Machine Learning Algorithms in Bioinformatics

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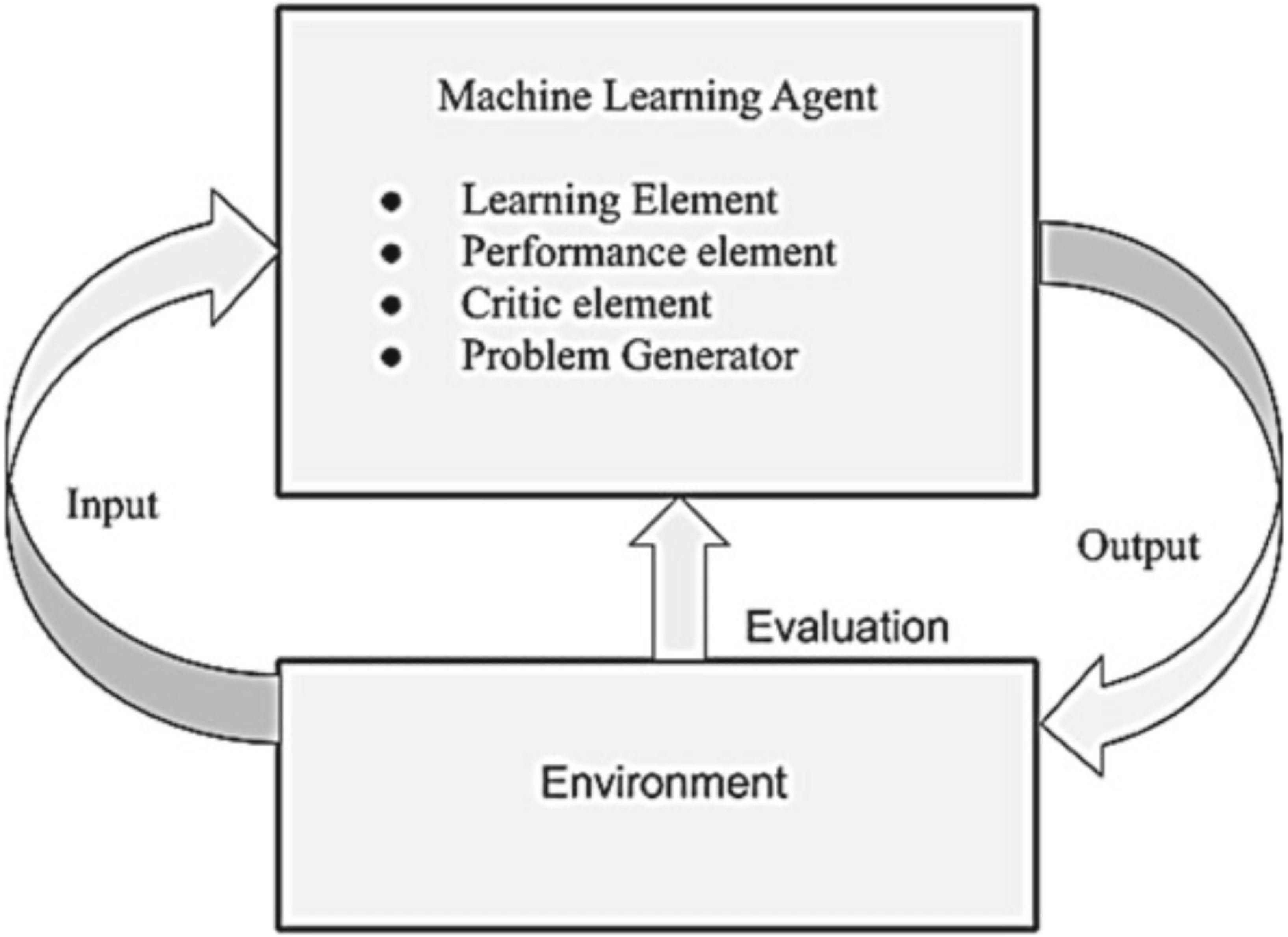
https://bmoraffa.github.io/presentations

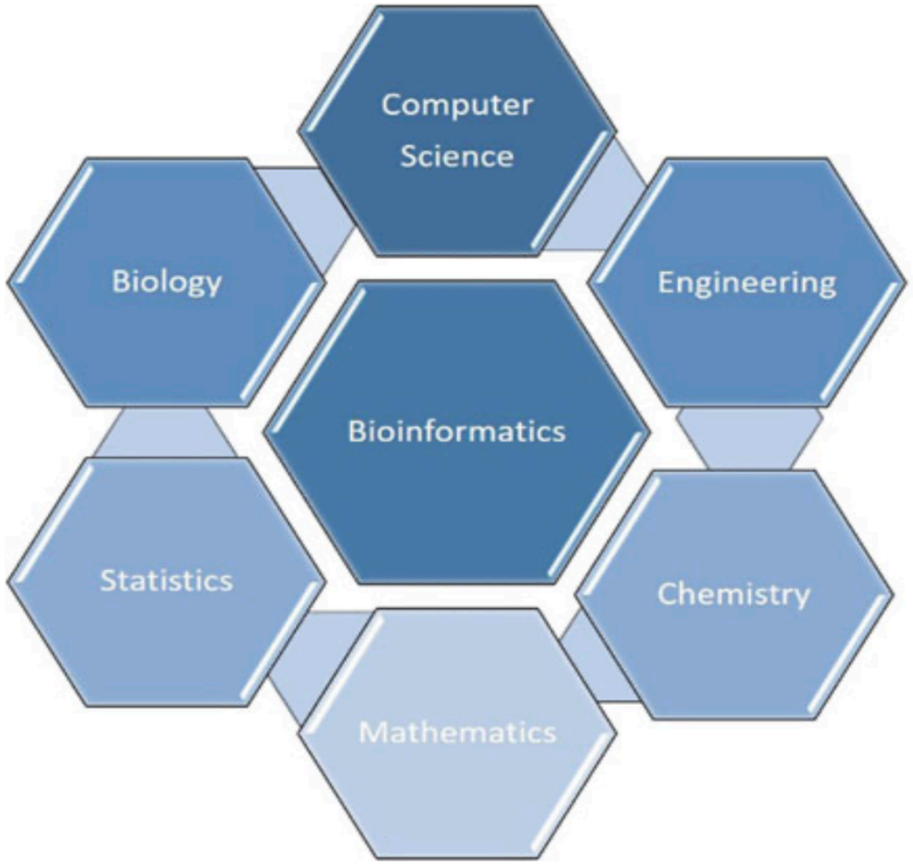
What Is Machine Learning?



What Is Bioinformatics?

Role of Machine Learning in Bioinformatics?

- Bioinformatics as a hybrid science that connects biological data with analytical advanced technique to withdraw meaningful information for various scientific research including biomedicine.
- In Bioinformatics, data is collected, stored, manipulated, in addition, this includes modeling of data for analysis, data visualization and foresight by the deployment of algorithms and software.
- Bioinformatics uses computation to get relevant information from biological data through different methods to explore, analyze, manage and store data.
- It is mainly used for the identification of genes and nucleotides for a better understanding of disease based on genes.
- Classification of gene sequence has an important role to understand the principle within nucleic acid and protein sequence.



Some Problems In Bioinformatics

DNA Structure and Biological Sequence:

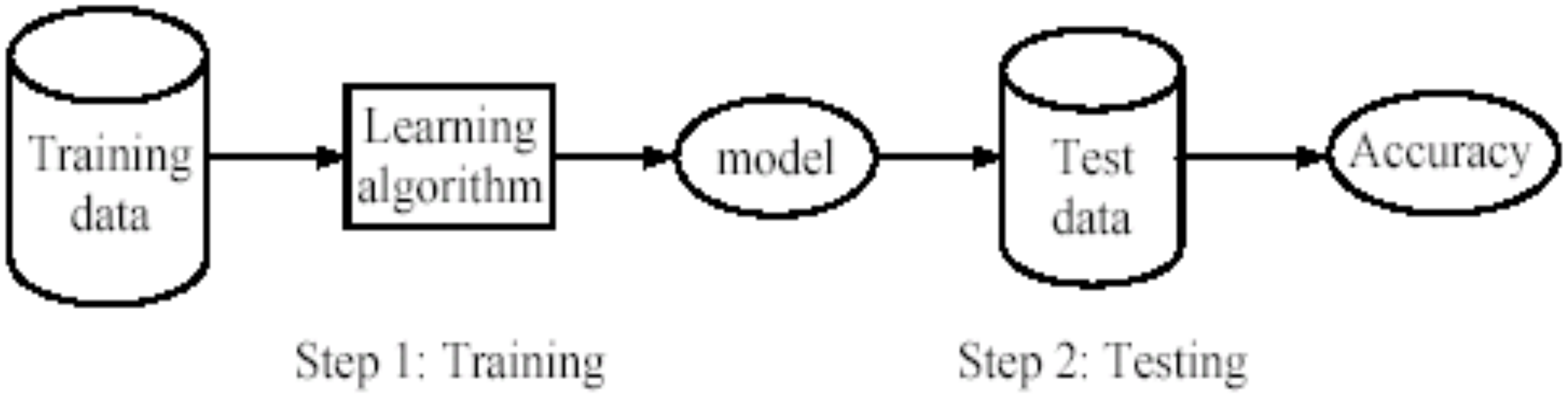
- Predicting the protein structure
- Analysis of structures of protein for marks of a functioning
- Alignment of structures
- Biological networks such as gene regulatory network, protein-protein interaction network requires an extensive amount of care
- Prediction and classifications of genes
- Gene finding: Finding introns and exons in DNA-sequence segment
- Genome annotation: analyzing the repetitive DNA which is copied from the same or nearly the same sequence within the genome

Supervised Learning Vs Unsupervised Learning

- Supervised learning: classification is seen as supervised learning from examples.
  - Supervision: The data (observations, measurements, etc.) are labeled with pre-defined classes. It is like that a “teacher” gives the classes (supervision).
  - Test data are classified into these classes too.
- Unsupervised learning (clustering)
  - Class labels of the data are unknown
  - Given a set of data, the task is to establish the existence of classes or clusters in the data

Supervised Learning

- Data: A set of data records (also called examples, instances or cases) described by
  - k attributes: A_1, A_2, … A_k.
  - a class: Each example is labelled with a pre-defined class.
- Goal: To learn a classification model from the data that can be used to predict the classes of new (future, or test) cases/instances.
- Learn: Learn a classification model from the data



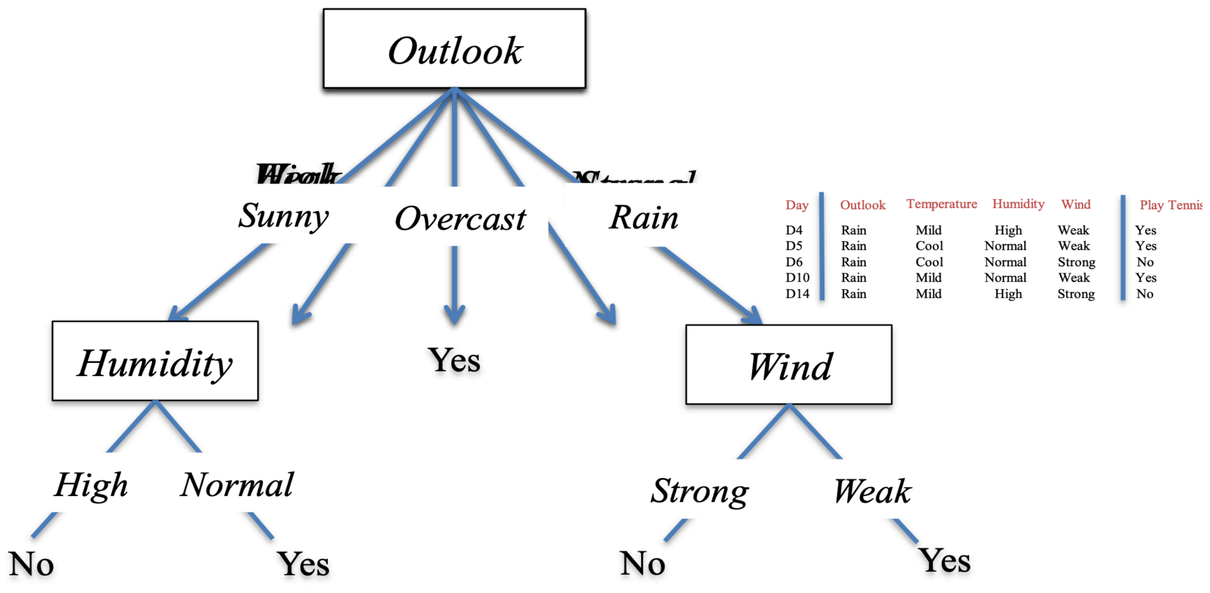
Supervised Learning Methods

- Decision tree
- Naïve Bayesian classification
- Support vector machines (SVD)
- K-nearest neighbor
- Ensemble Methods (Boosting and Bagging)

Supervised Classification: Decision Tree Learning

- Decision tree learning is one of the most widely used techniques for classification.
  - It is very efficient
- Algorithm:
  - Pick "best" attribute to split at the root based on training data.
  - Recurse on children that are impure (e.g. have both Yes and No).
  - If training examples perfectly classified, Then STOP, Else iterate over new leaf nodes.

What is the best? Information gain/ entropy



Day	Outlook	Temperature	Humidity	Wind	Play Tennis
D4	Rain	Mild	High	Weak	Yes
D5	Rain	Cool	Normal	Weak	Yes
D6	Rain	Cool	Normal	Strong	No
D10	Rain	Mild	Normal	Weak	Yes
D14	Rain	Mild	High	Strong	No

Top-Down Decision Tree Learning

- Basic algorithm (a greedy divide-and-conquer algorithm)
  - Assume attributes are categorical now (continuous attributes can be handled too)
  - Tree is constructed in a top-down recursive manner
  - At start, all the training examples are at the root
  - Examples are partitioned recursively based on selected attributes
  - Attributes are selected on the basis of an impurity function (e.g., information gain, Gini index)
- Conditions for stopping partitioning
  - All examples for a given node belong to the same class
  - There are no remaining attributes for further partitioning – majority class is the leaf
  - There are no examples left

How to Avoid Overfitting in Decision Tree

- Overfitting: A tree may overfit the training data
  - Good accuracy on training data but poor on test data
  - Symptoms: tree too deep and too many branches, some may reflect anomalies due to noise or outliers
- **Approaches to avoid overfitting**
  - Pre-pruning: Halt tree construction early
    - Difficult to decide because we do not know what may happen subsequently if we keep growing the tree.
  - Post-pruning: Remove branches or sub-trees from a “fully grown” tree.
    - A validation set may be used for pruning as well.

