Computational Systems Biology
Deep Learning in the Life Sciences

6.802 20.390 20.490 HST.506
6.874 Area II TQE (AI)

David Gifford
Lecture 1
February 4, 2019

http://mit6874.github.io

mit6874.github.io

6.874staff@mit.edu

Please use Piazza or the staff email for any questions

You should have received the Google Cloud coupon URL in your email

Teaching Staff

David Gifford
Gifford@mit.edu

Manolis Kellis
manoli@mit.edu

Tim Truong
ttruong@mit.edu

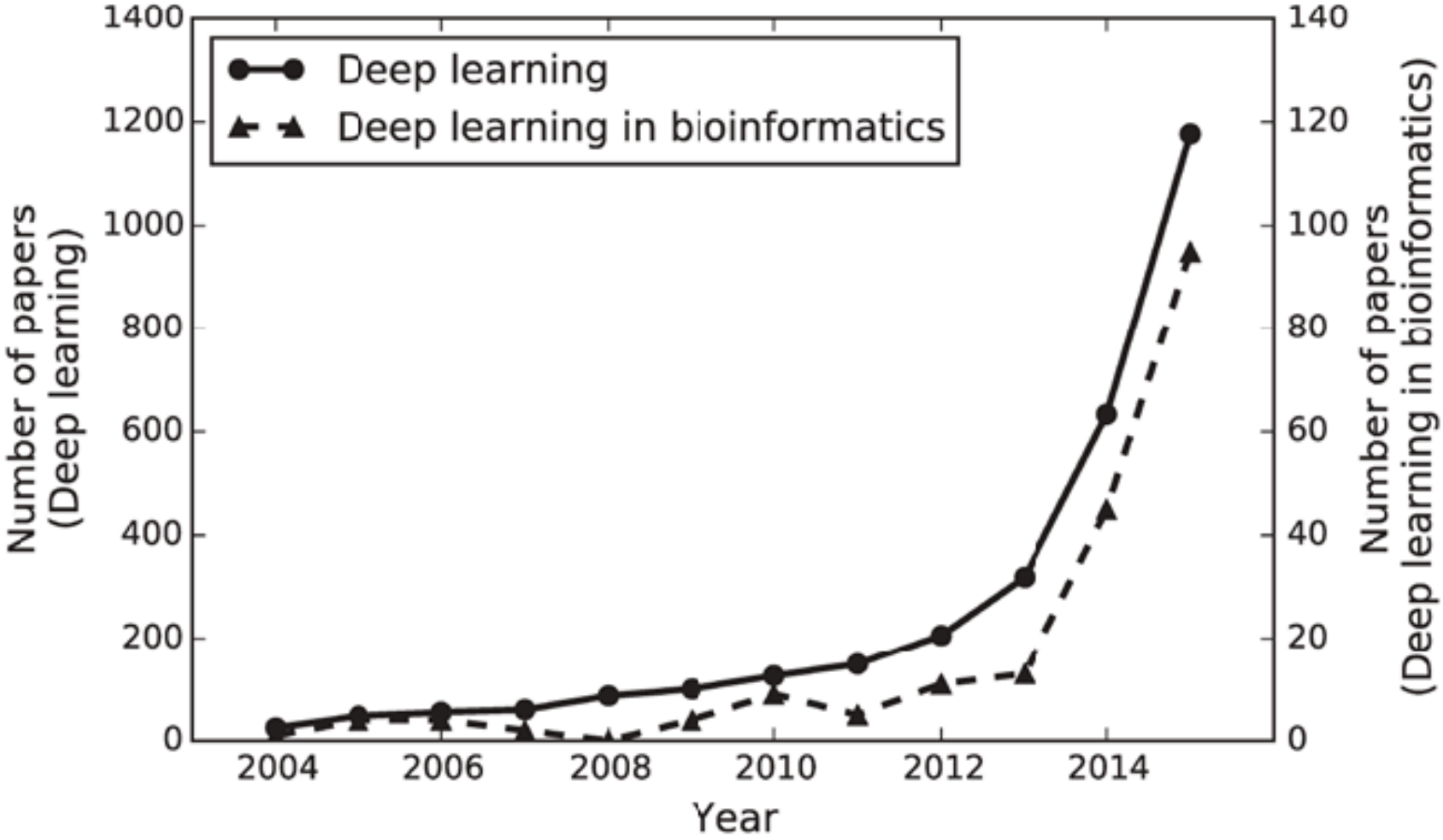
Sachit Saksena
sachit@mit.edu

Corban Swain
c_swain@mit.edu

Recitations (this week)
Thursday 4 - 5pm 36-156
Friday 4 - 5pm 36-156

Office hours are after recitation at 5pm in same room
(PS1 help and advice)

Approximately 8% of deep learning publications are in bioinformatics

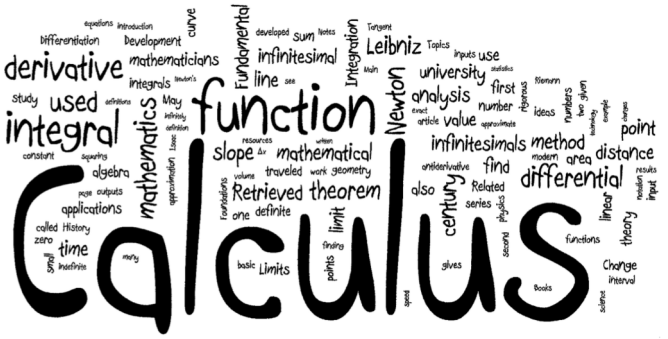


Welcome to a new approach to life sciences research

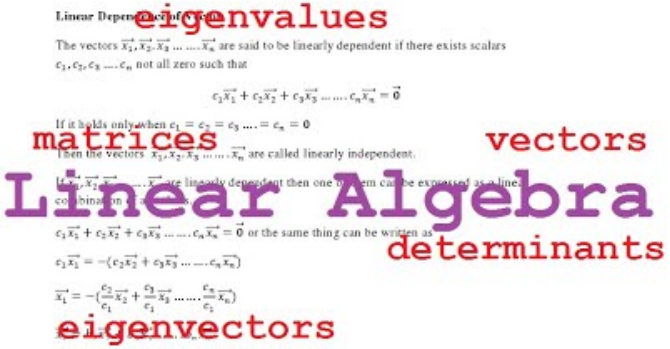
- Enabled by the convergence of three things
  - Inexpensive, high-quality, collection of large data sets (sequencing, imaging, etc.)
  - New machine learning methods (including ensemble methods)
  - High-performance Graphics Processing Unit (GPU) machine learning implementations
- Result is completely transformative

