoid pitfalls in specialized protocols.

Limitations of AI-2 tools: Will machine intelligence ever reach, if not surpass, the human (expert) level is not only a million dollar question, but perineal utopian pursuit of computer scientists. If it is realized, the computer (stand alone or humanoid robot) system becomes self-aware. The time scale is unpredictable to fully understand and implement the functional behavior of the brain structure and developing a model of it and evolve into an artificial system executing in response to the external stimuli. Buttazzo [38] discussed several pros and cons related to the possibility of developing a conscious artificial brain. Multifold knowledge of medicine, AI, NN and translation of medical task into general problem of AI in medicine is still awaited.

Chart 76b: Typical NN models and their function

$$_NN	Function
Associative memory	Abbreviation Acronym/concept (linguistic) Figures
SOM	Under supervised Data clustering
FF_MLP	Cause-effect models Static
Recurrent	Dynamic Time/different points in space
Sequential Hierarchical	Multi-organ brain Drug discovery pharmaceutical cycle
Ensembles Forests	Brain like
EP GA SAA PSO	Nature mimicking Global Multi criteria Statistical/fuzzy /possibilistic/ Mathematical

Neural Networks

Data driven non-collapsing models: Neural network, a data driven paradigm, is increasingly productive with larger databases and excelled not only in performance but also in ensuring reliable and non-collapsing models. A NN builds the best multi-dimensional, multi-response and non-linear model possible for the user given response and causative factor data. The results offer complimentary/supplementary information.

Non-monotonic NNs: Non-monotonic reasoning is used to mimic human's common sense reasoning. The multiple inheritance schemes are used to represent the knowledge. Non-monotonous NN acquires this feature but not the knowledge present in non-monotonic inheritance. Non-monotonic NNs employ hybrid learning [40] with non-monotonic reasoning as one of the components. These NNs offer explanation of trained NNs. The symbolic knowledge of the domain is acquired and refined with classified examples using connectionist learning techniques and finally extracting comprehensible symbolic information.

NNs Ensemble: Now, it is established undeniably that ensembles of NNs out perform a single constituent NN [38]. The approaches to generate ensemble of NNs are bagging, boosting, GASEN etc. [42]. Yet, the pragmatic hurdle is to develop an ensemble. It is like implementing universal function approximation theorem in NNs. There are no theorems and not even heuristics for the choice of architecture and other criteria. But, the heuristics are that the members of the ensemble should be accurate and diverse to the extent possible. These are of course mutually conflicting criteria. Hence, the optimal compromise is to adopt several hitherto invoked approaches to come out with a hybrid or altogether new set of procedures. A popular algorithm for this purpose is sequential aggregation and the effect of bad NN members in the ensemble are discussed. GASEN generates ensembles with very small size but of high generalization. The success of GASEN lies in diminishing both bias and variance. It effectively selects NNs from available set. The analysis of ensemble approach for regression/classification shows that 'ensemble of many is better than ensemble of all'.

Transparency of ensemble output: The comprehensibility of ensembles is so far focused on global models that mirror the behavior. Wall [78] analysed the output of ensemble on case by case basis. Obviously, the

comprehensibility of the component NN gives major transparency to the ensemble. This is acceptable and gains scores over black box models. It is like the sensitivity analysis to sort/prune the input variables/weights in a single NN based on case by case study. Another similar instance is that a weakly quadratic model looks like a linear one in a limited range of input space.

Translation of symbolic rule to NNs: Bologna [76] reported a method to translate symbolic rules into discretized interpretable MLP based on the discrimination of hyper plane frontiers. This procedure extracts rules from trained NNs also.

High order of petri-NNs: High order petri nets are similar to NNs [49]. They represent McCulloch-Pitts-NN and also higher order NNs. Here, 5-tuple higher order petri nets are proposed and applied to a polynomial higher order NN with five antecedents using fifth order predicate logic.

Limitations of NNs:

The modeling of volume of distribution in burn patients with NNs is inadequate. Linear modeling many a time shows better performance in prediction compared to NNs for linear systems. It is not a deathblow for the imbibing character of NNs, if not read in between the lines like 'xor' problem for perceptron model. Except in computations with fuzzy logic of type II, the computations are limited to numbers/attributes/Boolean. The computation/knowledge extraction with words/sentences and automatic generation of hypothesis is on the way. A unified representation which subsumes the earlier ones and leaving a scope for expansion of knowledge representation is reported with a generic name "think: formalism". This paves way for cooperative operation of existing data bases and knowledge extraction tools in a distributive manner. Although NNs accept many types of data, still it is difficult to represent trees and lists (variable sized recursive data structures) in a fixed width patterns. Recently, NN architectures are developed which automatically develops a compact distributed representation of trees and lists. Further, they can be efficiently accessed. The recursive use of three layer auto associative encoded NN with BP successfully performs these operations like combining apparently immiscible aspects of features, pointers and symbolic structures. It is a bridge between data structures essential in high level cognitive tasks. Yet, they haven't raised to the stage of even partial emulation of brain and thus cannot solve the inverse problems in a complete sense. Further, this approach cannot establish existence of causative (functional) relation and thus, it is not a probe to elucidate the mechanistic details of the whole/sub process. The accuracy of the evolved model depends upon the availability of sufficient data in all regions of the changing trends. The prediction capability relies on how close the test data is to the available training patterns, their quality and consistency. The 'no free lunch' theorem, in optimization and equation solving paradigms, holds good in modeling as well as in software development.