Naïve Bayesian Classification

- Bayesian Method in classification

$$p(Y|X) = \frac{p(X|Y)p(Y)}{p(X)}$$

- Posterior distribution $p(Y|X)$ provides the decision rule. Given a test point

$$y^* = argmax_y p(y|X)$$

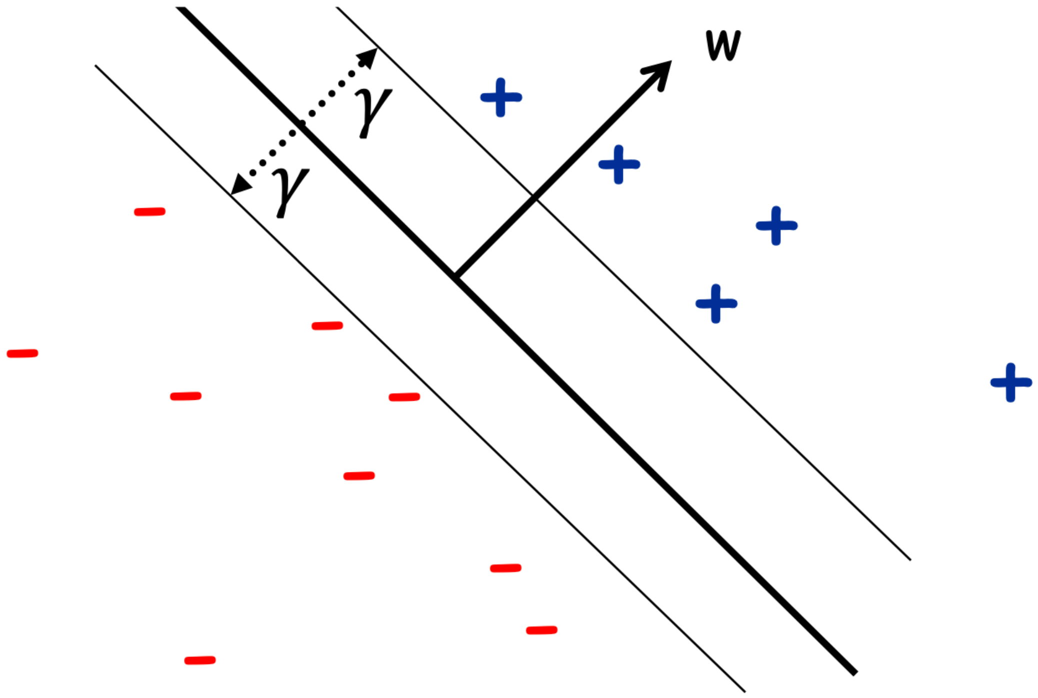
- Naïve Bayes assumption:

$$p(x_1, \ldots, x_n|Y) = \prod_i p(x_i|Y)$$

Bayes, Thomas (1763) An essay towards solving a problem in the doctrine of chances. *Philosophical Transactions of the Royal Society of London,* **53:370-418**

Support Vector Machine (SVM)

- SVMs are linear classifiers that find a hyperplane to separate two class of data, positive and negative.
- Kernel tricks are used for nonlinear separation.
- SVM not only has a rigorous theoretical foundation, but also performs classification more accurately than most other methods in applications, especially for high dimensional data.



[Vapnik 1990]

Support Vector Machines (SVMs)

- Looking to optimize for the maximum margin separator

Algorithm:

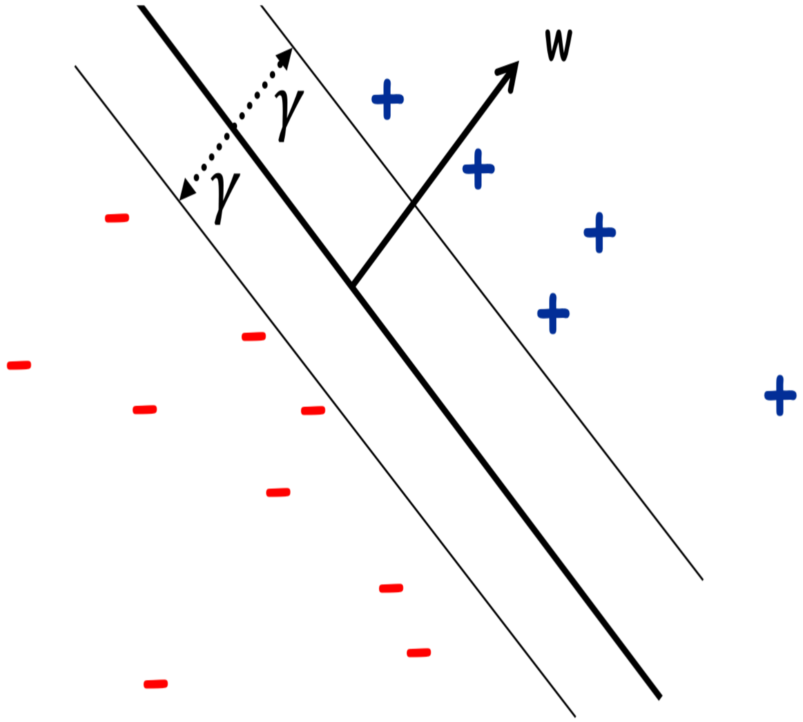
Input: $\mathcal{D} = \{(x_i, y_i)\}_{i=1}^{N}$

Maximize γ under the constraints:

$$||w||^2 = 1$$

$$y_i w.x_i \geq 0 \qquad \forall i$$

Non-convex constraint



$$\min_{w} ||w||^2$$

$$\forall i, y_i w.x_i \geq 1$$

(quadratic programming)

[Vapnik 1990]

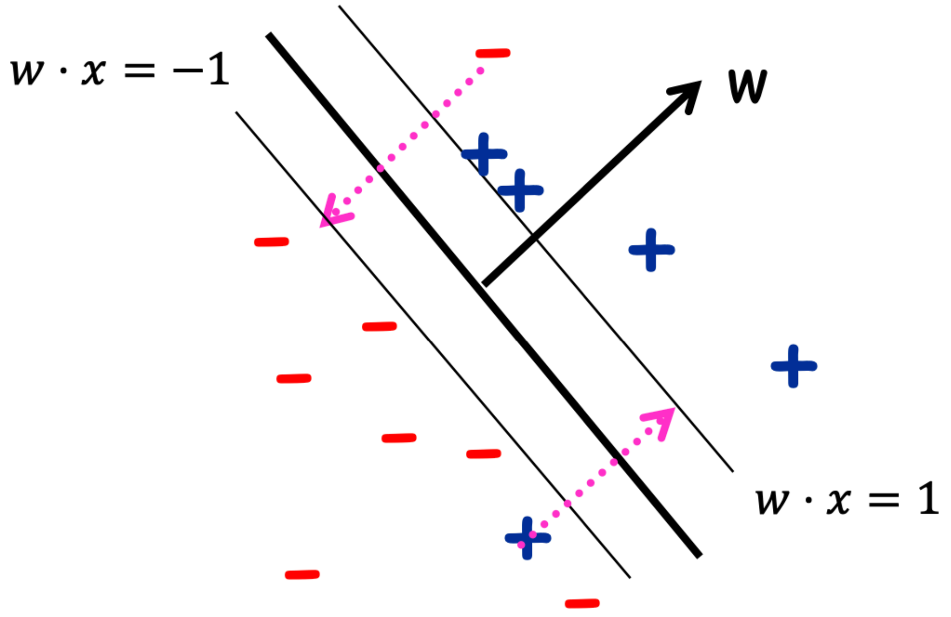
Support Vector Machines (SVMs)

- Question: what if data isn't perfectly linearly separable? Replace "# mistakes" with upper bound called "hinge loss"

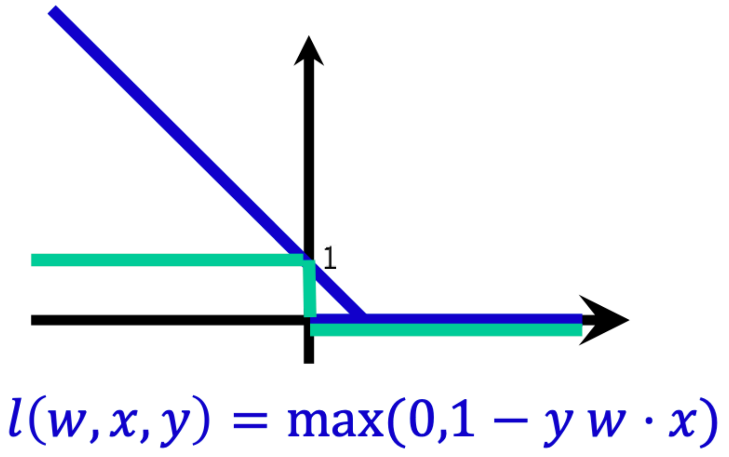
$$\min_{w,\xi_1,\ldots,\xi_N} ||w||^2 + C\sum \xi_i$$

$$\forall i, y_i w.x_i \geq 1 - \xi_i$$

$$\xi_i \geq 0$$



C controls the relative weighting between the goals of making $||w||^2$ small (margin is large) and ensuring that most examples have functional margin ≥ 1.



$l(w,x,y) = \max(0, 1 - y\, w \cdot x)$

Idea: Maximize the margin and minimize # of misclassification

SVMs and Kernelization

$$\min_{w,\xi_1,\ldots,\xi_N} ||w||^2 + C\sum \xi_i$$

(Primal Form)

$$\forall i, y_i w.x_i \geq 1 - \xi_i$$

$$\xi_i \geq 0$$

Can be replaced by any kernel $K(x_i, x_j)$

$$\text{argmin}_\alpha \frac{1}{2}\sum_i \sum_j y_i y_j \alpha_i \alpha_j x_i.x_j - \sum_i \alpha_i$$

$$\forall i,\ 0 \leq \alpha_i \leq C_i$$

(Lagrangian Dual Form)

$$\sum_i y_i \alpha_i = 0$$

Final Classifier is $w = \sum_i \alpha_i y_i x_i$

The point x_i for which $\alpha_i \neq 0$ are called support vectors.

Applications of SVMs in Bioinformatics

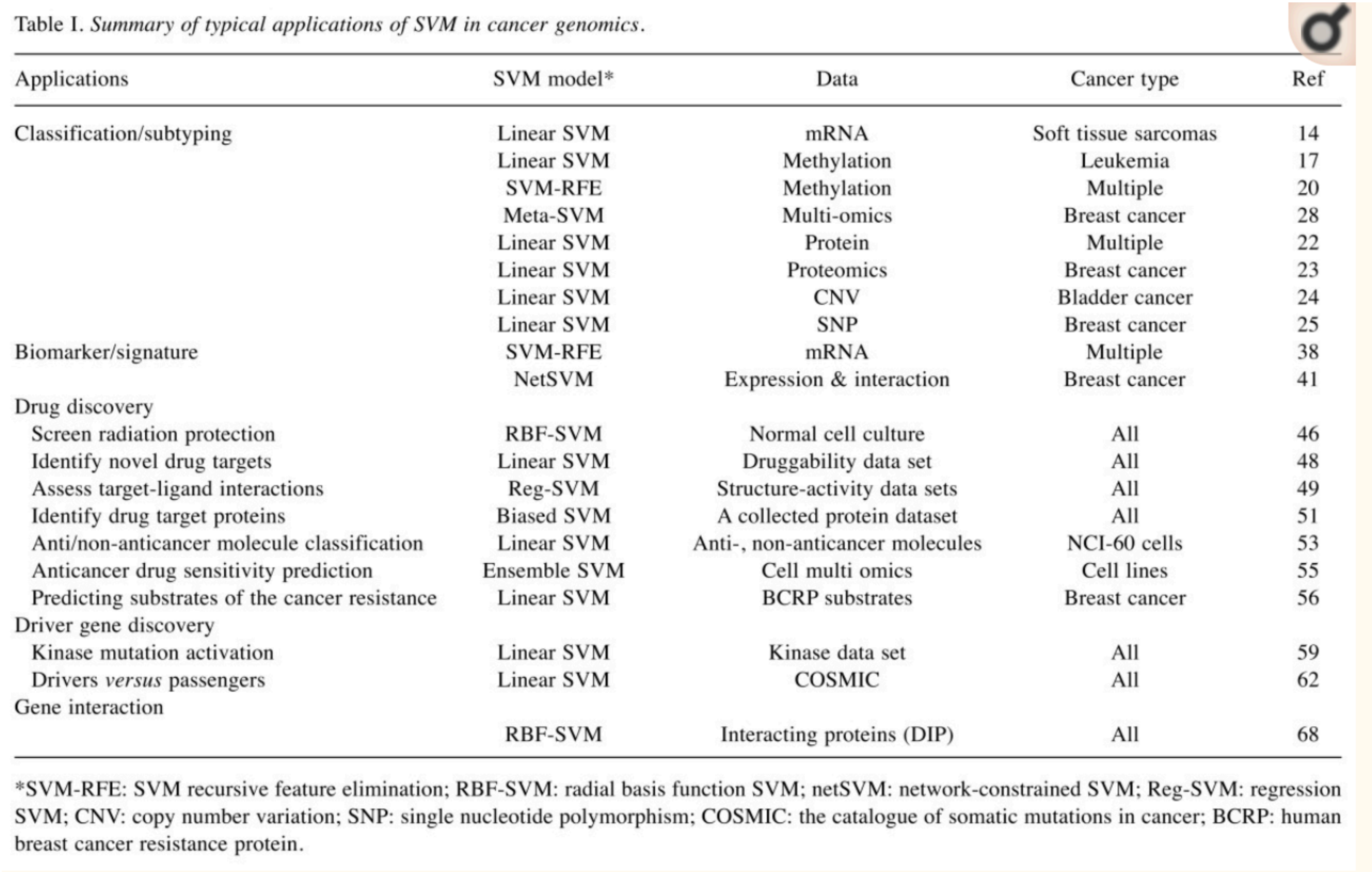


Table I. *Summary of typical applications of SVM in cancer genomics.*

Applications	SVM model*	Data	Cancer type	Ref
Classification/subtyping	Linear SVM	mRNA	Soft tissue sarcomas	14
	Linear SVM	Methylation	Leukemia	17
	SVM-RFE	Methylation	Multiple	20
	Meta-SVM	Multi-omics	Breast cancer	28
	Linear SVM	Protein	Multiple	22
	Linear SVM	Proteomics	Breast cancer	23
	Linear SVM	CNV	Bladder cancer	24
	Linear SVM	SNP	Breast cancer	25
Biomarker/signature	SVM-RFE	mRNA	Multiple	38
	NetSVM	Expression & interaction	Breast cancer	41
Drug discovery				
Screen radiation protection	RBF-SVM	Normal cell culture	All	46
Identify novel drug targets	Linear SVM	Druggability data set	All	48
Assess target-ligand interactions	Reg-SVM	Structure-activity data sets	All	49
Identify drug target proteins	Biased SVM	A collected protein dataset	All	51
Anti/non-anticancer molecule classification	Linear SVM	Anti-, non-anticancer molecules	NCI-60 cells	53
Anticancer drug sensitivity prediction	Ensemble SVM	Cell multi omics	Cell lines	55
Predicting substrates of the cancer resistance	Linear SVM	BCRP substrates	Breast cancer	56
Driver gene discovery				
Kinase mutation activation	Linear SVM	Kinase data set	All	59
Drivers *versus* passengers	Linear SVM	COSMIC	All	62
Gene interaction				
	RBF-SVM	Interacting proteins (DIP)	All	68

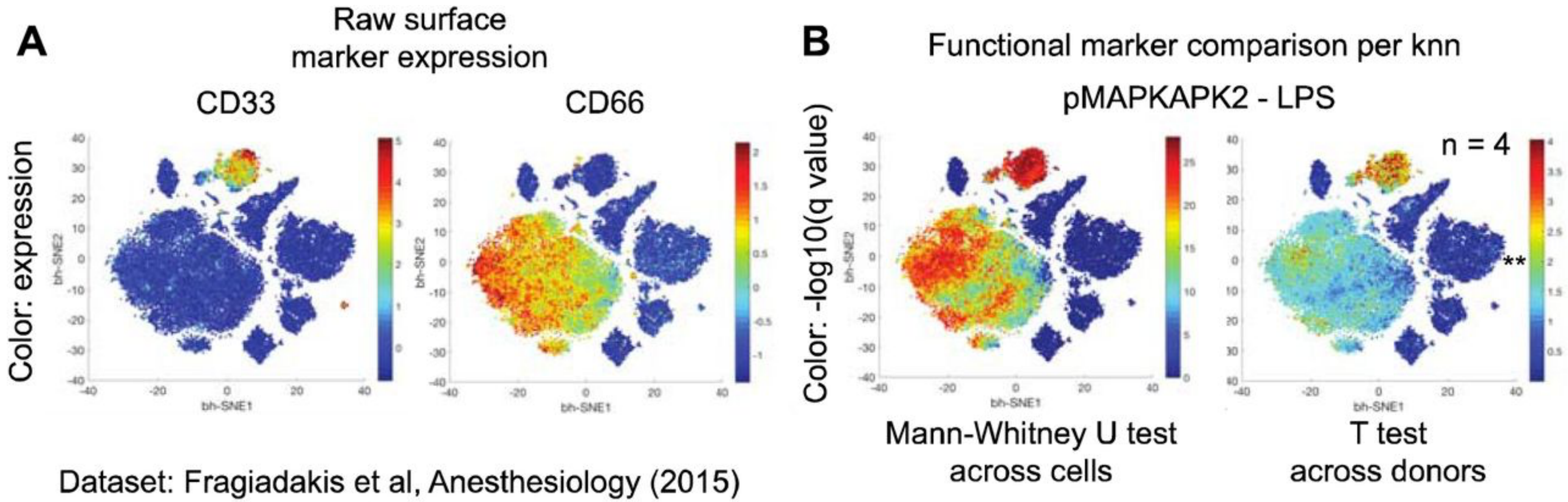
*SVM-RFE: SVM recursive feature elimination; RBF-SVM: radial basis function SVM; netSVM: network-constrained SVM; Reg-SVM: regression SVM; CNV: copy number variation; SNP: single nucleotide polymorphism; COSMIC: the catalogue of somatic mutations in cancer; BCRP: human breast cancer resistance protein.