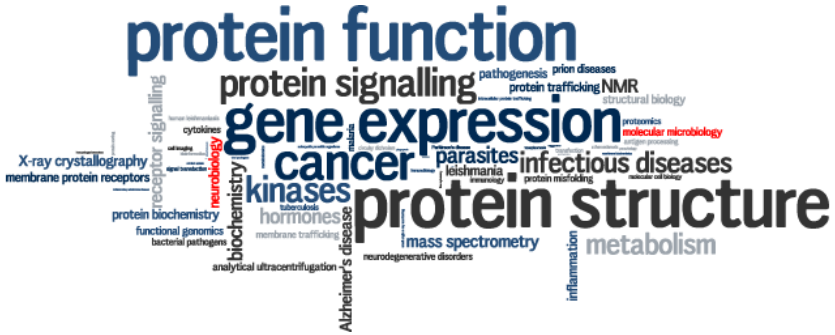
Your background

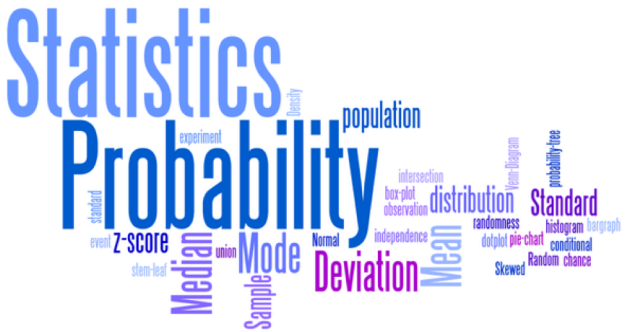
- Calculus, Linear Algebra
- Probability, Programming
- Introductory Biology




```
def loadstable(ver):
    return _loadversion(ver, prefix="_stable_")

def loadunstable(ver):{...}
def loadexact(ver):{...}
def _loadversion(ver, prefix):
    targetname = prefix + ver.replace('.', '_')
    mainpackage = _original__import__("tools", globals(), locals(),
        [targetname])
    global currentversion
    currentversion = getattr(mainpackage, targetname)

    # Let users change versions after choosing this one
    currentversion.loadstable = loadstable
    currentversion.loadunstable = loadunstable
    currentversion.loadexact = loadexact

    return currentversion

currentversion = None
```







Grade contributions

- Four Problem Sets (40%)
  - Individual contribution
  - Done using Google Cloud, Jupyter Notebook
- Two quizzes (1.5 hours), one sheet of notes (30%)
- Final Project (25%)
  - Done in teams of two
- Scribing (5%)

Alternative MIT subjects

- 6.047 / 6.878 Computational Biology: Genomes, Networks, Evolution
- 6.S897/HST.956: Machine Learning for Healthcare (2:30pm 4-270)
- 8.592 Statistical Physics in Biology
- 7.09 Quantitative and Computational Biology
- 7.32 Systems Biology
- 7.33 Evolutionary Biology: Concepts, Models and Computation
- 7.57 Quantitative Biology for Graduate Students
- 18.417 Introduction to Computational Molecular Biology
- 20.482 Foundations of Algorithms and Computational Techniques in Systems Biology

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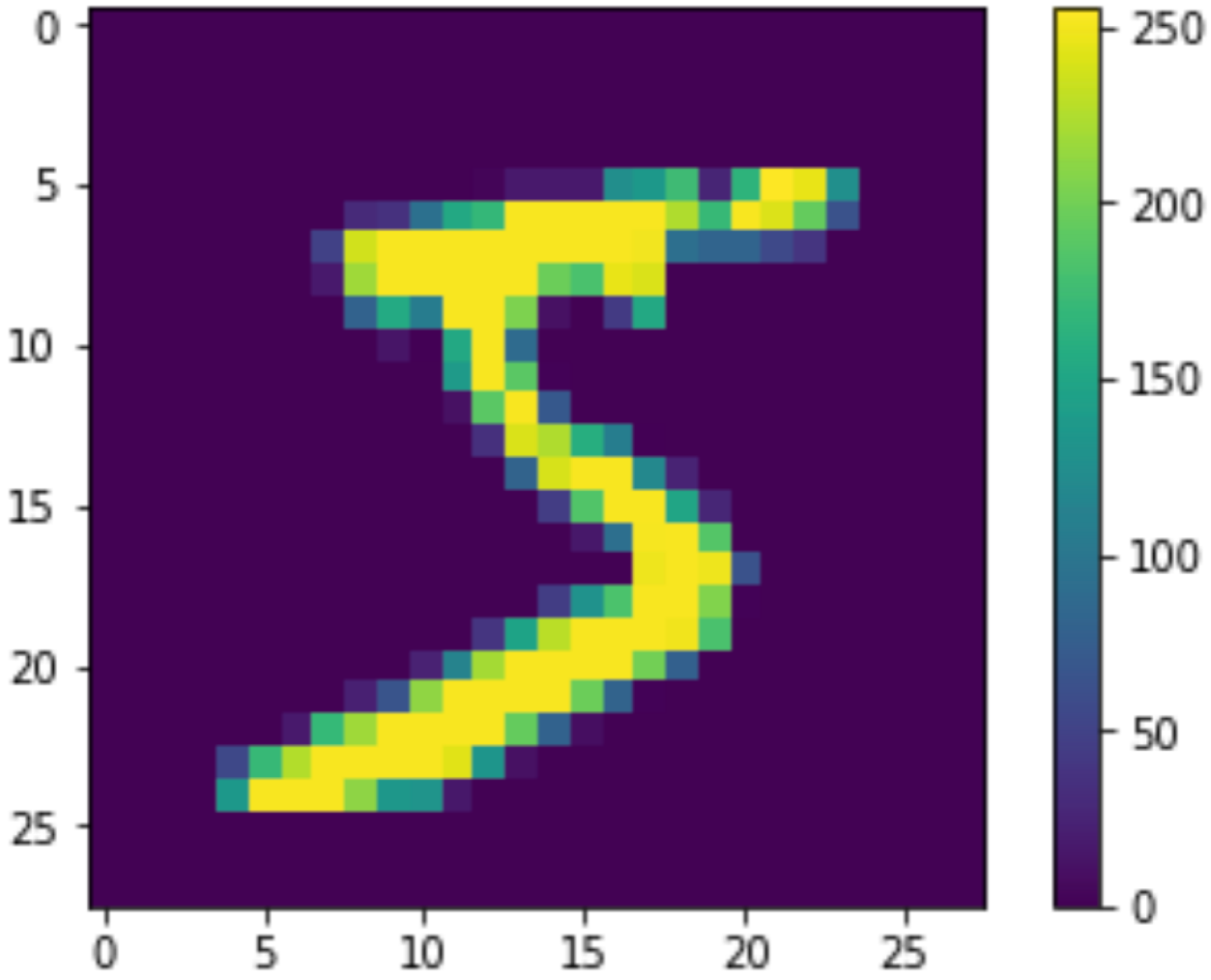
PS 1: Tensor Flow Warm Up




```
ground truth: 5
```