Bias in NNs: Since the model is biased towards commonly occurring training data, it fails to predict extreme values. The bias in training data is similar to minority class in classification. Namee [90] applied stratified sampling on boosting to overcome the problem of bias in NNs to predict the clotting time in anti-coagulating drug therapy.

24. Future prospects

The scientific endeavors evolve with developed knowledge/ technology, fixing short comings, surmounting pitfalls, finding solutions for inherent/ acquired/cumulated/ mutated/ overgrown malicious faults and financial/ ethical support of governance. The inspiration and motto is societal prosperity (in this case best possible health for all) and natural instinct of perceiving the growth of knowledge from more to more to be nearer to absolute (not relative) truth of universe and human brain.

Futuristic NNs: Just like a general problem solver envisaged in the early days of artificial intelligence (AI), NN with multiple layers and different TFs is not of pragmatic significance. Instead a set of simple NNs

combined does the job better. Another aspect in NN research is to improve the predictability by developing an ensemble of NNs. This is like Monte Carlo method. Of the various forms and technologies of ensemble development even a basic white box NN becomes opaque. A positive attitude, if not a craze, is to attempt rendering ensemble too as transparent as a white box approach.

Future scope & prospects of evolving-AI: With ever increasing paradigms (conceptual/ model driven and/or data driven), improved mathematical logic, the number of models at one's disposal is ever increasing beyond leaps and bounds. It is outside limits of comprehension for an optimum choice [101]. A set of hard and fast rules are neither available in black-and-white nor incorporated even in best set of trend setting software packages. The error profiles in input/output measurements, hardware and the desirable accuracy against cost limit, the choice of models to a small subspace should be part of commercial software. It is time to make a beginning of cooperatively upgrading the rules with expert feedback in packages in a research mode. This will open a new era in not only consolidating the method bases, but bring out the gaps and to march forward for innovative intelligent computation procedures with numbers, words and ideas. This leads to finally living with a favorite model which of course will be argued as sufficient/adequate for the task on hand.

Synergy is popular concept in solvent extraction of chemical substances in mixture of organic solvents. Marquardt procedure is an earliest hybrid algorithm mimicking steepest descent, first and second order Newton methods. Mathematical statistics is coveted interface of mathematics and statistics. Chemical biology, chemical genomics etc. are recent hybrid scientific disciplines serving specific tasks. The metrics era is a multiple-inter-intra-cross disciplinary and interface of (chart 77) deep rooted scientific paradigms. There is no single software package or modeling algorithm (just like generalized problem solver of AI of 1950's) that can solve a problem in all ranges or all tasks even in a restricted domain.

Chart 77: Inter-and intra- scientific disciplines

($$$chemistry+++)
Immunocytochemistry
Chemical biology
Analytical biochemistry
Inorganic biochemistry
Bioinorganic chemistry
Organic biochemistry
Bio organic chemistry
Chemical physics
Physical chemistry
PCCP

($$$Physiology)
Psycho-physiology

Futuristic computer intelligent (CI) based mega systems increase predictive accuracy at the same time reducing both false positive and false negatives. The accuracy will slowly go up to six sigma level (SSL). The cost, time and expertise appear to mismatch the increase in outcome. But, the low morbidity and mortality rate, enhanced life span with highest possible comfort and above all (both physiological and psychological) functional ability over compensates the progress of human intelligence in taking science and technology to higher and higher heights and in turn to be nearer to cited utopian ambitious targets [80]. Although AI paradigm has been used to probe into the meta cognitive processes, consciousness/ un-consciousness, still not even tip of iceberg is chiseled.

Neuroscience and brain chemistry engulfed multiple disciplines during the last half a century and now awaiting for breakthrough. Recently, the focus is to bridge the gaps of sparkles of Descartes, Einstein, Heisenberg, Hebb and Hayek with the explanatory formulations paving way to a new horizon for evolution. It has been proved that cognitive processes and brain has super-synchronization emphasizing the need for a holistic approach of brain/body-mind complex. One should resort Gedanken-models exploiting intelligent information imbibing (3Is, I^3, three eyes) of physics, physiology, psychology and philosophy (four Ps or P^4), leaving the long practiced and indispensable discrete structures and/or functions of organs with loose connections of yesteryears. The oscillatory responses settling to stable state is coveted explanation of functional dynamics of the brain/body–mind on genetics basis. A sparkling breakthrough

involves shift of the present mechanistic Cartesian system to a nebulous Cartesian system. The latter is parallel to quantum mechanics and inherent parallel computing.