[Huang 2018]

K-Nearest Neighbor (KNN)

- Unlike all the previous learning methods, KNN does not build model from the training data.
- To classify a test instance x, define K-neighborhood P as k nearest neighbors of x
- Count number n of training instances in P that belong to class c_j
- Estimate Pr(c_j|d) as n/k
- No training is needed. Classification time is linear in training set size for each test case
- This method suffers from curse of dimensionality
- K is usually chosen through validation set or cross-validation by trying a range of K values.
- Distance function is crucial but depends on applications.

KNN to Visualize Differences between Biological Conditions



Dataset: Fragiadakis et al, Anesthesiology (2015)
Donors: healthy human
Cells: whole blood
Cell number: 40,000
Patient number: 4

Per-KNN statistical tests can reveal differences both across cells and across donors or replicates. (A) t-SNE maps colored by surface marker expression. (B) Per-cell Mann-Whitney U test or per-donor t test (n = 4) median values of pMAPKAPK2 expression between untreated and LPS-treated cells. **, q < 0.01.

[Burns 2020]

Ensemble Methods

- Combining classifiers to get a better classifier
  - Boosting [Schapire, 1996]
    - Take weak classifiers and results in a strong classifier
    - Useful when there is high bias
    - Training for AdaBoost
      1. Produce a sequence of classifiers (weak)
      2. Each classifier is dependent on the previous one, and focuses on the previous one's errors
      3. Examples that are incorrectly predicted in previous classifiers are given higher weights
    - Test
      1. For a test case, the results of the series of classifiers are combined to determine the final class of the test case.

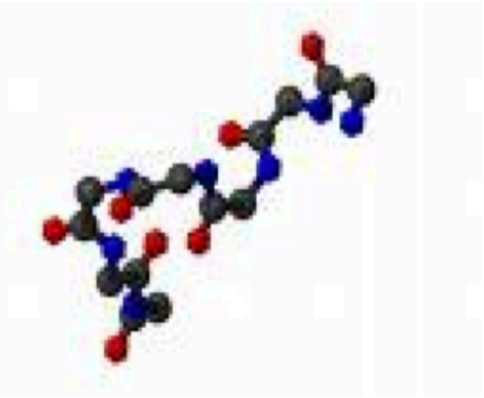
  - Bagging (Bootstrap Aggregating) [Breiman 1996]
    - Based on the idea of bootstrap (sampling with replacement)
    - Useful when high variance
    - Training
      1. Create K bootstrap samples from data D
      2. Train each data set and get the corresponding classifier
    - Test
      1. Classify each new instance by voting of the k classifiers (equal weights)

Unsupervised Learning Methods

- Clustering
- Objective-based clustering
- Gaussian mixture model
- Hierarchical clustering
- Dimension reduction
- Principal component analysis (PCA)
- Factor analysis
- Probabilistic PCA (pPCA)

Clustering

- Clustering is one main approach to unsupervised learning.
  - Automatically partitions unlabeled data into groups of similar datapoints
  - Useful for:
    1. Automatically organizing data.
    2. Understanding hidden structure in data.
    3. Preprocessing for further analysis e.g. dimension reduction
  - Applications:
    - Cluster protein sequences by function or genes according to expression profile.



- And many more applications

Objective-based Clustering

- **Input:** Data and a distance/ dissimilarity function
- **Output:** A partition of data
- Objective-based clustering
  1. K-means
     - Find center points $c_1, \ldots, c_k$ to minimize

$$\sum_{i=1}^{N} \min_{j \in \{1,\ldots,k\}} d^2(x_i, c_j)$$

(Euclidean distance)

(d = 1, k=1 only easy to solve)

  2. K-median
     - Find center points $c_1, \ldots, c_k$ to minimize

$$\sum_{i=1}^{N} \min_{j \in \{1,\ldots,k\}} d(x_i, c_j)$$

  3. K-center
     - Find partitions to minimize the maximum radius.

Lloyd's Method(Heuristic Method)

Input: Data points $x_1, \dots, x_N \in \mathbb{R}^d$

Initialize: Center points: $c_1, \dots, c_k \in \mathbb{R}^d$

Clusters: $C_1, \dots, C_k$

Repeat till there is no drastic change in the cost

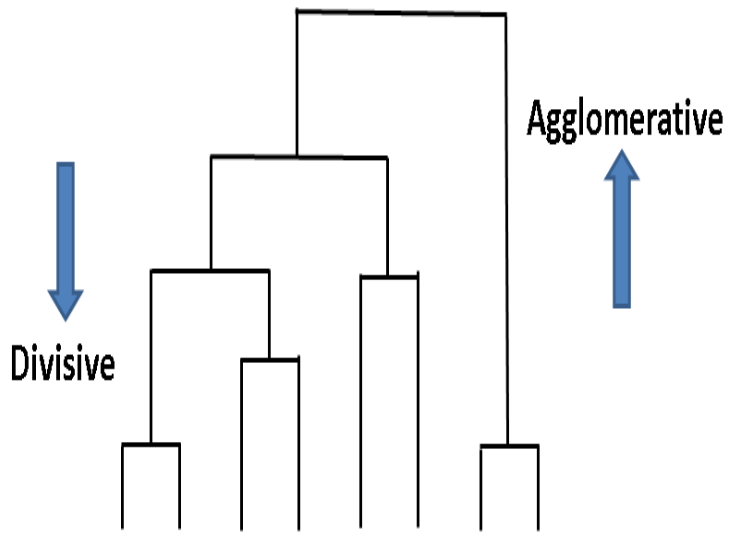
- For each $j : C_j \leftarrow \{x \in \mathcal{D} \text{ whose closet center is } c_j\}$
- For each $j : c_j \leftarrow \text{mean}(C_j)$

- Initialization is crucial:
  - Random centers from the datapoints
  - Furthest traversal
  - K-means ++ (works well and has mathematical guarantee)

[Lloyd 1982]

Hierarchical Clustering

- Top-down (divisive, fragmentation)
  - Partition data into 2-groups (e.g., 2-means)
  - Recursively cluster each group.



- Bottom-Up (agglomerative, coalescent)
  - Start with every point in its own cluster.
  - Repeatedly merge the "closest" two clusters.
  - Different definitions of "closest" give different algorithms.
  - Have a distance measure on pairs of objects.
    - Single linkage: $dist(C,\tilde{C}) = \min_{x\in C,\tilde{x}\in\tilde{C}} dist(x,\tilde{x})$
    - Complete linkage: $dist(C,\tilde{C}) = \max_{x\in C,\tilde{x}\in\tilde{C}} dist(x,\tilde{x})$
    - Average linkage: $dist(C,\tilde{C}) = \text{average}_{x\in C,\tilde{x}\in\tilde{C}} dist(x,\tilde{x})$

Dimension Reduction

- Powerful unsupervised learning techniques for extracting hidden (potentially lower dimensional) structure from high dimensional datasets
- Useful for:
    - Visualization
    - More efficient use of resources (e.g., time, memory, communication)
    - Statistical: fewer dimensions → better generalization Noise removal (improving data quality)
    - Further processing by machine learning algorithms

Principal component analysis (PCA)

- Unsupervised technique for extracting variance structure from high dimensional datasets.
- PCA provides the directions along which data are most spread.
- PCA is an orthogonal projection or transformation of the data into a (possibly lower dimensional) subspace so that the variance of the projected data is maximized.

Interpretation of PCA

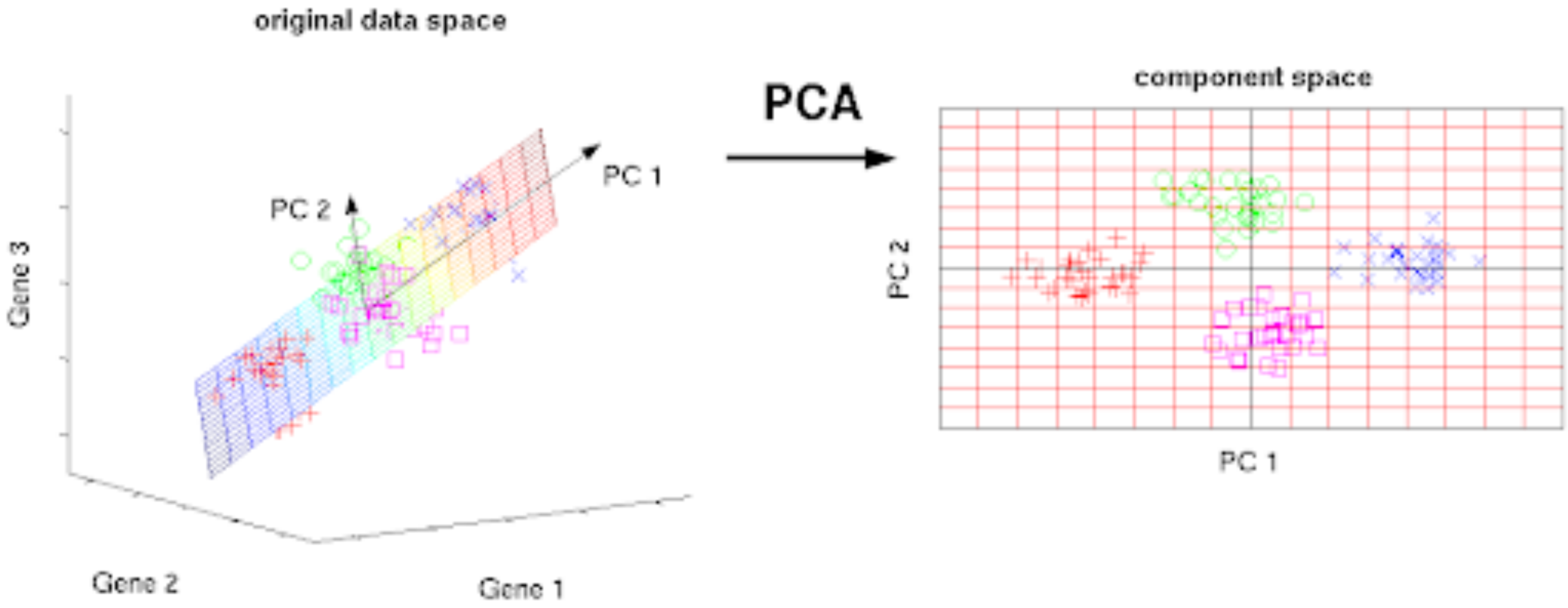
- Interpretation 1: Maximum Variance Subspace. PCA finds vectors v such that projections on to the vectors capture maximum variance in the data

$$\max_{v:||v||=1} v^T X X^T v$$

- Interpretation 2: Minimum Reconstruction Error. PCA finds vectors v such that projection on to the vectors yields minimum MSE reconstruction

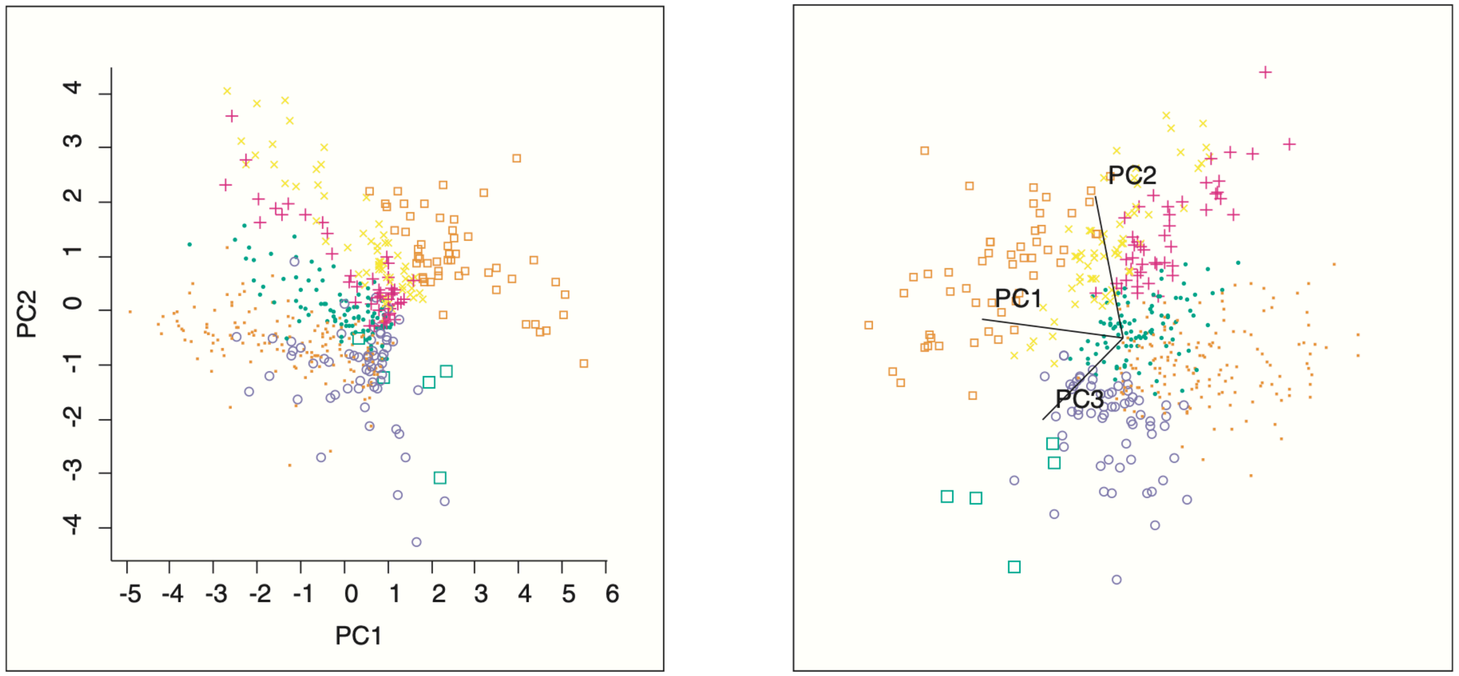
$$\min_{v:||v||=1} \sum_{i=1}^{N} ||x_i - (v^T x_i)v||^2$$