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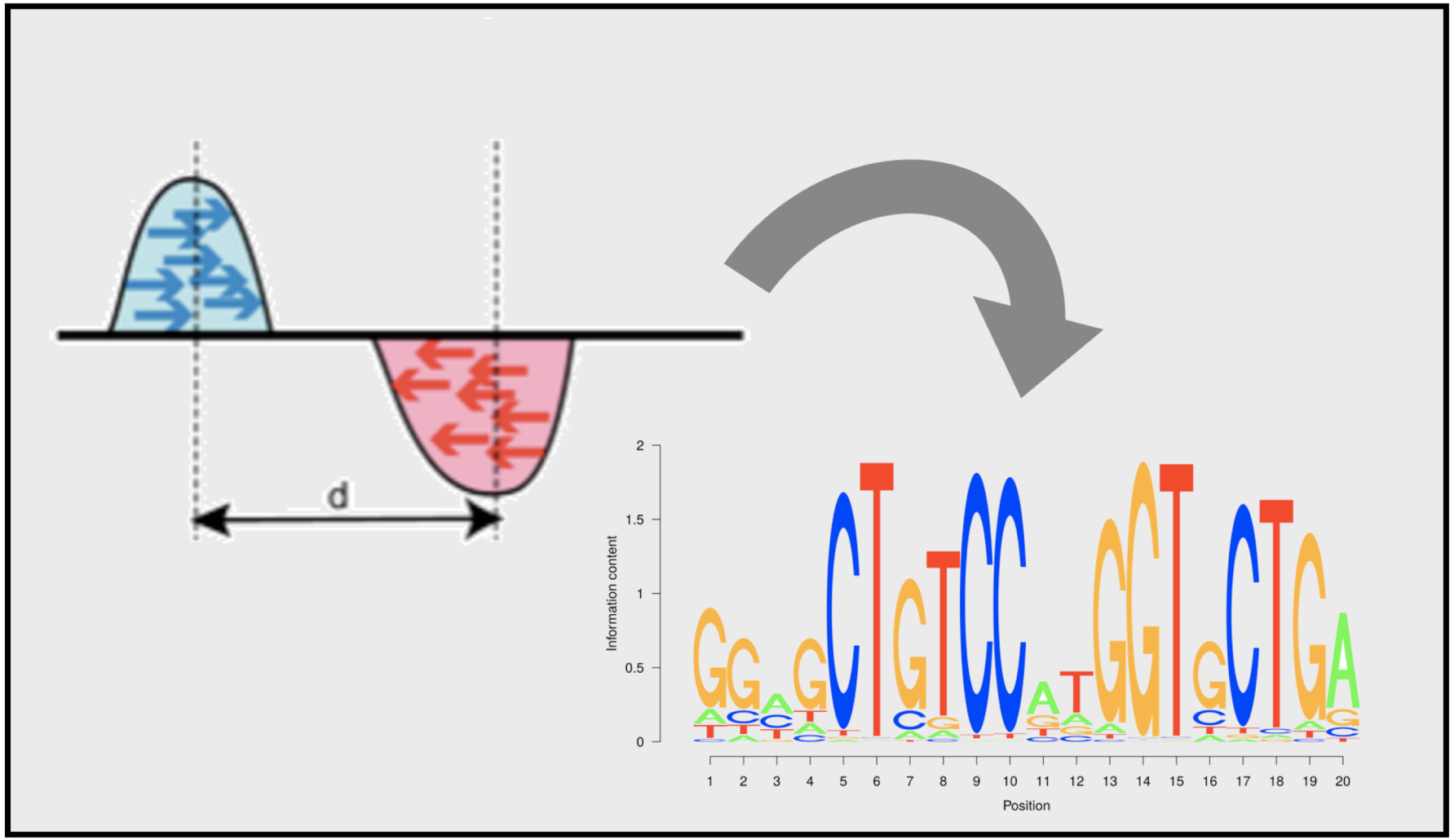
PS 2: Genomic regulatory codes



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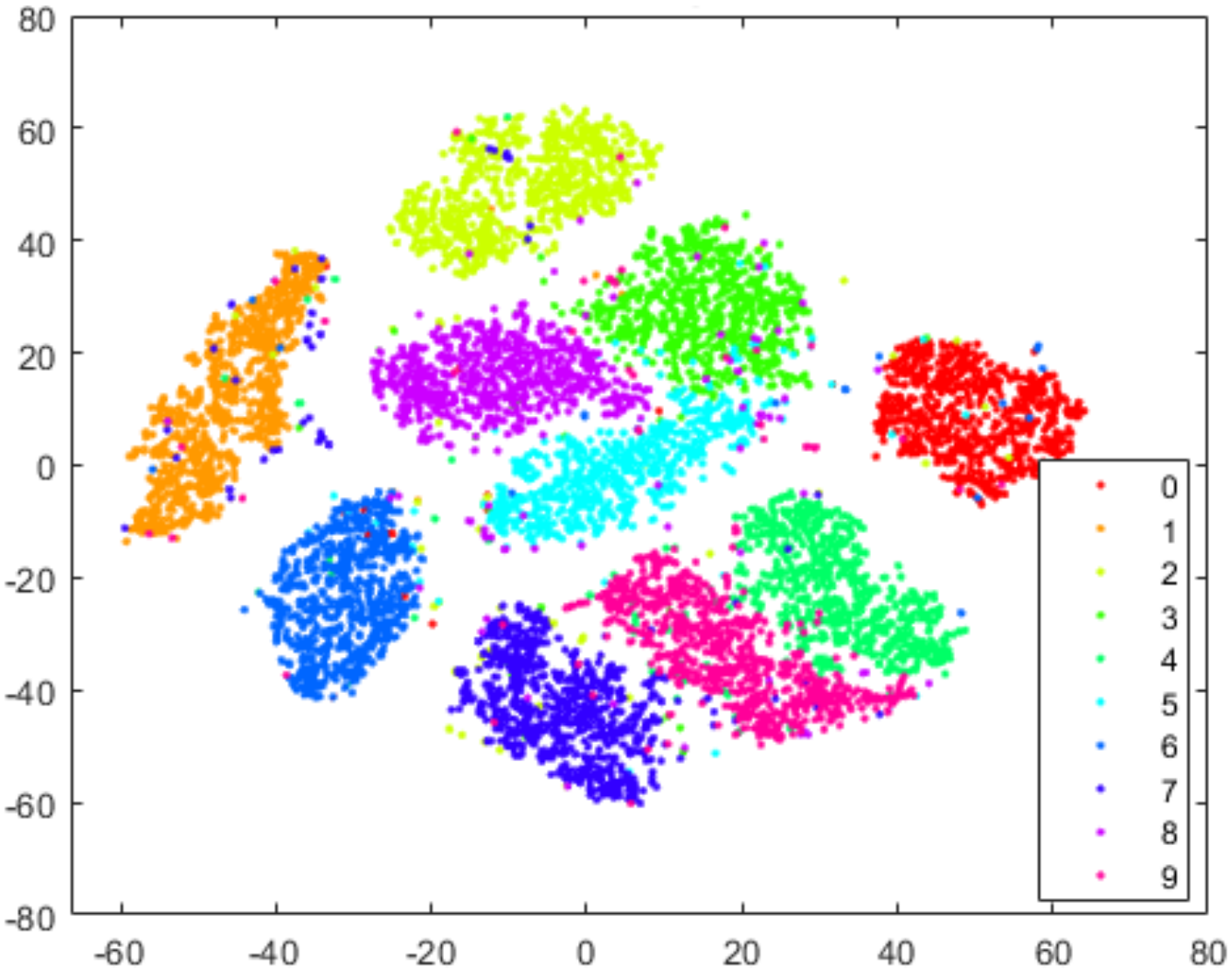
PS 3: Parametric tSNE
Single Cell RNA-seq data



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Your programming environment

Problem 2

In this problem, we wish to use CNN to learn the motif of CTCF from sequences with similar di-nucleotide frequency. The positive samples are 101bp sequences centered at CTCF ChIP-seq peaks from GM12878 cell line. The negative sequences are generated by permuting the nucleotides in the positive sequences while keeping the di-nucleotide frequency.