Future track (2015- onwards) perspectives in Medical treatment: The sumptuous strive (untiring efforts) over a century drastically reduced the morbidity and mortality rate. The discovery of a new drug is need based. The current interest mostly is around reducing the side effects and increasing the efficacy by modifying the structure of lead compound of each drug and directing towards personalized drug treatment using DNA targets too. Now, synergy between the chemical, biological and physical properties of nanoparticles (for instance AuNPs) rendered them key winning players in the future track of medical imaging, therapy, implants and diagnosis. The education and counseling to avoid high risk food/ habits / addiction /life style should be an ongoing paramedical program.

Next generation Pharma industry: The future trends of pharma industry are to develop new formulations and bringing a new era in controlled drug delivery systems. All these activities are purely experimental, but quite opaque in probing into in vivo processes, the ultimate interest.

Data space: High quality diverse datasets are scarce. Statistically designed experimental data with high information content as well as high signal to noise (S/N) ratio is time consuming and expensive.

Explanatory variables: From the explanatory variables stand point, 1500 to 4000 molecular descriptors are available for a conformer of a compound. SA galaxy of procedures is available for the choice, but relevancy and selection from equivalent models is still a big question [148]. Yet, one-to-one mapping of structural features and descriptor space is not well understood [140].

Solution phase chemistry: The solution phase chemical interactions are light houses to search for molecular level processes involving proteins, drugs, small molecules, biomaterials in organs, cells and consequences in life progress. Twenty first century is heading towards new level of hierarchy in understanding the phenomena in backdrop of scientific probes matured during last century. It is molecular level perturbations/mutations in biological sense, interactions with nearby molecules, self-proliferation, dissociation, aggregation, rearrangements and on so on. From chemistry point of view molecular processes in gas phase was the coveted study in early 1900. Later processes in solution (water) drew the attention. But to understand the very role of water itself, large quantum of research was around probing into processes in methanol, ethanol and many water miscible solvents. The other direction was studies in water immiscible solvents, sulphuric acid, HF, organic solvents and their mixtures. But, the detailed picture of solvent structure itself was not complete. Now quantum chemical calculations under the head molecular interactions, a detailed picture of monomers, dimers, large clusters of solvents are reinvestigated and the book of knowledge bits of aqueous and water-solvent mixtures of simple organic moieties and ions is rewritten. The small forces like non-electro-static contributions viz. Van der Waal, non-covalent, low energy hydrogen bonding, cation-cation interactions, etc. which are much lower than chemical energy band brought a large database of data awaiting complete transformation into knowledge level and up surging of intelligent sparkles. The added information is from multi response high tech instruments NMR, gas phase IR, time resolved/FT-spectroscopy, MD calculations (along with MC of yester years') under extreme variation of T, P and concentration. The recent mission of studies at zero gravity in space science and nearly equal environment at the time of origin of universe will not only absorb/imbibe all earlier doctrines, but will open a new chapter in the annals of science.

Future perspective of drug discovery: An intelligent machine exploration for gaps in discovery map at primary level and leaving output for experts' scrutiny will save several brain years of time. Intrinsic query base at cell-/ molecular- level, for hitherto unanswered queries/ vague answers /inadequate explanations will navigate towards the healthier society. Newer probes to cover more than hither to explored chemical- / biological- / pharma- / disease-/ high-risk space in computational experiments to be carried out with state-

of-art- statistical experimental designs need to be initiated. The RSM models with Pareto optimal fronts rather than hither to routinely used quadratic or rarely used NNs will take a quantum leap in optimized solution of mutually contradictory objectives.

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FIR
- Focused information reviews
- Fast information report
- Fourier infrared
- Far infra red

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One of the authors (RSR) started his research career with analytical estimation of isonicotinic acid hydrazide in pharmaceutical preparations (isonex) by redox titrations with potentiometric and colorimetric procedures. Soon, he switched over to proton-ligand and metal-ligand complex-equilibria of divalent metal ions in aquo-orgnaic mixtures to probe into solute-solvent interactions and understanding drug metabolism. Since, three decades impact of chemometric techniques on chemical estimations and speciation, kinetic studies have been published. In mid-nineties, experimental design and RSM were used for optimum conditions of estimation of labetalol hydrochloride and other drugs. The heuristic expert systems, rule generation from numerical data, intelligent databases were developed for chemical speciation. In the last decade, computational quantum chemical calculations, molecular descriptors and NN modeling were used for gas chromatographic data, isoniazid and its isomers. In this decade exploratory studies of prospects of nature inspired algorithms in SXR, equilibrium/ rate constant estimation, multi-sensor-multi-component calibration have been published. KRK, kineticist also published widely in computational quantum chemistry and micellar catalysis. He published synthesis, purity and impurity profiles of pharmaceutical preparation using state-of-art- instrumentation.

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