PCA analysis for clustering gene expression data



PCA Weakness:

- PCA only considers the second statistics
- PCA is only limited to linear projection



(a) In the subspace of the first 2 PC's

(b) In the subspace of the first 3 PC's

[Yeung, 2001]

Factor Analysis (FA)

- Data Reduction: Factor analysis is a technique that is used to reduce a large number of variables into fewer numbers of factors (explain covariation between d variables using r < d latent factors), i.e., (exploratory FA)
- Maximum Common Variance: This technique extracts maximum common variance from all variables and puts them into a common score
- Theory Testing: Determine if hypothesized factor structure fits observed data (confirmatory FA)
- FA and PCA have the same theme however, they are different:
  - FA assumes a statistical model that describes covariation in observed variables via linear combinations of latent variables
  - PCA finds uncorrelated linear combinations of observed variables that explain maximal variance (no latent variables here)

FA refers to a statistical model, whereas PCA refers to the eigenvalue decomposition of a covariance (or correlation) matrix

Factor Analysis

- Data $x_1, \ldots, x_N \in \mathbb{R}^d$
- Latent Structure $z_1, \ldots, z_N \in \mathbb{R}^r \ (r < d)$
- Probabilistic Modelling

$$z_i \sim \mathcal{N}(z_i|\mu_0, \Sigma_0)$$

$$x_i|z_i, W, \mu, \Psi \sim \mathcal{N}(Wz_i + \mu, \Psi),$$

$$\text{where } W \in \mathbb{R}^{d \times r}, \Psi \in \mathbb{R}^{d \times d}, \mu \in \mathbb{R}^d$$

- Marginalizing out z,

$$x_i|W, \mu, \Psi \sim \mathcal{N}(W\mu_0 + \mu, \Psi + W\Sigma_0 W^T),$$

- Inference

$$argmax_{\{W,\mu,\Psi\}} \log p(X|W, \mu, \Psi)$$

EM Algorithm to Do Inference

Probabilistic PCA (pPCA)

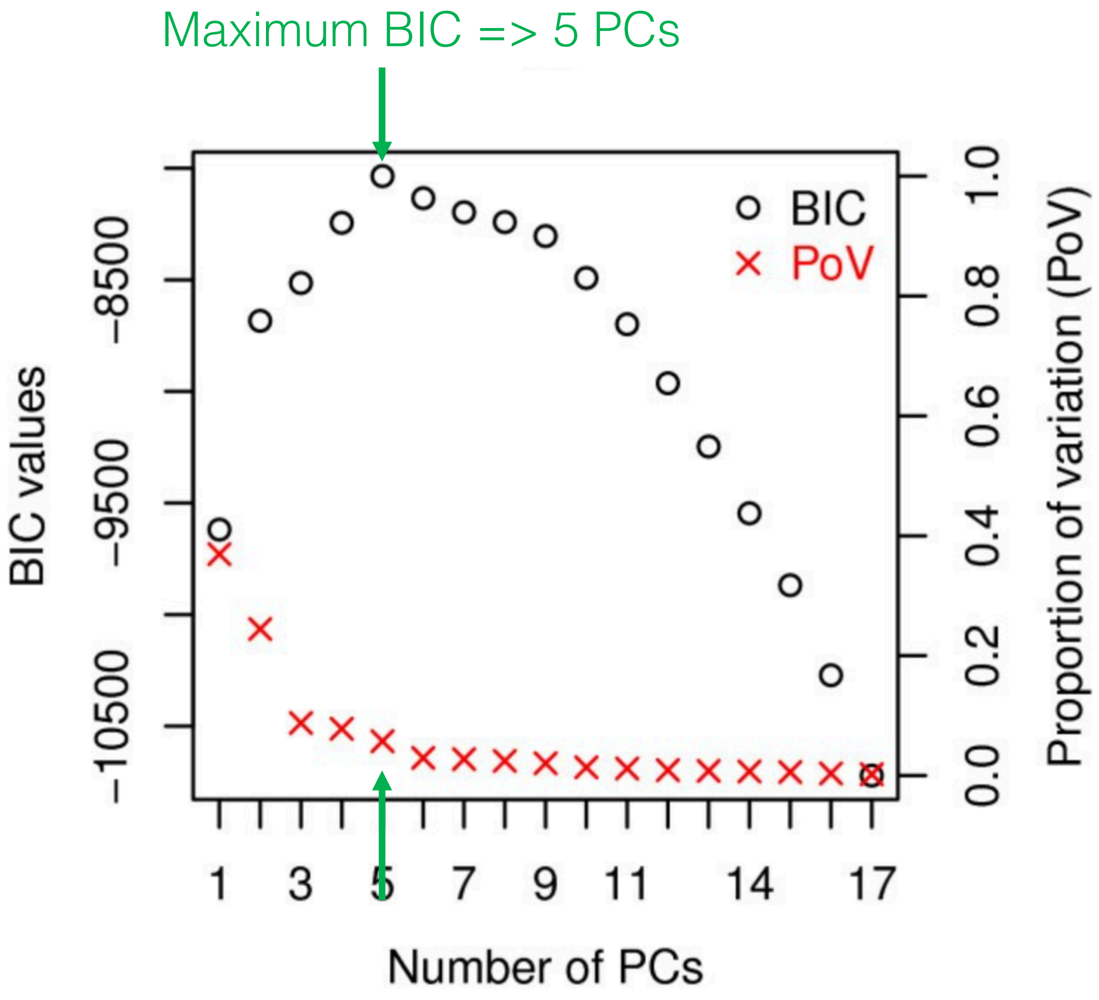
- Without loss of generality we can assume $z_i \sim \mathcal{N}(0, I)$, then

$$x_i | W, \Psi \sim \mathcal{N}(\mu, \Psi + WW^T)$$

- pPCA is special case of Factor analysis
    - Assume $\Psi = \sigma^2 I$
    - Assume data is centered $\mu = 0$
- Inference can be done though Expectation-Maximization algorithm
- Observation: Assume centered data, If $\sigma \to 0$, the solution for W gives back the same solution as PCA.

pPCA for Metabolic Data

- To explore the effect of treatment with PTZ, a pPCA model was fitted to the urinary metabolomic data.
- Parameter estimation was achieved via the EM algorithm.
- A number of pPCA models with varying numbers of principal components was fitted; a modified Bayesian Information Criterion (BIC) is used to aid selection of the optimal model.

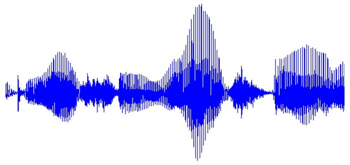


Fitting a pPCA model to the urine dataset. A. Plot of the modified BIC values and the proportion of variation explained by each model (different number of PCs)

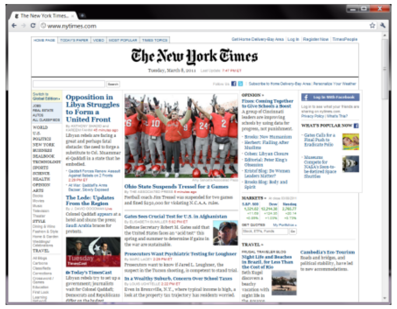
[Nyamundanda 2010]

What Do We Want a Machine to Do?

Label: “Motorcycle”
Suggest tags
Image search
…



Speech recognition
Speaker identification
Music classification
…



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Opposition in Libya Struggles to Form a United Front

By ANTHONY SHADID and KAREEM FAHIM 45 minutes ago

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- Qaddafi Forces Renew Assault Against Rebels on 2 Fronts 2:29 PM ET
- At War, Qaddafi's Arms Bazaar, Slowly Exposed

The Lede: Updates From the Region

By J. DAVID GOODMAN Live

Colonel Qaddafi appears at a hotel and shuns the press; Saudi Arabia braces for protests.

Tuesday TimesCast

Today's TimesCast

Libyan rebels try to set up a government; journalists wait for Colonel Qaddafi; Democrats and Republicans differ on the budget.

Amy Sancetta/Associated Press

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By THE ASSOCIATED PRESS 8 minutes ago

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By ELISABETH BUMILLER 5:52 PM ET

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By MARC LACEY 2:26 PM ET

Prosecutors want to know if Jared L. Loughner, the suspect in the Tucson shooting, is competent to stand trial.

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By LOUIS UCHITELLE 2:22 PM ET

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OPINION »

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- Brooks: New Humanism
- Herbert: Flailing After Muslims
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- Kristof Blog: Do Women Leaders Matter?
- Brooks Blog: Body and Spirit

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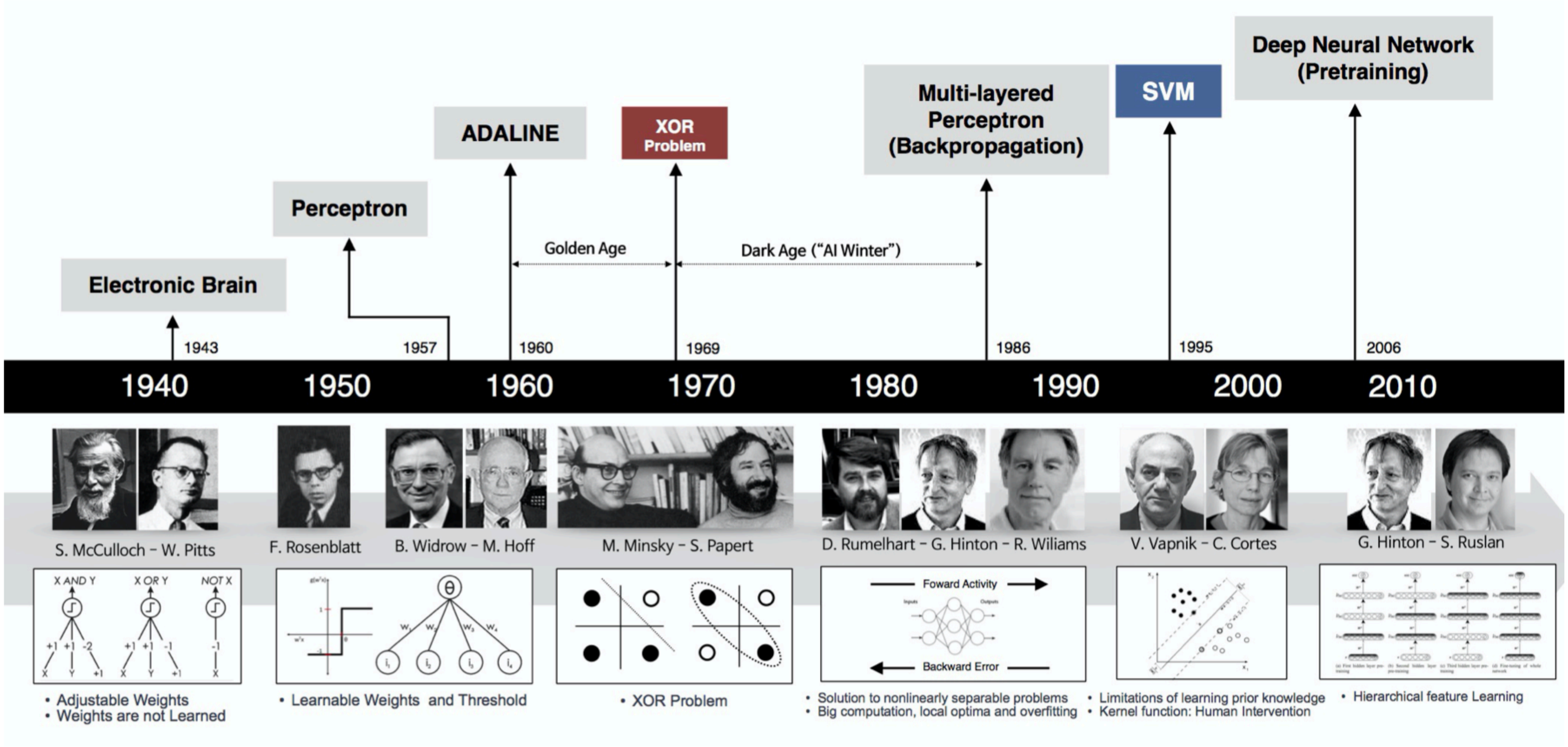
Why are machine learning algorithms not enough
for these problems?

Deep Learning

- History
- Deep learning in a nutshell
  - Neural networks (NNs)
  - Convolutional neural networks (CNNs)
  - Recurrent neural networks (RNNs)
- Deep learning in bioinformatics

Neural Network


Electronic Brain
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XOR Problem
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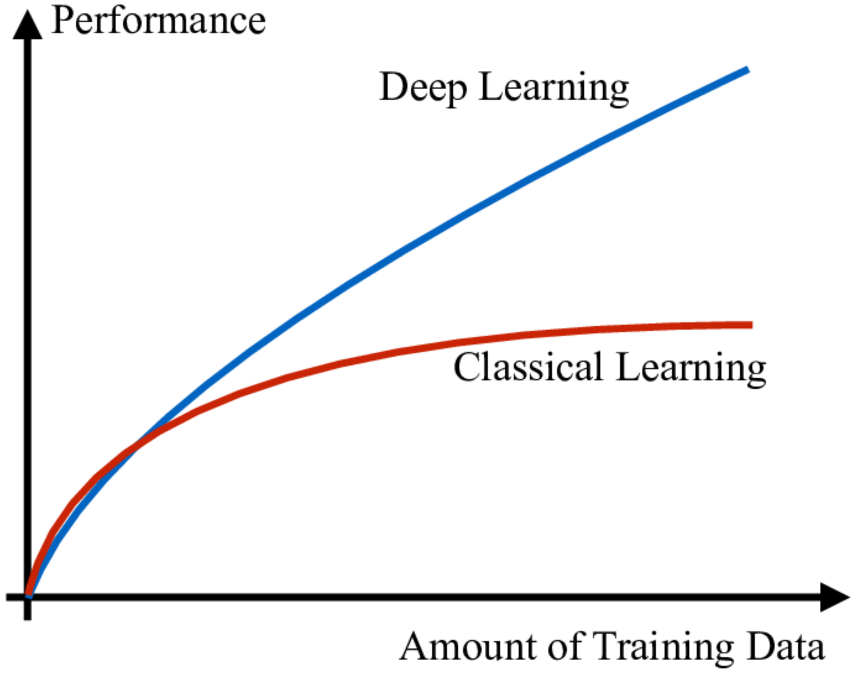
B. Widrow - M. Hoff
M. Minsky - S. Papert
D. Rumelhart - G. Hinton - R. Wiliams
V. Vapnik - C. Cortes
G. Hinton - S. Ruslan
X AND Y
X OR Y
NOT X
θ
Foward Activity
Inputs
Outputs
Backward Error
• Adjustable Weights
• Weights are not Learned
• Learnable Weights and Threshold
• XOR Problem
• Solution to nonlinearly separable problems
• Big computation, local optima and overfitting
• Limitations of learning prior knowledge
• Kernel function: Human Intervention
• Hierarchical feature Learning