We will provide functions for loading data, training and testing. You will:

- implement a CNN model with given specifications
- specify the initilization of parameters in the model
- train the model and evaluate on the test set

All the places where you need to fill in begins with "TODO" and ends with "END OF YOUR CODE".

In [1]:
```
import tensorflow as tf, sys, numpy as np, h5py
from os.path import join,dirname,basename,exists,realpath
from os import makedirs
from tensorflow.examples.tutorials.mnist import input_data
from sklearn.metrics import roc_auc_score
```

In [2]:
```
data_folder = '../data/motif_disc'
batch_size = 128
valid_size = 2000
epochs = 20
best_model_file = join('../output',basename(data_folder),'best_model.ckpt')
if not exists(dirname(best_model_file)):
    makedirs(dirname(best_model_file))
```

In [3]:
```
# Function to load the data embedded in the previous problem and their labels
def load_data(mydir):
    train = h5py.File(join(mydir,'train.h5'),'r')
```


Your computing resourc

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Submit

What is Machine Learning?

[Shalev-Shwartz and Ben-David, 2014]:

"Learning is the process of converting experience into expertise or knowledge."

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> *"The goal of machine learning is to develop methods that can automatically detect patterns in data, and then to use the uncovered patterns to predict future data or other outcomes of interest."*

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[Hastie et al., 2001]:

> *"[...] state the learning task as follows: given the value of an input vector* $\boldsymbol{x}$*, make a good prediction of the output* $\boldsymbol{y}$*, denoted by* $\hat{\boldsymbol{y}}$*"*

What is Machine Learning?

A computer program is said to learn from
experience E

with respect to some
class of tasks T

and
performance measure P,

if its performance at tasks in T, as measured by P, improves with experience E.

[Mitchell, 1997]

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Problem Set 1

- experience E: training set of images of handwritten digits with labels (training set)
- task T: classifying handwritten digits within new images (test set)
- performance measure P: percent of test set digits correctly classified in new images (test set)

Welcome to 6.802 / 6.874 / 20.390 / 20.490 / HST.506 - Spring 2020

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Notation

a, b, c_i	scalar (slanted, lower-case)
$\boldsymbol{a}, \boldsymbol{b}, \boldsymbol{c}$	vector (bold, slanted, lower-case)
$\boldsymbol{A}, \boldsymbol{B}, \boldsymbol{C}$	matrix (bold, slanted, upper-case)
$\mathbf{A}, \mathbf{B}, \mathbf{C}$	tensor (bold, upright, upper-case)
$\mathcal{A}, \mathcal{B}, \mathcal{C}$	set (calligraphic, slanted, upper-case)

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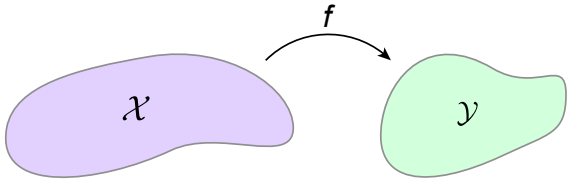
$\mathcal{A}, \mathcal{B}, \mathcal{C}$	set (calligraphic, slanted, upper-case)
$\mathcal{X}$	input space or feature space
$\boldsymbol{X}, \mathbf{X}$	dataset example matrix or tensor
$\boldsymbol{x}^{(i)}$	ith example of dataset, one row of $\boldsymbol{X}$
$x_j^{(i)}, x_j$	feature j of example $\boldsymbol{x}^{(i)}$
$\mathcal{Y}$	label space
$\boldsymbol{y}^{(i)}$	label of example i
$\hat{\boldsymbol{y}}^{(i)}$	predicted label of example i

Terminology



Input $\boldsymbol{X} \in \mathcal{X}$:

- **features** (in machine learning)
- predictors (in statistics)
- independent variables (in statistics)
- regressors (in regression models)
- input variables
- covariates

Output $\boldsymbol{y} \in \mathcal{Y}$:

- **labels** (in machine learning)
- responses (in statistics)
- dependent variables (in statistics)
- regressand (in regression models)
- target variables

Training set $\mathcal{S}_{\text{training}} = \{(\boldsymbol{X}^{(i)}, \boldsymbol{y}^{(i)})\}_{i=1}^{N} \in \{\mathcal{X}, \mathcal{Y}\}^N$, where N is number of training examples

An example is a collection of features (and an associated label)

Training: use $\mathcal{S}_{\text{training}}$ to learn functional relationship $f : \mathcal{X} \to \mathcal{Y}$

Terminology

$$f: \quad \mathcal{X} \to \mathcal{Y}$$
$$f(\boldsymbol{x}; \boldsymbol{\theta}) = \hat{\boldsymbol{y}}$$

$\boldsymbol{\theta}$:

- **weights** and **biases** (intercepts)
- coefficients $\boldsymbol{\beta}$
- parameters

f:

- model
- hypothesis h
- classifier
- predictor
- discriminative models: P(Y|X)
- generative models: P(X, Y)

Problem Set 1

$$\boldsymbol{x} \in [0, 1]^{784}$$
$$\hat{\boldsymbol{y}} \in [0, 1]^{10}$$
$$\boldsymbol{W} \in \mathbb{R}^{784 \times 10}$$
$$\boldsymbol{b} \in \mathbb{R}^{10}$$
$$f(\boldsymbol{x}; \boldsymbol{W}, \boldsymbol{b}) = \phi_{\text{softmax}}(\boldsymbol{W}^{\mathsf{T}}\boldsymbol{x} + \boldsymbol{b})$$

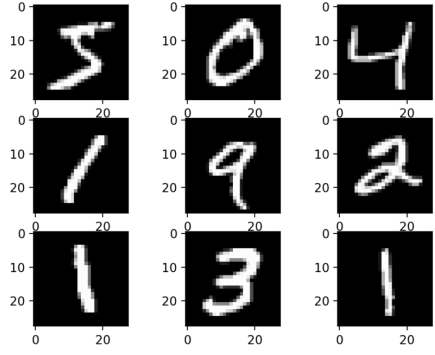
Problem Set 1

input space:
$\mathcal{X} = \{0, 1, \ldots, 255\}^{28 \times 28}$

after rescaling:
$\mathcal{X}' = [0, 1]^{28 \times 28}$

after flattening:
$\mathcal{X}'' = [0, 1]^{784}$

Classification



Problem Set 1

input space:
$\mathcal{X} = \{0, 1, \ldots, 255\}^{28 \times 28}$

after rescaling:
$\mathcal{X}' = [0, 1]^{28 \times 28}$

after flattening:
$\mathcal{X}'' = [0, 1]^{784}$

integer-encoded label space:
$\mathcal{Y}_\text{i} = \{0, 1, \ldots, 9\}$

one-hot-encoded label space:
$\mathcal{Y}_\text{h} = [0, 1]^{10}$

$$\overbrace{\boldsymbol{x}^{(i)} \in \mathcal{X}}$$

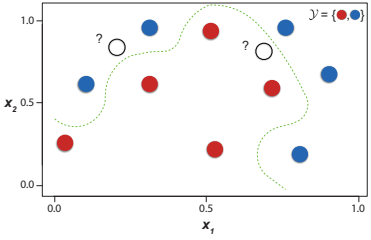
$$\begin{array}{c} \\ 1 \\ 2 \\ \vdots \\ 28 \end{array} \begin{array}{c} \begin{array}{cccc} 1 & 2 & \cdots & 28 \end{array} \\ \begin{bmatrix} x_{1,1} & x_{1,2} & \cdots & x_{1,28} \\ x_{2,1} & x_{2,2} & \cdots & x_{2,28} \\ \vdots & \vdots & \ddots & \vdots \\ x_{28,1} & x_{28,2} & \cdots & x_{28,28} \end{bmatrix} \end{array}$$