Slide credit: Mert Pilanci

Classical Learning vs Deep Learning

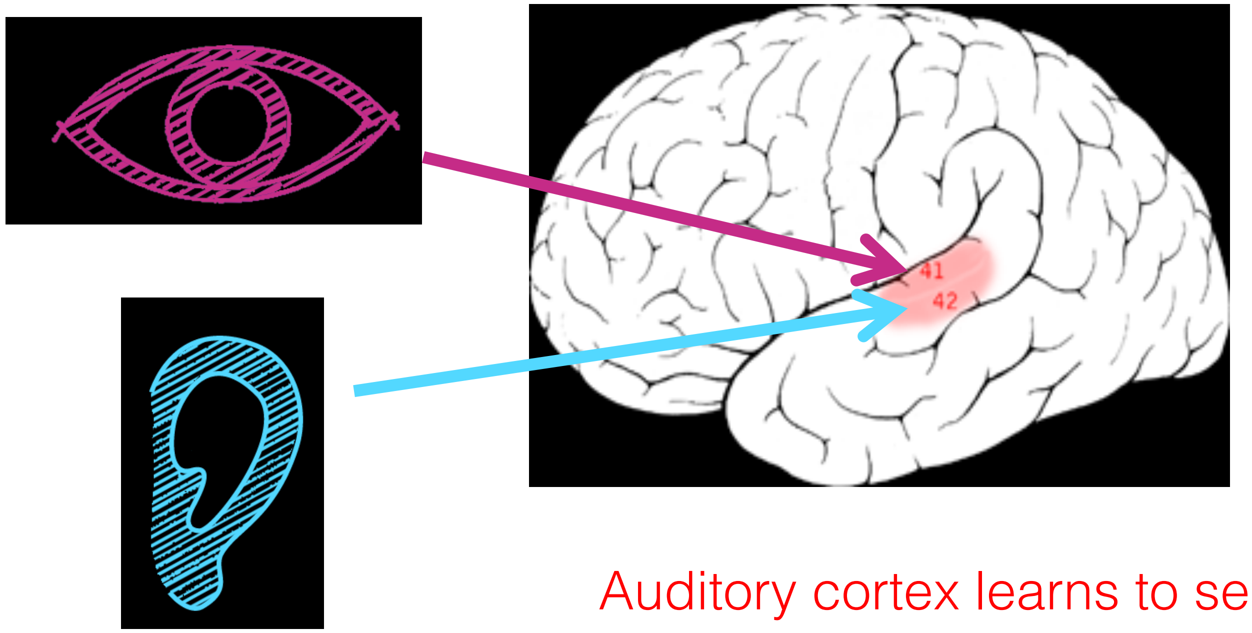


- Deep learning scales much better with more data than classical learning algorithms
- Deep learning have achieved accuracies that are far beyond that of classical learning methods in speech processing, natural language processing, computer vision, and reinforcement learning
- Classical learning algorithms often require feature engineering where there is no need for feature engineering in deep learning: features are earned through optimization

Is deep learning the solution for all the problems?

Intro to Deep Learning

- Build learning algorithms that mimic the brain.
  - Biological systems built of very complex webs of interconnected neurons.
  - Highly connected to other neurons and performs computations by combining signals from other neurons.
- Using brain simulations:
  - Make learning algorithms much better and easier to use.
  - Make advances in machine learning and AI.



Auditory cortex learns to see

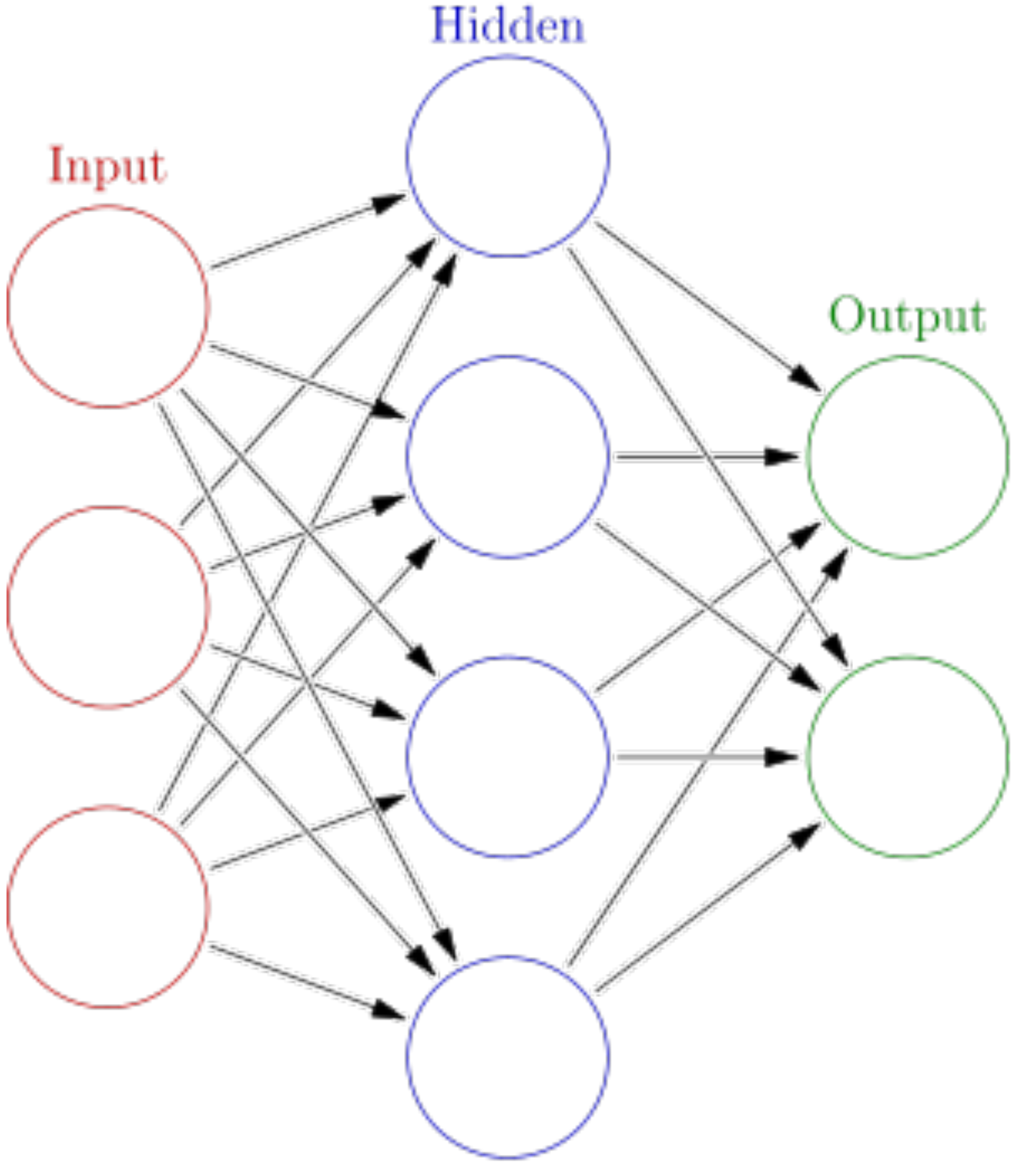
[Roe 1992]

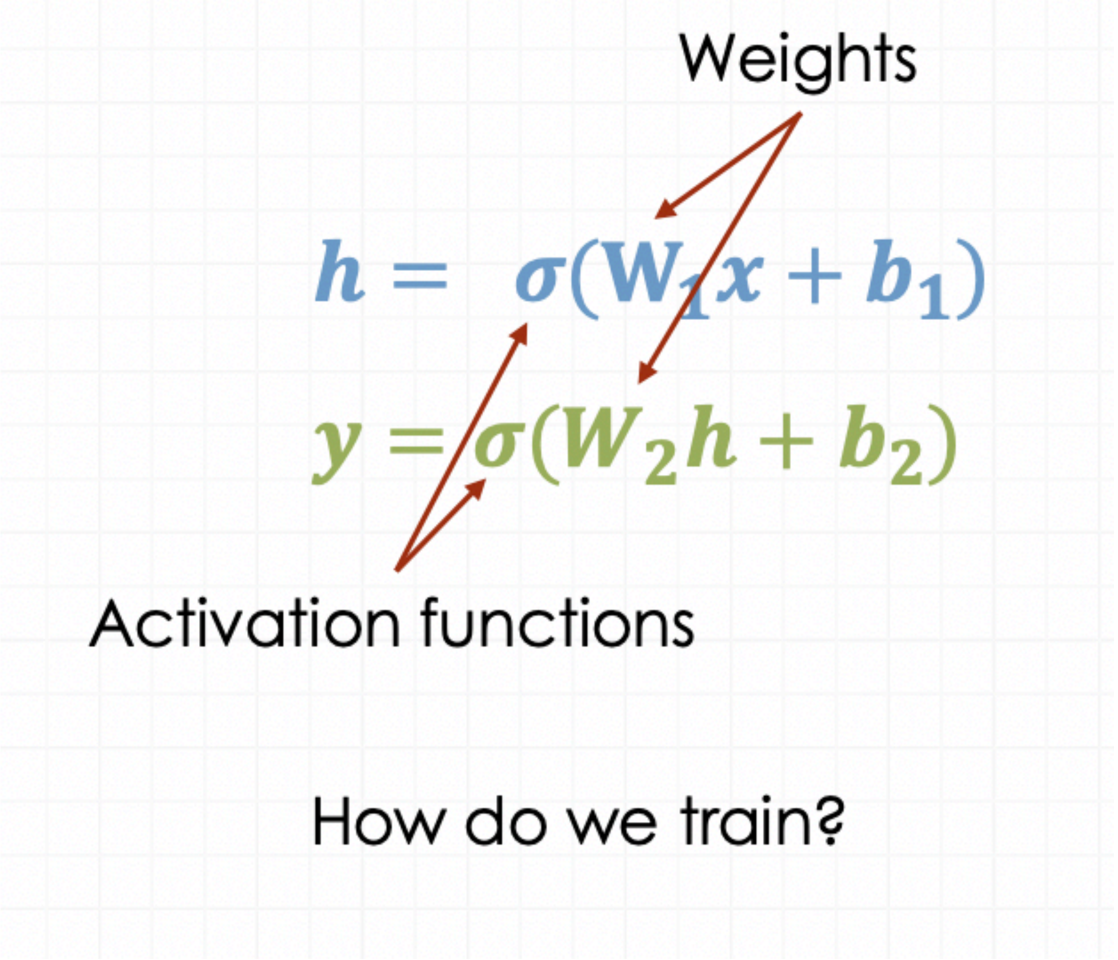
Main Idea of Deep Learning

- Linear classifier: $h(x) = W^T x$
- Kernelized classifiers: $h(x) = W^T \phi(x)$
- Idea: Use other functions instead of those well-crafted kernels, e.g. $\phi(x) = \sigma(Ax + b)$
- What is the benefit over kernel?
    - Scales linearly with data but for kernel is quadratic in number of data points
    - With more data kernel must be approximated

There is no function that can be learned by deep network but cannot be learned by shallow learners

Neural Network




Weights

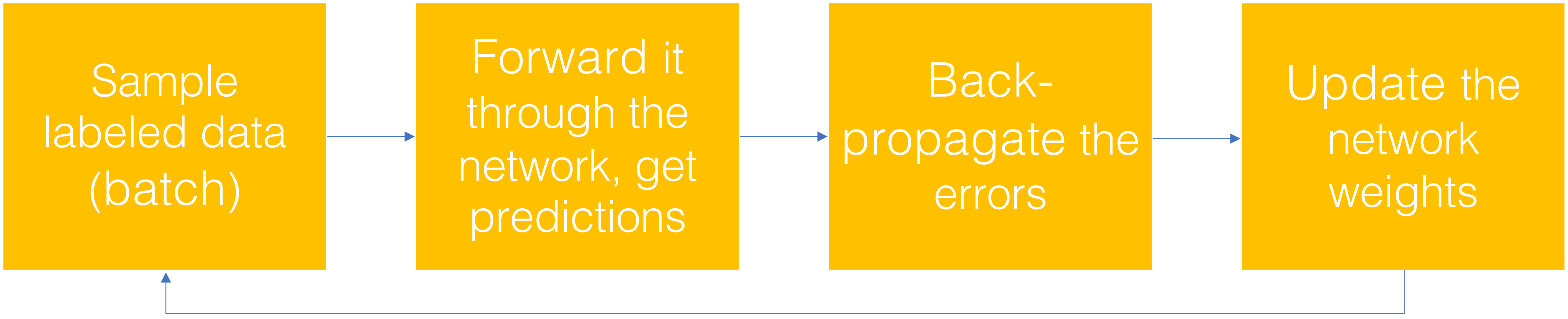
$$h = \sigma(\mathbf{W}_1 x + b_1)$$

$$y = \sigma(W_2 h + b_2)$$

Activation functions

How do we train?

Training

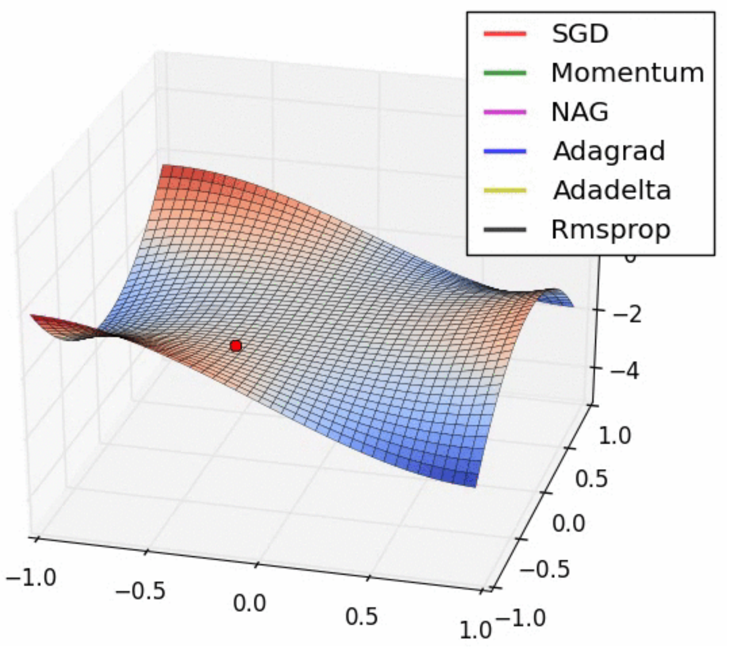


Sample labeled data (batch)

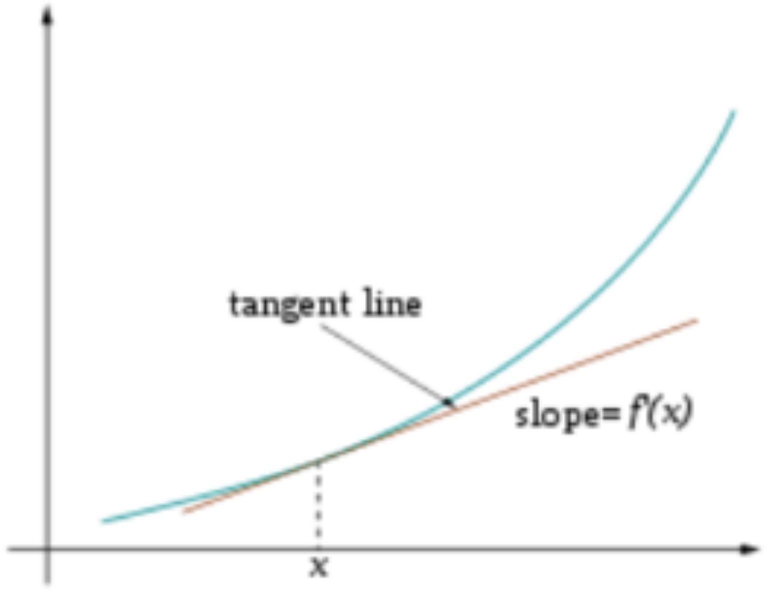
Forward it through the network, get predictions