$$\overbrace{\boldsymbol{y}^{(i)} \in \mathcal{Y}_h}$$

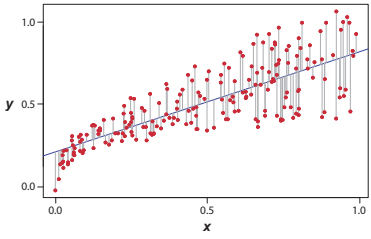
$$\begin{array}{cccc} 1 & 2 & \cdots & 10 \end{array}$$
$$\begin{bmatrix} y_1 & y_2 & \cdots & y_{10} \end{bmatrix}$$

Types of Machine Learning

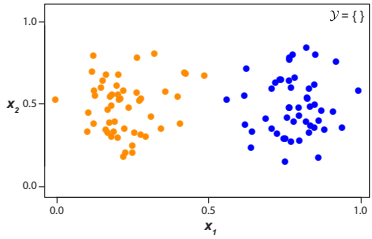
Classification



Regression



Unsupervised learning



$\mathcal{Y} \neq \emptyset$	supervised or semi-supervised learning
$\mathcal{Y} = \mathbb{R}$	regression
$\mathcal{Y} = \mathbb{R}^K, K > 1$	multivariate regression
$\mathcal{Y} = \{0, 1\}$	binary classification
$\mathcal{Y} = \{1, ..., K\}$	multi-class classification (integer encoding)
$\mathcal{Y} = \{0, 1\}^K, K > 1$	multi-label classification
$\mathcal{Y} = \emptyset$	unsupervised learning

Types of Machine Learning

Problem Set 1

- task: every $\boldsymbol{X}$ has an associated $\boldsymbol{y}$ $\implies$ supervised learning
- subtask: $\mathcal{Y} = \{0, ..., 9\}$ $\implies$ multi-class classification
- method: we use softmax regression (also known as multinomial logistic regression) as multi-class classification method

Objective functions

An **objective function** $\mathcal{J}(\Theta)$ is the function that you optimize when training machine learning models. It is usually in the form of (but not limited to) one or combinations of the following:

Loss / cost / error function $\mathcal{L}(\hat{\boldsymbol{y}}, \boldsymbol{y})$:

Classification

- 0-1 loss
- cross-entropy loss
- hinge loss

Regression

- mean squared error (MSE, L_2 norm)
- mean absolute error (MAE, L_1 norm)
- Huber loss (hybrid between L_1 and L_2 norm)

Probabilistic inference

- Kullback-Leibler divergence (KL divergence)

Likelihood function / posterior:

- negative log-likelihood (NLL) in maximum likelihood estimation (MLE)
- posterior in maximum a posteriori estimation (MAP)

Regularizers and constraints

- L_1 regularization $||\Theta||_1 = \lambda \sum_{i=1}^{N} |\theta_i|$
- L_2 regularization $||\Theta||_2^2 = \lambda \sum_{i=1}^{N} \theta_i^2$
- max-norm $||\Theta||_2^2 \leq c$

0-1 loss:

$$\mathcal{L}_{0\text{-}1}(\hat{\boldsymbol{y}}, \boldsymbol{y}) = \sum_{i=1}^{N} \mathbb{1}([\hat{y}^{(i)}] \neq y^{(i)}) = \sum_{i=1}^{N} \begin{cases} 1, & \text{for } \hat{y}^{(i)} \neq y^{(i)} \\ 0, & \text{for } \hat{y}^{(i)} = y^{(i)} \end{cases}$$

where $[x]$ is the function that rounds x to the nearest integer.

Loss functions for classification

0-1 loss:

$$\mathcal{L}_{0\text{-}1}(\hat{\boldsymbol{y}}, \boldsymbol{y}) = \sum_{i=1}^{N} \mathbb{1}([\hat{y}^{(i)}] \neq y^{(i)}) = \sum_{i=1}^{N} \begin{cases} 1, & \text{for } \hat{y}^{(i)} \neq y^{(i)} \\ 0, & \text{for } \hat{y}^{(i)} = y^{(i)} \end{cases}$$

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Binary cross-entropy loss (for binary classification):

$\mathcal{L}_{\text{BCE}} = \text{NLL}$ (Negative Log Likelihood)
Likelihood is defined using the Bernoulli distribution

$$p(\hat{y}^{(i)}, y^{(i)}) = (\hat{y}^{(i)})^{y^{(i)}}(1 - \hat{y}^{(i)})^{(1-y^{(i)})}$$

0-1 loss:

$$\mathcal{L}_{\text{0-1}}(\hat{\boldsymbol{y}}, \boldsymbol{y}) = \sum_{i=1}^{N} \mathbb{1}([\hat{y}^{(i)}] \neq y^{(i)}) = \sum_{i=1}^{N} \begin{cases} 1, & \text{for } \hat{y}^{(i)} \neq y^{(i)} \\ 0, & \text{for } \hat{y}^{(i)} = y^{(i)} \end{cases}$$

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$p(\hat{y}^{(i)}, y^{(i)}) = (\hat{y}^{(i)})^{y^{(i)}}(1 - \hat{y}^{(i)})^{(1-y^{(i)})}$

$$\begin{aligned} \mathcal{L}_{\text{BCE}}(\hat{\boldsymbol{y}}, \boldsymbol{y}) &= \sum_{i=1}^{N} -y^{(i)} \log(\hat{y}^{(i)}) - (1 - y^{(i)}) \log(1 - \hat{y}^{(i)}) \\ &= \sum_{i=1}^{N} \begin{cases} -\log(\hat{y}^{(i)}), & \text{for } y^{(i)} = 1 \\ -\log(1 - \hat{y}^{(i)}), & \text{for } y^{(i)} = 0 \end{cases} \end{aligned}$$

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$$= \sum_{i=1}^{N} \begin{cases} -\log(\hat{y}^{(i)}), & \text{for } y^{(i)} = 1 \\ -\log(1 - \hat{y}^{(i)}), & \text{for } y^{(i)} = 0 \end{cases}$$

$\boldsymbol{y}$	$\hat{\boldsymbol{y}}$	$[\hat{\boldsymbol{y}}]$	$\mathcal{L}_{\text{0-1}}(\hat{\boldsymbol{y}}, \boldsymbol{y})$	$\mathcal{L}_{\text{BCE}}(\hat{\boldsymbol{y}}, \boldsymbol{y})$
$[1, 0, 0]$	$[0.9, 0.2, 0.4]$	$[1, 0, 0]$	0	0.84
$[1, 1, 0]$	$[0.6, 0.4, 0.1]$	$[1, 0, 0]$	1	1.53
$[1, 0, 1]$	$[0.1, 0.7, 0.3]$	$[0, 1, 0]$	3	4.71

Problem Set 1

Categorical cross-entropy loss (for multi-class classification with K classes):

$$\mathcal{L}_{\text{CCE}}(\hat{\boldsymbol{y}}, \boldsymbol{y}) = \sum_{i=1}^{N} \sum_{j=1}^{K} y_j^{(i)} \log(\hat{y}_j^{(i)}),$$

$$\text{where} \quad \hat{y}_j^{(i)} = \frac{\exp(z_j^{(i)})}{\sum_{k=1}^{K} \exp(z_k^{(i)})} \quad \text{if softmax is used}$$

note: $y_j^{(i)} = 1$ only if $\boldsymbol{x}^{(i)}$ belongs to class j and otherwise $y_j^{(i)} = 0$

Probabilistic interpretation:
$\mathcal{L}_{\text{CCE}} = \text{NLL}$, if likelihood is defined using the categorical distribution

Loss functions for regression

Mean squared error:

$$\mathcal{L}_{\text{MSE}}(\hat{\boldsymbol{y}}, \boldsymbol{y}) = \frac{1}{N} \sum_{i=1}^{N} (y^{(i)} - \hat{y}^{(i)})^2$$

Probabilistic interpretation:
$\mathcal{L}_{\text{MSE}}$ = NLL, under the assumptation that the noise is normally distributed, with constant mean and variance

Loss functions for regression

Mean squared error:

$$\mathcal{L}_{\text{MSE}}(\hat{\boldsymbol{y}}, \boldsymbol{y}) = \frac{1}{N} \sum_{i=1}^{N} (y^{(i)} - \hat{y}^{(i)})^2$$

Probabilistic interpretation:
$\mathcal{L}_{\text{MSE}} = \text{NLL}$, under the assumptation that the noise is normally distributed, with constant mean and variance

Mean absolute error:

$$\mathcal{L}_{\text{MAE}}(\hat{\boldsymbol{y}}, \boldsymbol{y}) = \frac{1}{N} \sum_{i=1}^{N} |y^{(i)} - \hat{y}^{(i)}|$$

Mean squared error:

$$\mathcal{L}_{\text{MSE}}(\hat{\boldsymbol{y}}, \boldsymbol{y}) = \frac{1}{N} \sum_{i=1}^{N} (y^{(i)} - \hat{y}^{(i)})^2$$

Probabilistic interpretation:
$\mathcal{L}_{\text{MSE}} = \text{NLL}$, under the assumptation that the noise is normally distributed, with constant mean and variance

Mean absolute error:

$$\mathcal{L}_{\text{MAE}}(\hat{\boldsymbol{y}}, \boldsymbol{y}) = \frac{1}{N} \sum_{i=1}^{N} |y^{(i)} - \hat{y}^{(i)}|$$

$\boldsymbol{y}$	$\hat{\boldsymbol{y}}$	$\mathcal{L}_{\text{MSE}}(\hat{\boldsymbol{y}}, \boldsymbol{y})$	$\mathcal{L}_{\text{MAE}}(\hat{\boldsymbol{y}}, \boldsymbol{y})$
$[3.2, 1.2, 0.3]$	$[3.1, 1.3, 0.4]$	0.01	0.1
$[2.1, 0.1, -5.1]$	$[2.0, -0.1, 1.2]$	13.25	2.2
$[-0.1, 3.1, 0.5]$	$[0.1, 3.3, -0.5]$	0.36	0.47

Empirical risk minimization

Expected risk (loss) associated with hypothesis $h(\boldsymbol{x})$:

$$\mathcal{R}_{\text{exp}}(h) = \mathbb{E}(\mathcal{L}(h(\boldsymbol{x}), \boldsymbol{y})) = \int_{\mathcal{X}\times\mathcal{Y}} \mathcal{L}(h(\boldsymbol{x}), \boldsymbol{y}) p(\boldsymbol{x}, \boldsymbol{y}) d\boldsymbol{x} d\boldsymbol{y}$$

Minimize $\mathcal{R}_{\text{exp}}(h)$ to find optimal hypothesis h:

$$h = \underset{h\in\mathcal{F}}{\text{argmin}}\, \mathcal{R}_{\text{exp}}(h)$$

Problem:

- distribution $p(\boldsymbol{x}, \boldsymbol{y})$ unknown
- $\mathcal{F}$ is too large (set of all functions from $\mathcal{X}$ to $\mathcal{Y}$)

Empirical risk minimization

Empirical risk associated with hypothesis $h(\boldsymbol{x})$:

$$\mathcal{R}_{\text{emp}}(h) = \frac{1}{N} \sum_{i=1}^{N} \mathcal{L}(h(\boldsymbol{x}^{(i)}), \boldsymbol{y}^{(i)})$$

Minimize $\mathcal{R}_{\text{emp}}(h)$ to find $\hat{h}$:

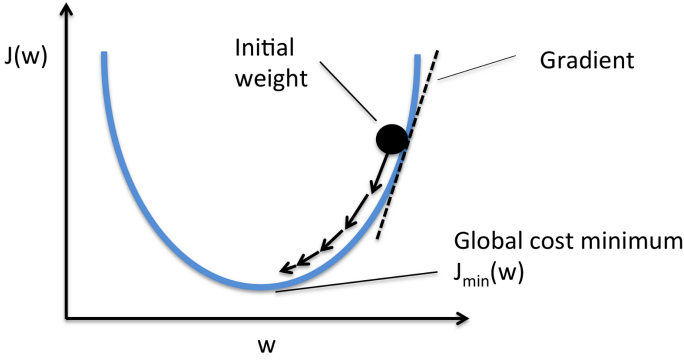
$$\hat{h} = \underset{h \in \mathcal{H}}{\operatorname{argmin}} \, \mathcal{R}_{\text{emp}}(h)$$

In practice:

- instead of $p(\boldsymbol{x}, \boldsymbol{y})$, we use training set $\mathcal{S}_{\text{training}}$
- instead of $\mathcal{F}$, we use $\mathcal{H} \subset \mathcal{F}$, e.g., all polynomials of degree 5

Optimizing objective function

Gradient descent



- initialize model parameters $\theta_0, \theta_1, ..., \theta_m$
- repeat until converge, for all θ_i

$$\theta_i^t \leftarrow \theta_i^{t-1} - \lambda \frac{\partial}{\partial \theta_i^{t-1}} \mathcal{J}(\Theta),$$

where the objective function $\mathcal{J}(\Theta)$ is evaluated over all training data $\{(\mathbf{X}^{(i)}, \mathbf{y}^{(i)})\}_{i=1}^N$.

Problem Set 1

Stochastic Gradient Descent (SGD): in each step, randomly sample a mini-batch from the training data and update the parameters using gradients calculated from the mini-batch only.