Back-propagate the errors

Update the network weights



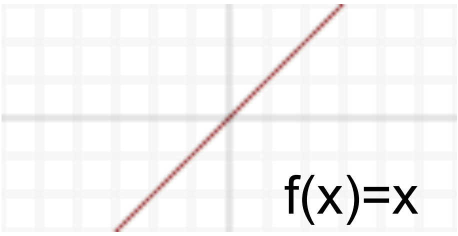
Optimize (min. or max.) objective/cost function J(θ)
Generate error signal that measures difference between predictions and target values



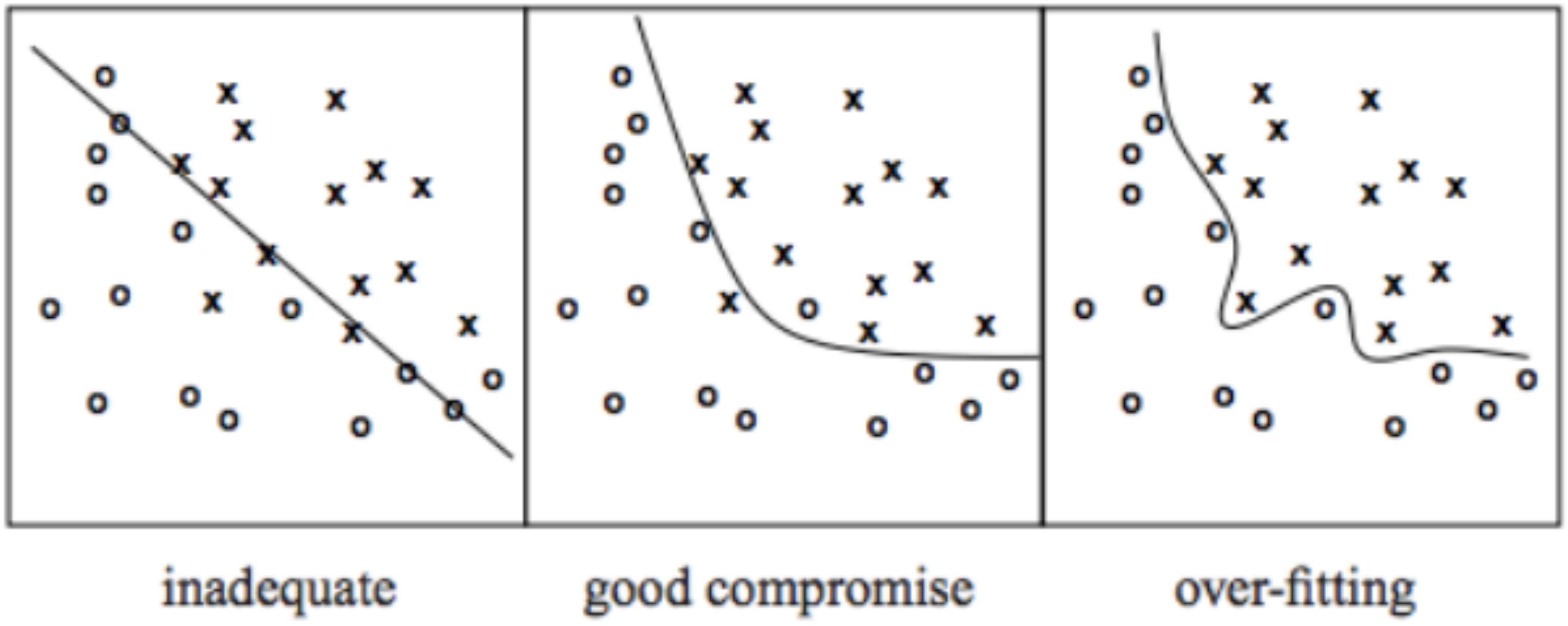
Use error signal to change the weights and get more accurate predictions
Subtracting a fraction of the gradient moves you towards the (local) minimum of the cost function

[https://medium.com/@ramrajchandradevan/the-evolution-of-gradient-descend-optimization-algorithm-4106a6702d39]

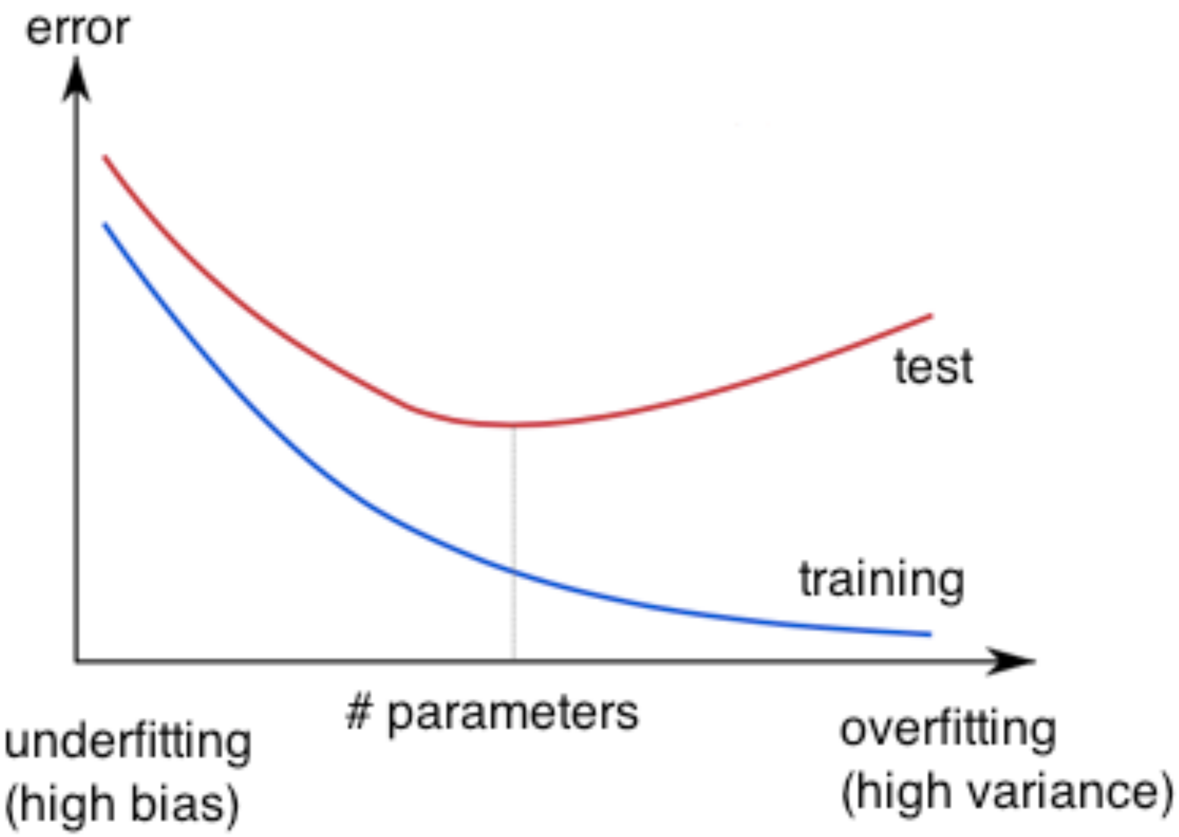
Loss Functions

	Classification	Regression
Training examples	R^n x {class_1, ..., class_n} (one-hot encoding)	R^n x R^m
Output Layer	Soft-max [map R^n to a probability distribution] $P(y=j \mid \mathbf{x}) = \frac{e^{\mathbf{x}^\mathsf{T}\mathbf{w}_j}}{\sum_{k=1}^{K} e^{\mathbf{x}^\mathsf{T}\mathbf{w}_k}}$	Linear (Identity) or Sigmoid 
Cost (loss) function	Cross-entropy $J(\theta) = -\frac{1}{n}\sum_{i=1}^{n}\sum_{k=1}^{K}\left[y_k^{(i)}\log\hat{y}_k^{(i)} + \left(1-y_k^{(i)}\right)\log\left(1-\hat{y}_k^{(i)}\right)\right]$	Mean Squared Error $J(\theta) = \frac{1}{n}\sum_{i=1}^{n}\left(y^{(i)} - \hat{y}^{(i)}\right)^2$ Mean Absolute Error $J(\theta) = \frac{1}{n}\sum_{i=1}^{n}\left\lvert y^{(i)} - \hat{y}^{(i)}\right\rvert$

Overfitting



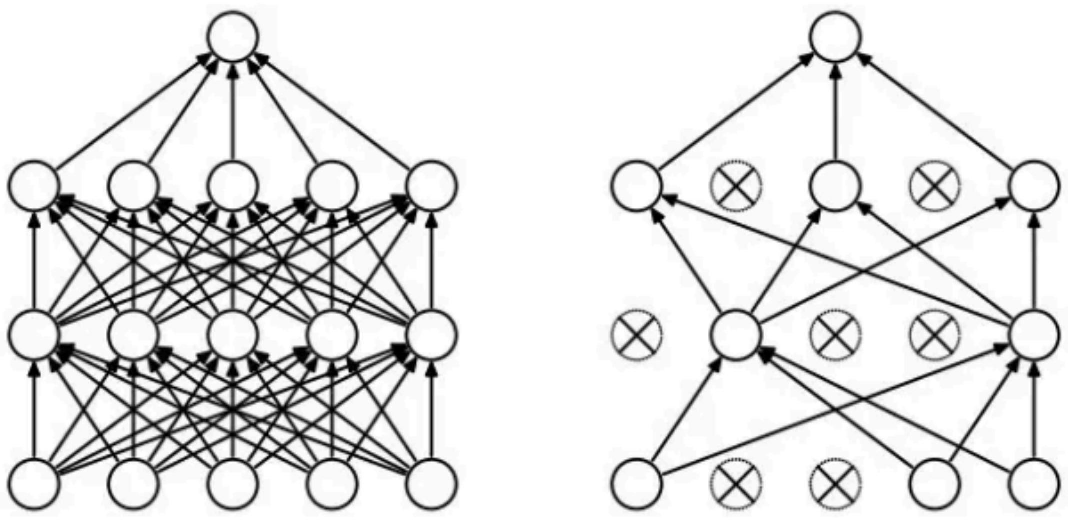
[http://wiki.bethanycrane.com/overfitting-of-data]



[https://www.neuraldesigner.com/images/learning/selection_error.svg]

Learned hypothesis may fit the training data very well, even outliers (noise) but fail to generalize to new examples (test data)

Regularization



Dropout

- Randomly drop units (along with their connections) during training
- Each unit retained with fixed probability p, independent of other units
- Hyper-parameter p to be chosen (tuned)

L2 = weight decay

- Regularization term that penalizes big weights, added to the objective
- Weight decay value determines how dominant regularization is during gradient computation
- Big weight decay coefficient → big penalty for big weights

$$J_{reg}(\theta) = J(\theta) + \lambda \sum_k \theta_k^2$$

Early-stopping

- Use validation error to decide when to stop training
- Stop when monitored quantity has not improved after n subsequent epochs
- n is called patience

[Srivastava 2014]

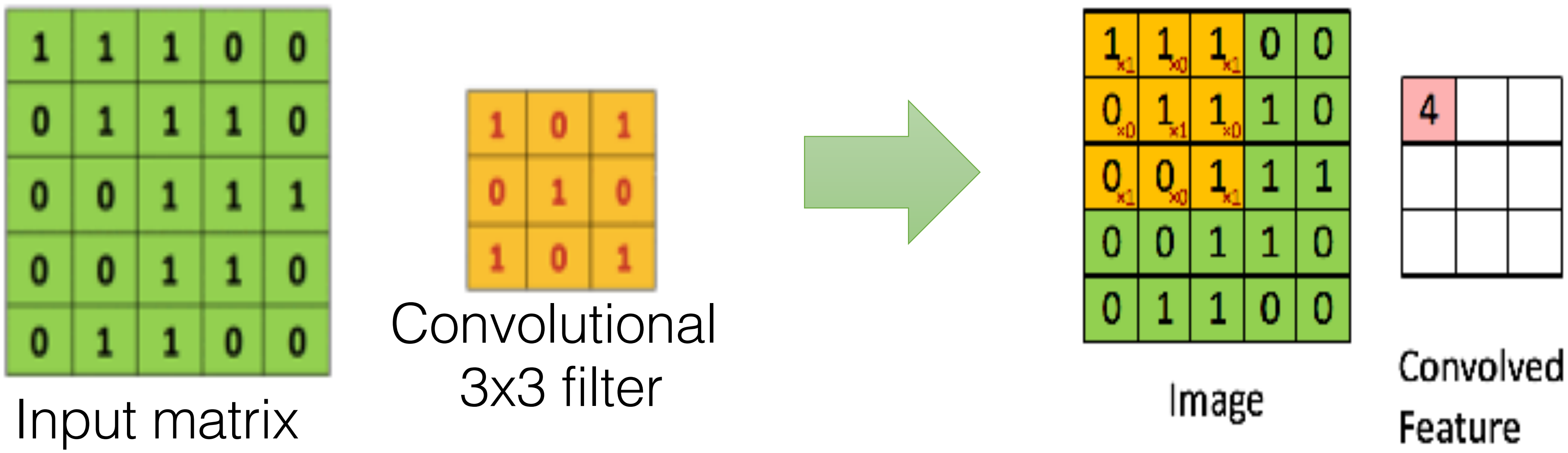
Convolutional Neural Networks (CNNs)

- A specialized kind of neural network for processing data that has a known grid-like topology.
    - E.g., time-series data, which can be thought of as a 1-D grid taking samples at regular time intervals, and image data, which can be thought of as a 2-D grid of pixels
- The name “convolutional neural network” indicates that the network employs a mathematical operation called convolution . Convolution is a specialized kind of linear operation.
- Convolutional networks are neural networks that use convolution in place of general matrix multiplication in at least one of their layers.