Training, validation, test sets

Training set ($\mathcal{S}_{\text{training}}$):

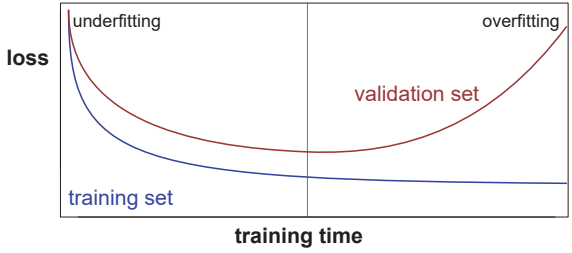
- set of examples used for learning
- usually 60 - 80 % of the data

Validation set ($\mathcal{S}_{\text{validation}}$):

- set of examples used to tune the model hyperparameters
- usually 10 - 20 % of the data

Test set ($\mathcal{S}_{\text{test}}$):

- set of examples used only to assess the performance of fully-trained model
- after assessing test set performance, model must not be tuned further
- usually 10 - 30 % of the data



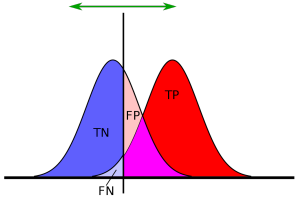
Confusion matrix and derived metrics

		True condition		
	Total population	Condition positive	Condition negative	Accuracy = $\frac{\Sigma \text{ True positive} + \Sigma \text{ True negative}}{\Sigma \text{ Total population}}$
Predicted condition	Predicted condition positive	**True positive**, Power	**False positive**, Type I error	Precision = $\frac{\Sigma \text{ True positive}}{\Sigma \text{ Predicted condition positive}}$
	Predicted condition negative	**False negative**, Type II error	**True negative**	
		Recall, Sensitivity = $\frac{\Sigma \text{ True positive}}{\Sigma \text{ Condition positive}}$	Specificity = $\frac{\Sigma \text{ True negative}}{\Sigma \text{ Condition negative}}$	F_1 score = $\frac{1}{\frac{1}{\text{Recall}} + \frac{1}{\text{Precision}}}{2}$

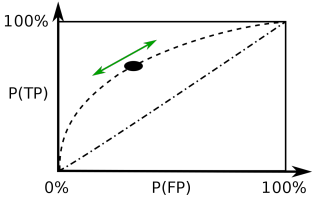
Problem Set 1

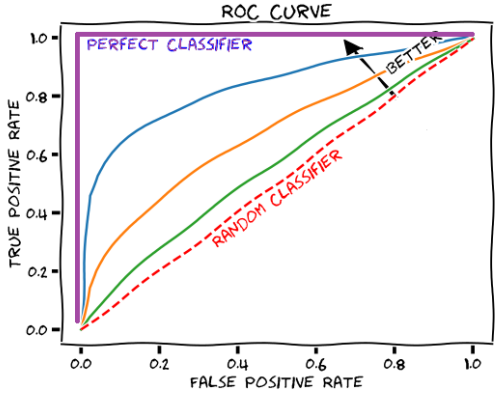
Accuracy: proportion of true predictions - (TP + TN) / (TP + FP + TN + FN)

Receiver Operating Characteristic (ROC) Performance



TP	FP
FN	TN





Area Under the ROC Curve (AuROC)

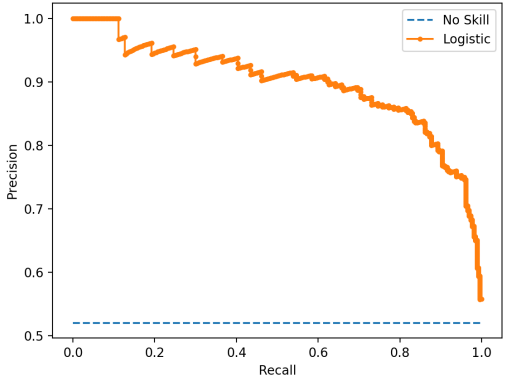
AuROC is a common metric for comparing classification methods

$TPR = TP / (TP + FN)$

$FPR = FP / (FP + TN)$

Problematic when we have an unbalanced dataset (example more positives than negatives)

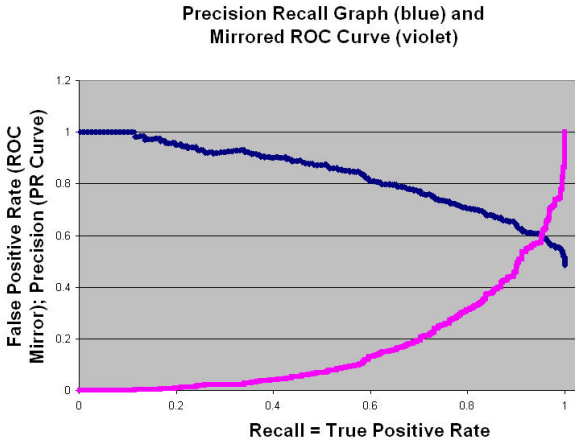
Precision Recall Curve (PRC) Performance



Area Under the PRC (AuPRC)

Precision = PPV = TP / (TP + FP) = 1 - FDR
Recall = TPR = TP / (TP + FN)
Useful when datasets are unbalanced

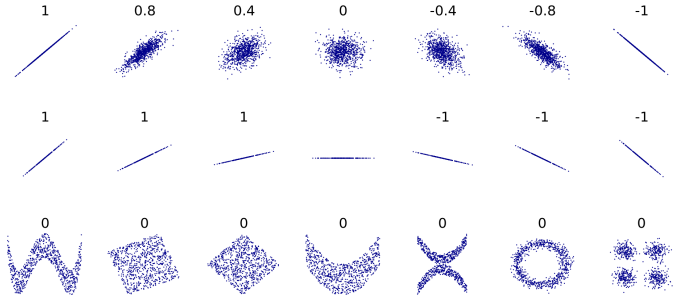
ROC and PRC curves are complementary



Recall

FPR = FP / (FP + TN)
Precision = PPV = TP / (TP + FP) = 1 - FDR
Recall = TPR = TP / (TP + FN)

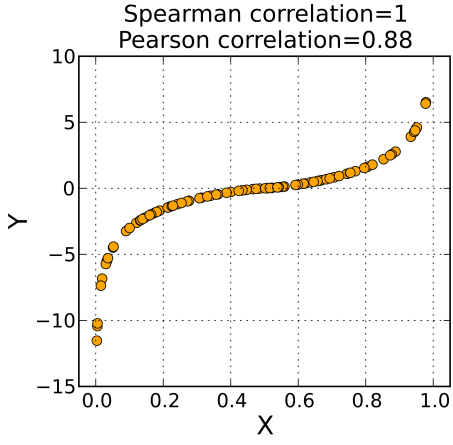
Regression Metric 1 - Pearson Correlation



Pearson correlation coefficient is r. r^2 is the fraction of linearly explained variance

$$r = \frac{(\boldsymbol{x}-\overline{\boldsymbol{x}})}{||\boldsymbol{x}||} \cdot \frac{(\boldsymbol{y}-\overline{\boldsymbol{y}})}{||\boldsymbol{y}||}$$

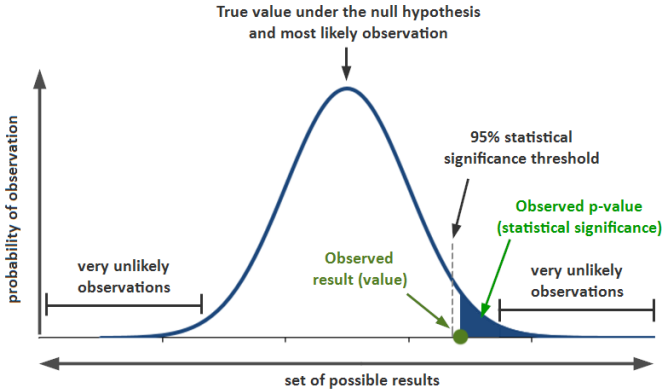
Regression Metric 2 - Spearman Rank Correlation