CNNs: Main Idea

- Main CNN idea for text:
  - Compute vectors for n-grams and group them afterwards

Example: “this takes too long” compute vectors for:
This takes, takes too, too long, this takes too, takes too long, this takes too long



1	1	1	0	0
0	1	1	1	0
0	0	1	1	1
0	0	1	1	0
0	1	1	0	0

Input matrix

1	0	1
0	1	0
1	0	1

Convolutional 3x3 filter

$1_{\times 1}$	$1_{\times 0}$	$1_{\times 1}$	0	0
$0_{\times 0}$	$1_{\times 1}$	$1_{\times 0}$	1	0
$0_{\times 1}$	$0_{\times 0}$	$1_{\times 1}$	1	1
0	0	1	1	0
0	1	1	0	0

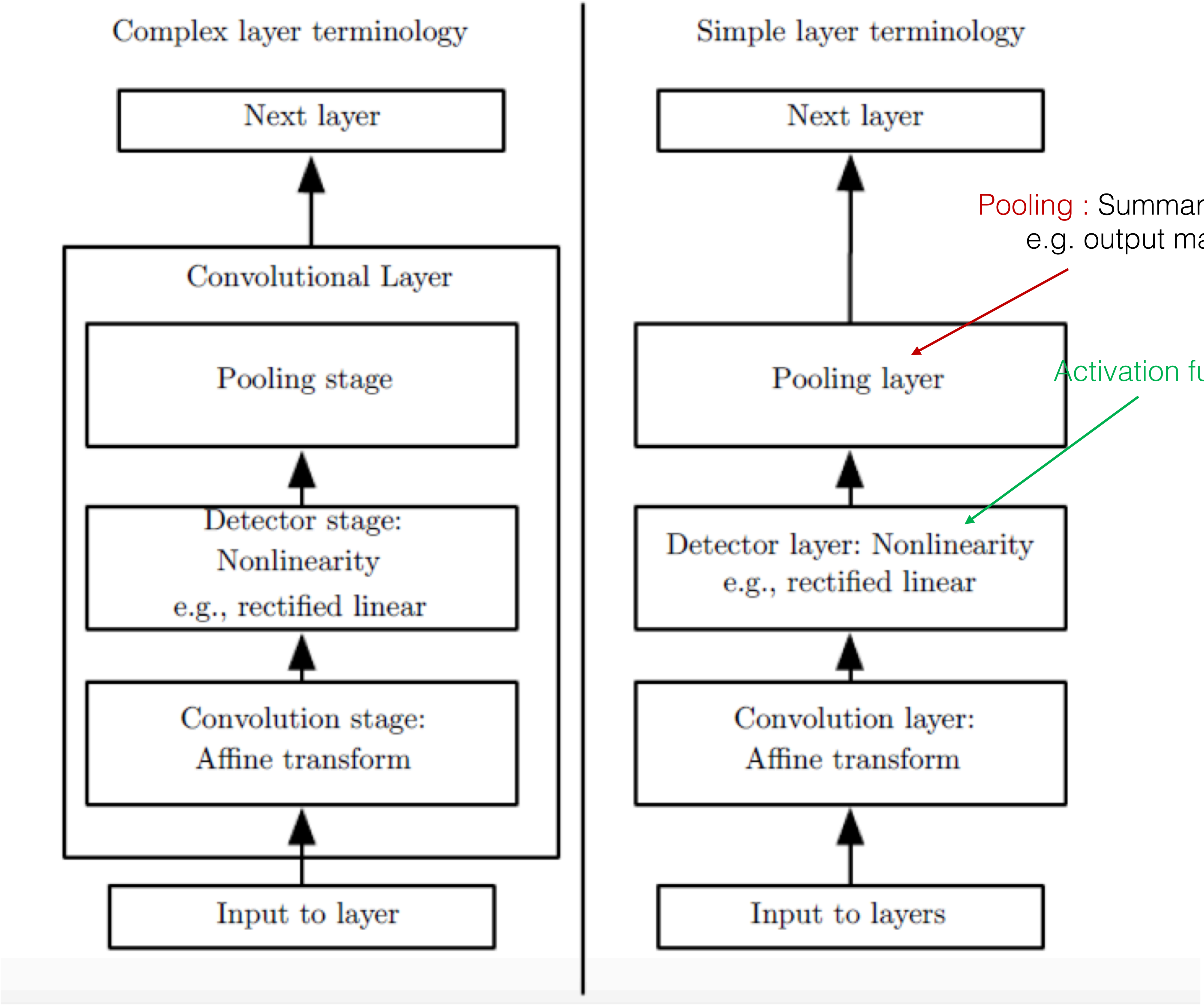
Image

4		

Convolved Feature

[http://deeplearning.stanford.edu/wiki/index.php/Feature_extraction_using_convolution]

CNNs and Terminology

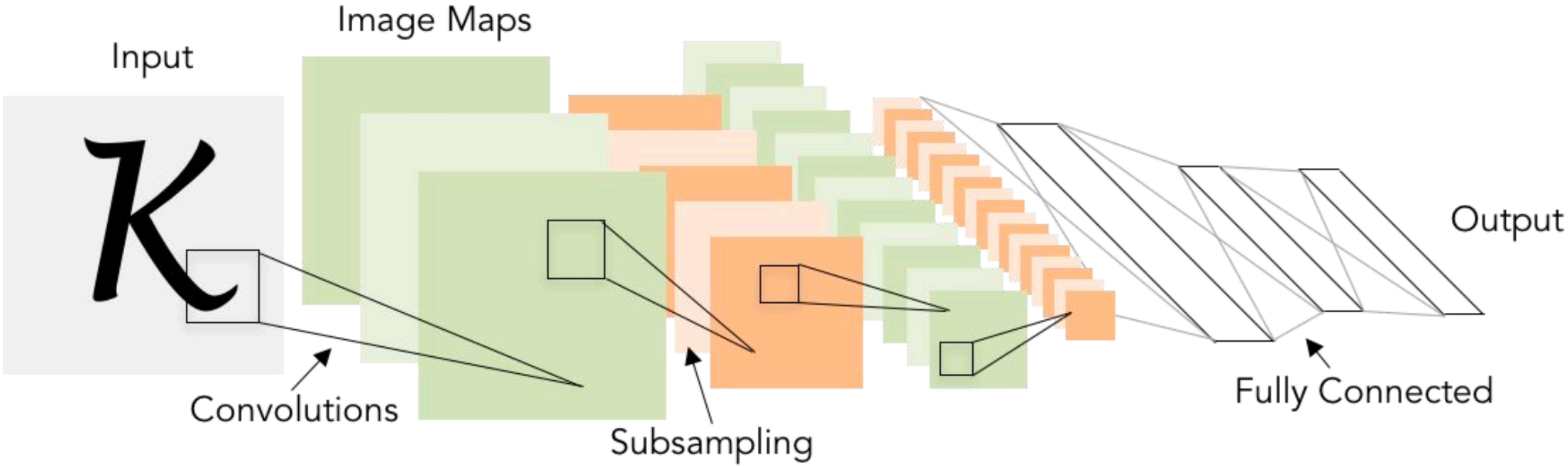


Pooling : Summarizing the input
e.g. output max of input, average

Activation function (non-linear)

[figure from Goodflow 2017]

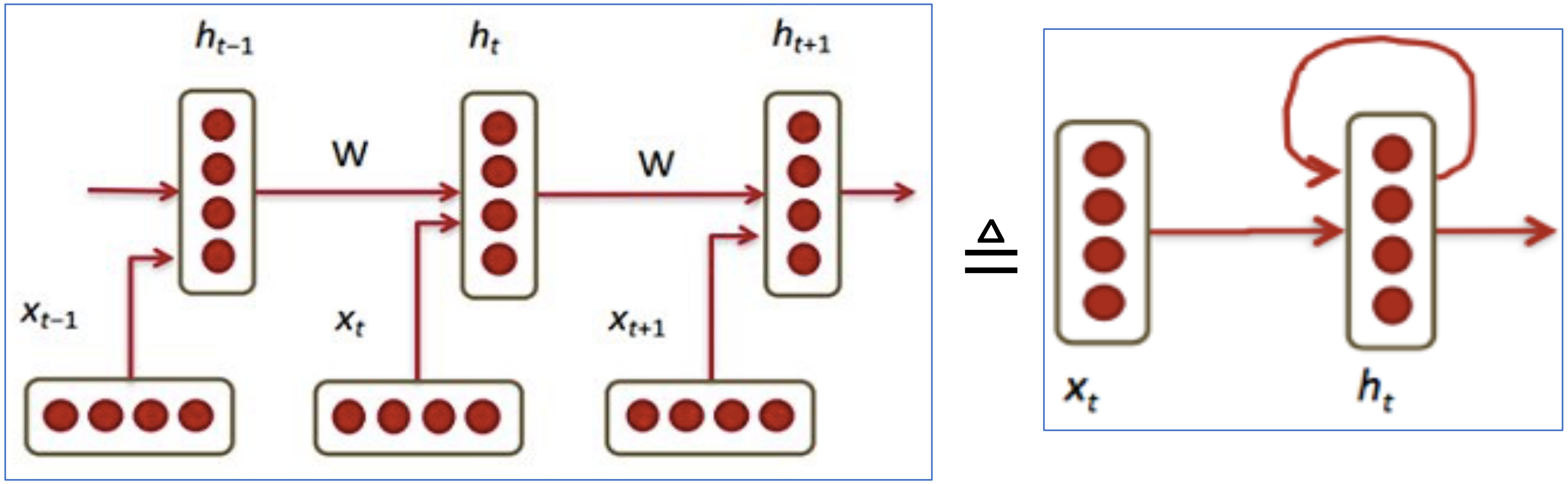
How Do CNNs Work?



[LeCun 1998, Goodfeloow 2017]

Recurrent Neural Networks (RNNs)

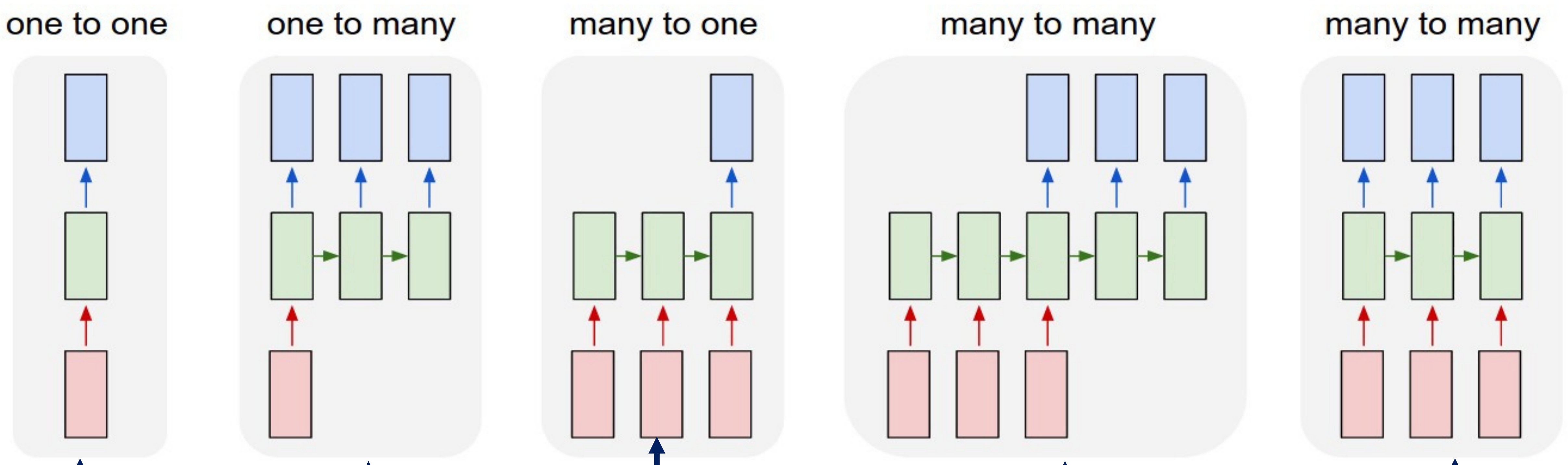
- Main RNN idea : Condition on all previous features
- Use same set of weights at all time steps



$$h_t = \sigma(W^{(hh)}h_{t-1} + W^{(hx)}x_t)$$

[https://discuss.pytorch.org/uploads/default/original/1X/6415da0424dd66f2f5b134709b92baa59e604c55.jpg]

RNNs



Vanilla NNs

e.g., image captioning
Image → sequence of words

e.g. Sentiment Classification
sequence of words -> sentiment

e.g. Machine Translation
sequence of words -> sequence of words

e.g. Video classification on frame level

$$h_t = f_W(h_{t-1}, x_t)$$

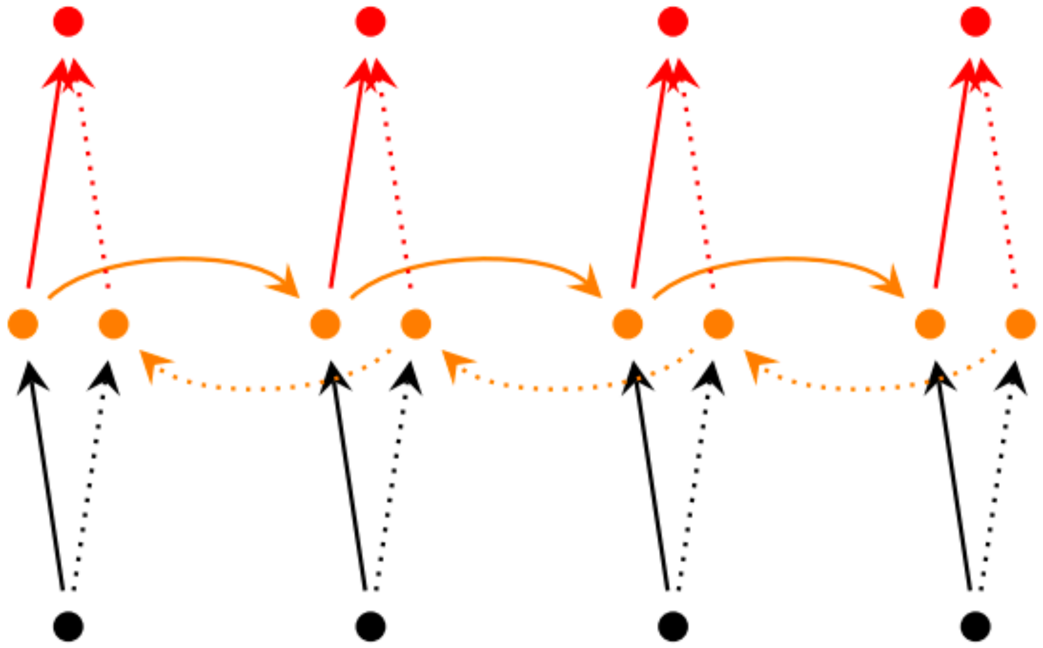
$$h_t = \tanh(W_{hh} h_{t-1} + W_{xh} x_t)$$

$$y_t = W_{hy} h_t$$

[https://discuss.pytorch.org/uploads/default/original/1X/6415da0424dd66f2f5b134709b92baa59e604c55.jpg]

Bidirectional RNNs

- **Main idea:** incorporate both left and right context
- Output may not only depend on the previous elements in the sequence, but also future elements.



$$\overrightarrow{h}_t = \sigma(\overrightarrow{W}^{(hh)}\overrightarrow{h}_{t-1} + \overrightarrow{W}^{(hx)}x_t)$$

$$\overleftarrow{h}_t = \sigma(\overleftarrow{W}^{(hh)}\overleftarrow{h}_{t+1} + \overleftarrow{W}^{(hx)}x_t)$$

$$y_t = f(\,[\overrightarrow{h}_t;\overleftarrow{h}_t\,]\,)$$

past and future around a single token

- Two RNNs stacked on top of each other
- Output is computed based on the hidden state of both RNNs $[\overrightarrow{h}_t;\overleftarrow{h}_t\,]$

[Figure from http://www.wildml.com/2015/09/recurrent-neural-networks-tutorial-part-1-introduction-to-rnns/]

Deep Learning: Applications in Bioinformatics

- CNN to better learn imaging features from CT scans and MRI images from head trauma, stroke diagnosis and brain (enlarged perivascular space) EPV [Chilumkurthy 2018]
- CNN has been adopted rapidly in biomedical imaging studies [Ravi 2017]

- RNN is suitable to deal with long and sequential data, such as DNA array and genomics sequence [Xu 2016, Alipanahi 2015]
- RNN cannot interact with hidden neurons far from the current one → construct an efficient framework of recalling deep memory
  - MD-RNN in analyzing electron microscopy and MRIs of breast cancer samples [Kim 2018]
  - BRNN in protein secondary structure prediction [Baldi 1999]

Deep Learning: Applications in Bioinformatics

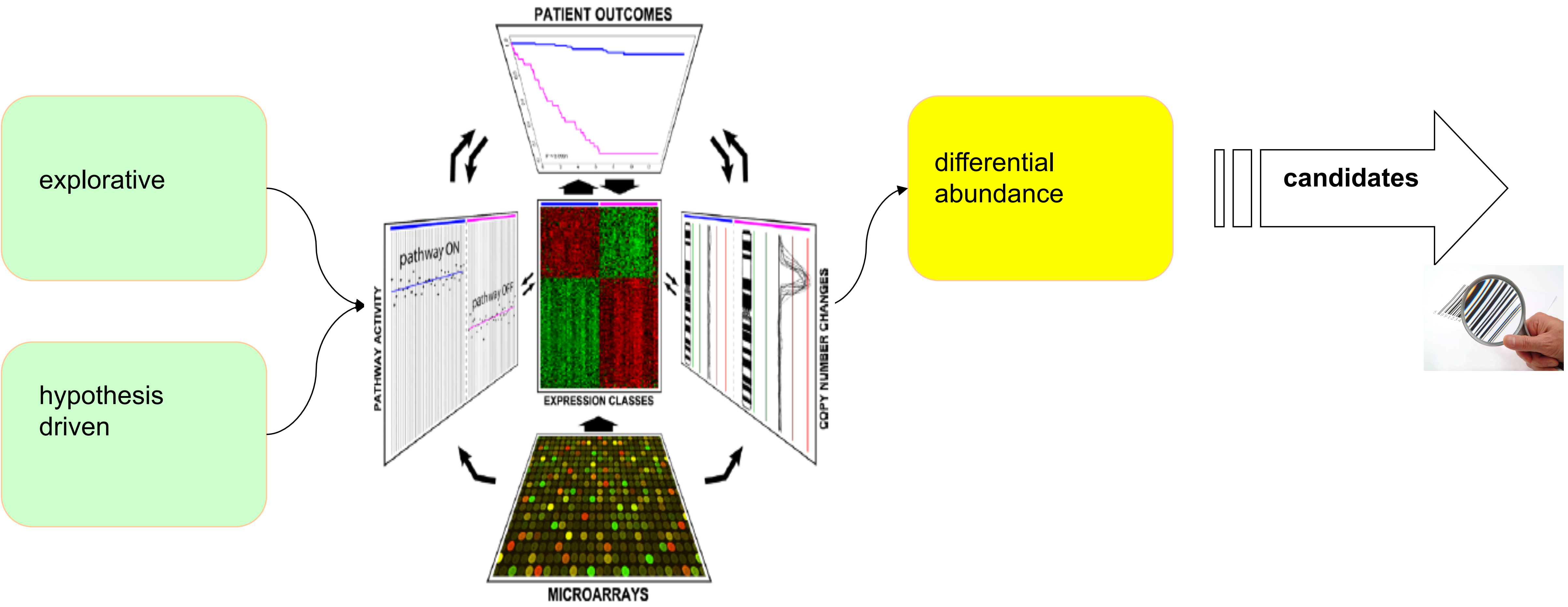
- CNN can be combined with other deep learning models, such as RNN to predict imaging content, where CNN encodes an image and RNN generates the corresponding image description [[Angermueller 2016]
- Ensembled RNN-CNN architecture, DeepCpG, on single-cell DNA methylation data [Angermueller 2017]
  - better predict missing CpG status for genome-wide analysis
  - model's interpretable parameters shed light on the connection between sequence composition and methylation variability
- Sparse autoencoder (SAE), denoising autoencoder (DAE). Stacked sparse autoencoder (SSAE) was proposed to analyze high-resolution histopathological images in breast cancer [Xu 2016]

Biomarker Discovery and Validation

Biomarkers

- **Biomarkers:** Molecules that indicate normal or abnormal process taking place in your body and may be a sign of an underlying condition or disease.
- Types of Biomarkers:
    - DNA (Genes)
    - Proteins
    - Hormones
- Biomarkers can be produced by cancer tissue itself or other cells in body in response to cancer (it is not limited to cancer, e.g. hearth disease, etc.)
- Cancer biomarkers can include:
    - Proteins
    - Gene mutations (changes)
    - Gene rearrangements
    - Extra copies of genes
    - Missing genes
- **Workflow:** Framework for a progression of computational steps, sequentially or in parallel, for identifying biomarkers and targets.

Biomarker Development



explorative

hypothesis driven

differential abundance

candidates

Biomarker Discovery → Clinical Validation → Implementation

t-Test

AUC

[Liu 2006]

Sequential Procedure

1. Filter genes

   Quality filter (80%)

2. Replace missing values

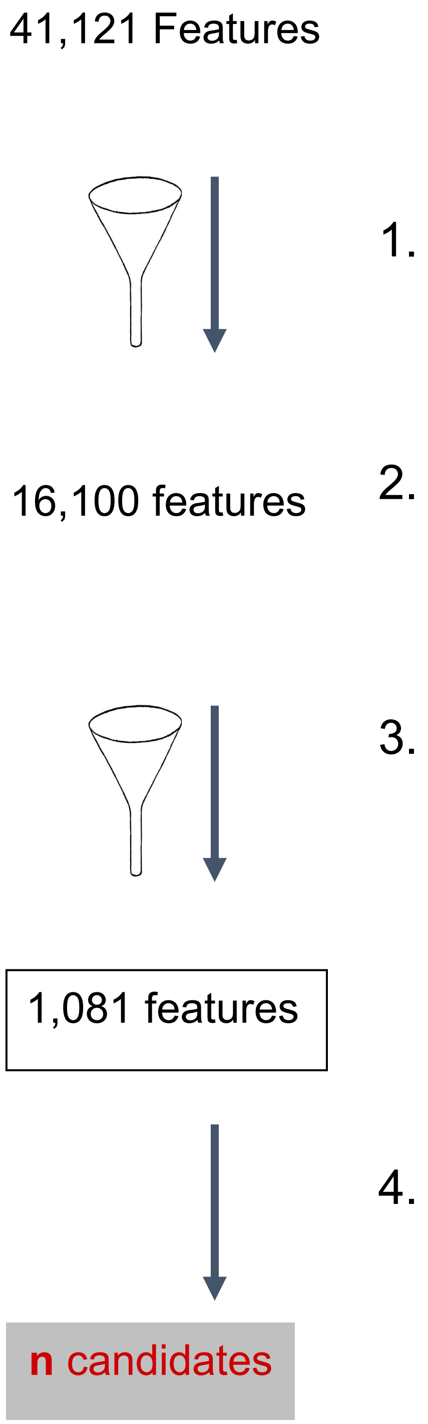
   e.g. with KNN

3. Filter genes

   Variation filter (SD>0.9)

4. Statistical Testing

   e.g. t-Test



41,121 Features

1.

16,100 features

2.

3.

1,081 features

4.

n candidates

[Slide credited to Mayer]

Power Analysis

- To maximize the impact of biomarker-based studies in precision aspects such as study design and statistical model and analysis should be taken into consideration.
    - Study objective
    - Adequate sample size
    - Confounding factors and biases
- Power of a Study: Probability that we reject null hypothesis when a specific alternative hypothesis is true, i.e. avoiding type II error.
    - Translation to Bioinformatics: Probability that a true difference in protein levels will be detected as statistically significant in a hypothesis test.
    - High power is desired.
    - Power analysis determines the sample size.
    - Power analysis should be performed before collecting data.

Why Power Analysis?

- Translating an experimental objective into a statistical model requires us to derive accurate power calculations for the study.
- Power analysis can be done analytically for simple statistical tests or through simulations for for complex ones.
- Power analysis provides:
    1. Effective sample size
        - Finding the sweet spot where the sample size is not too big (unethical) or too small (not meaningful results)
    2. Variance
        - How similar the collected data are
        - High variance requires larger sample size
    3. Significant level
        - p-value to control the type I error
        - If p-value is less than significant level, then the results are statistically significant
        - There is a trade-off between type I error and type II error

Power Analysis Tools for Biomarker Discovery

- Homogenous disease: Given a group of patients, the disease is the same for all of them
- Heterogenous disease: It is divided in endotypes.
- Biomarker Discovery: The way that these tests have been found can be viewed as biomarker discovery
    - Genomic Approach, Proteomic Approach, etc.
    - Goal: The goal in discovery research is to identify a subset of potentially useful markers from a large set of candidates assayed on case and control samples.
- Power analysis tools: Tools to conduct power analysis to determine the sample size for biomarker discovery studies.
- No tools to account for disease heterogeneity → Increased number of samples.
    - E.g. for 100 cases with 100 controls, a t-test detects 99% of biomarkers for a homogeneous disease and only 18% for a heterogeneous disease → Instead use partial AUC (does well for heterogeneous diseases but poorly for homogeneous diseases)

Biomarkers Performance

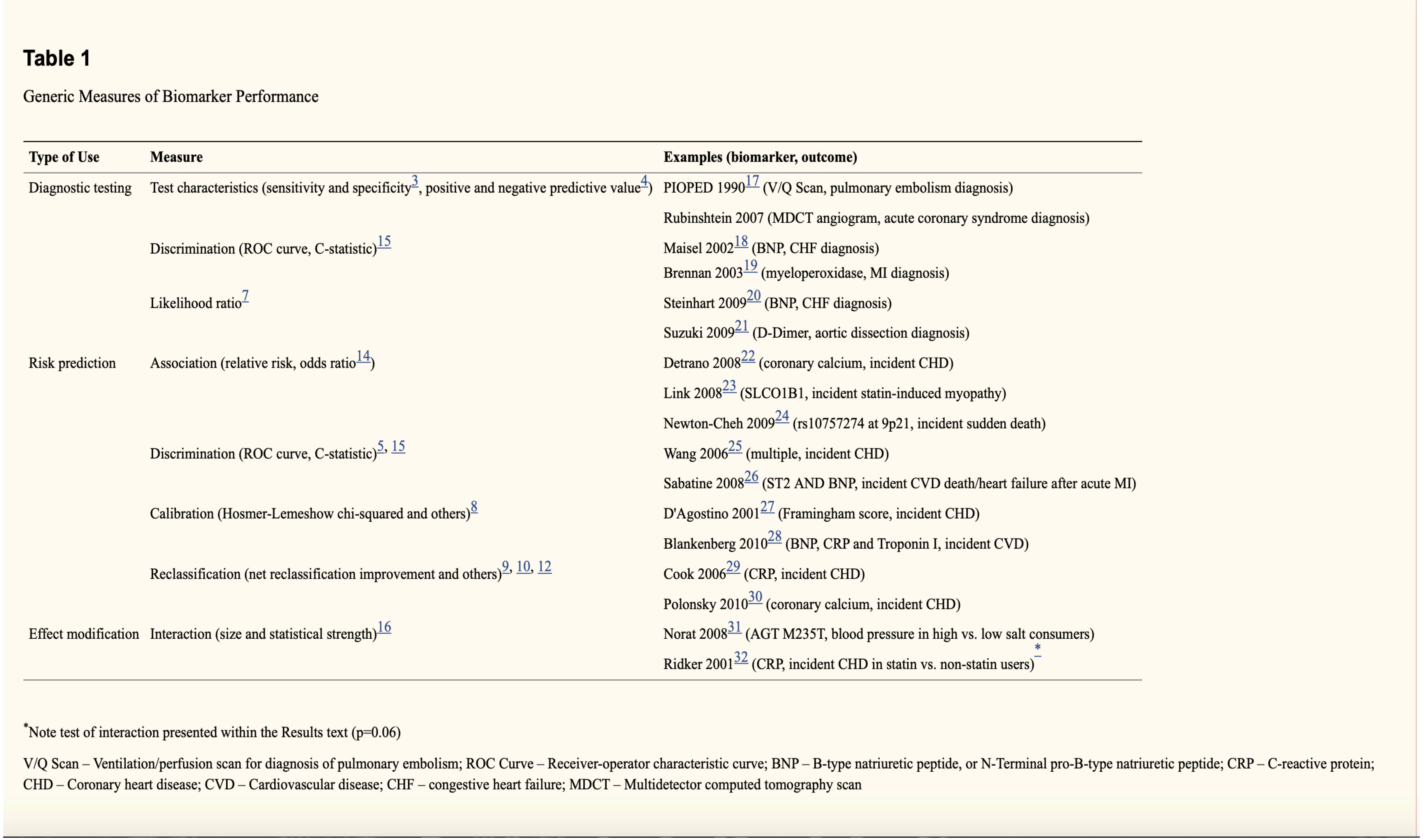


Table 1

Generic Measures of Biomarker Performance

Type of Use	Measure	Examples (biomarker, outcome)
Diagnostic testing	Test characteristics (sensitivity and specificity[3], positive and negative predictive value[4])	PIOPED 1990[17] (V/Q Scan, pulmonary embolism diagnosis)
		Rubinshtein 2007 (MDCT angiogram, acute coronary syndrome diagnosis)
	Discrimination (ROC curve, C-statistic)[15]	Maisel 2002[18] (BNP, CHF diagnosis)
		Brennan 2003[19] (myeloperoxidase, MI diagnosis)
	Likelihood ratio[7]	Steinhart 2009[20] (BNP, CHF diagnosis)
		Suzuki 2009[21] (D-Dimer, aortic dissection diagnosis)
Risk prediction	Association (relative risk, odds ratio[14])	Detrano 2008[22] (coronary calcium, incident CHD)
		Link 2008[23] (SLCO1B1, incident statin-induced myopathy)
		Newton-Cheh 2009[24] (rs10757274 at 9p21, incident sudden death)
	Discrimination (ROC curve, C-statistic)[5, 15]	Wang 2006[25] (multiple, incident CHD)
		Sabatine 2008[26] (ST2 AND BNP, incident CVD death/heart failure after acute MI)
	Calibration (Hosmer-Lemeshow chi-squared and others)[8]	D'Agostino 2001[27] (Framingham score, incident CHD)
		Blankenberg 2010[28] (BNP, CRP and Troponin I, incident CVD)
	Reclassification (net reclassification improvement and others)[9, 10, 12]	Cook 2006[29] (CRP, incident CHD)
		Polonsky 2010[30] (coronary calcium, incident CHD)
Effect modification	Interaction (size and statistical strength)[16]	Norat 2008[31] (AGT M235T, blood pressure in high vs. low salt consumers)
		Ridker 2001[32] (CRP, incident CHD in statin vs. non-statin users)[*]

[*] Note test of interaction presented within the Results text (p=0.06)

V/Q Scan – Ventilation/perfusion scan for diagnosis of pulmonary embolism; ROC Curve – Receiver-operator characteristic curve; BNP – B-type natriuretic peptide, or N-Terminal pro-B-type natriuretic peptide; CRP – C-reactive protein; CHD – Coronary heart disease; CVD – Cardiovascular disease; CHF – congestive heart failure; MDCT – Multidetector computed tomography scan

[Pletcher 2011]]

Machine Learning on Biomarkers

- Machine learning methods pool diverse information to perform computer-assisted diagnosis and predict future clinical decline, e.g. Boost power in clinical trials

  Alzheimer's Disease Neuroimaging Initiative

  - SVM that combines brain imaging and other biomarkers to classify ADNI subjects as Alzheimer’s Disease, Mild Cognitive Impairment, or normal controls.
- Hierarchical Dirichlet process mixture model to describe the distribution of profile contexts, which is able to capture dependencies between amino acids in each context position.
- Deep learning, which has evolved from the acquisition of big data, the power of parallel and distributed computing, and sophisticated training algorithms, has facilitated major advances in numerous domains such as image recognition.
- Dissemination of dynamic CT and MRI lead to the incorporation of RNNs and CNNs and elevate their importance in the long term.

Deep Learning in Bioinformatics

Deep Neural Network:

Omics:
Protein Structure
Gene expression regulation
Protein classification
Anomaly classification

Biomedical Imaging:
Anomaly classification
Segmentation
Recognition
Brain decoding

Biomedical Signal Processing:
Brain decoding
Anomaly classification

Convolutional Neural Network:

Omics:
Gene expression regulation

Biomedical Imaging:
Anomaly classification
Segmentation
Recognition

Biomedical Signal Processing:
Brain decoding
Anomaly classification

Recurrent Neural Network:

Omics:
Protein Structure
Gene expression regulation
Protein classification

Biomedical Imaging:

Biomedical Signal Processing:
Brain decoding
Anomaly classification