Pearson correlation of observation ranks

For ties assign fractional ranks by average rank in ascending order

Correlation significance tests



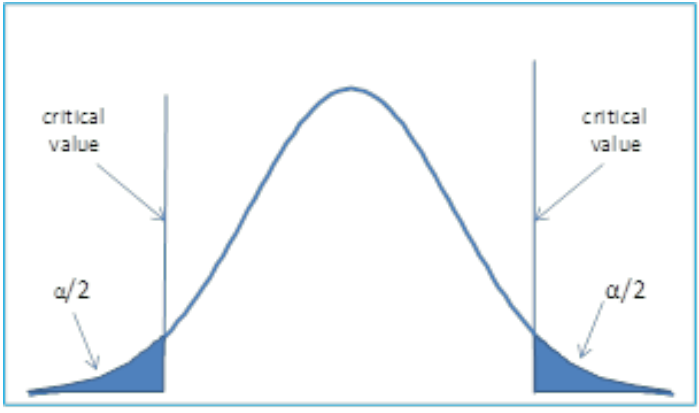
t is distributed as Student's t-distribution with $n-2$ degrees of freedom under the null hypothesis

n is the number of observations

$t = r\sqrt{\frac{n-2}{1-r^2}}$

Alternatively we can permute values to observe the empirical distribution of null correlations

One sided vs. two sided test



Two sided tests are used when we are testing for a difference without regard to direction

Two sided tests allocate half the area to each direction
Thus they are more strict if you only wish to test in one direction

Classifier significance test

Binomial test for probability that null model would produce observed results

n is the number of observations in test set
k is the number classified correctly test set
p is the probability classifier will make correct choice at random
Probability that exactly k observations are classified correctly by null
$Pr(x = k) = \binom{n}{k} p^k (1-p)^{n-k}$

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p is the probability classifier will make correct choice at random
Probability that exactly k observations are classified correctly by null
$Pr(x = k) = \binom{n}{k} p^k (1-p)^{n-k}$
Test that k or greater would have been classified correctly by null
$p = \sum_{i=k}^{n} Pr(x = i)$
This can be approximated by a Chi-squared test

Multiple hypothesis correction is important

If we ask m questions we need to adjust our probability that the null is likely

p_{single} Probability one test occurred by chance

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Benjamini-Hochberg uses a desired false discover rate to provide a relaxed bound

α is our desired false discovery rate (FDR)
m is the number of tests $H_1 \dots H_m$
$P_1 \dots P_m$ are their p-values in ascending order

- Find the largest k such that $P_k \leq \frac{k}{m}\alpha$
- Reject the null hypothesis for all H_i for $i = 1, \dots, k$

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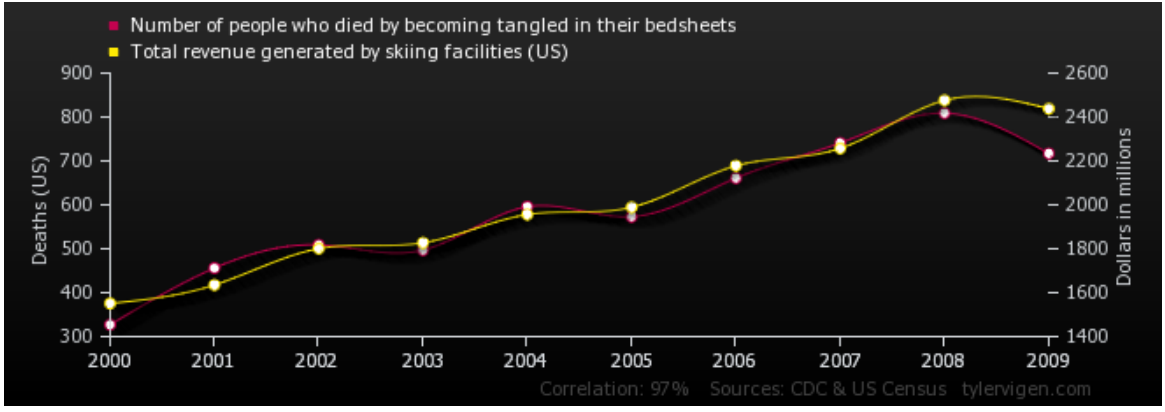
Which transcription factors $TF_1 \ldots TF_5$ bind with a corrected significance of .05?

Single test p-values are $0.003, 0.006, 0.020, 0.045, 0.600$

Correlation is not causation



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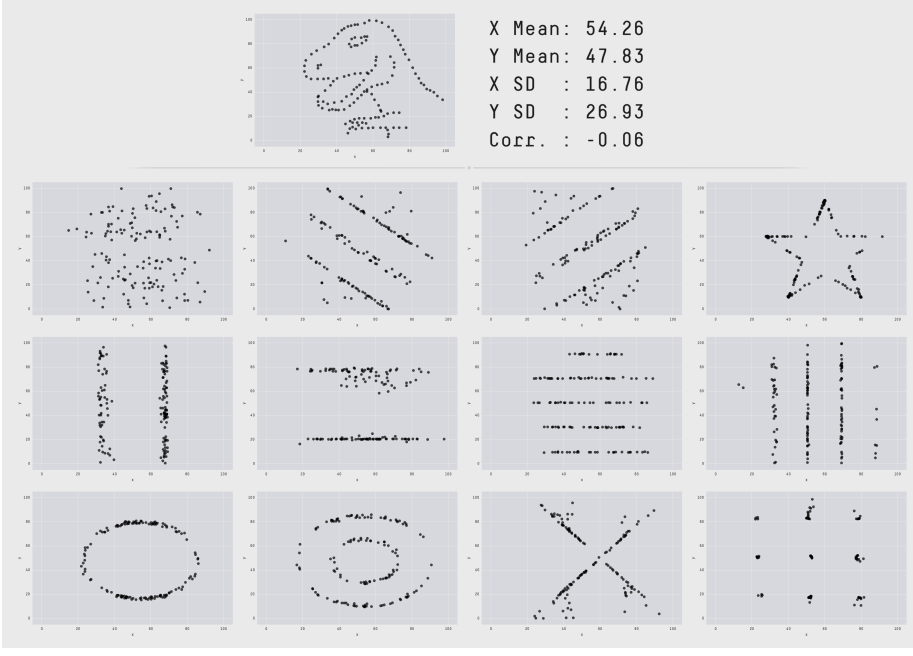

Quo vadis, 6.874?

- neural networks (NNs)
  - convolutional neural networks (CNNs)
  - recurrent neural networks (RNNs)
  - residual neural networks
  - (variational) autoencoders (VAEs)
  - generative adversarial networks (GANs)
- regularization
  - L_1 regularization
  - L_2 regularization
  - dropout
  - early stopping
- model selection
  - cross-validation (CV)
  - Akaike information criterion (AIC)
  - Bayesian information criterion (BIC)
- model interpretation methods
  - sufficient input subsets (SIS)
  - saliency maps
- model uncertainty
  - identifying out of distribution inputs
  - ensembles and calibrated uncertainty
- dimensionality reduction methods
  - principal component analysis (PCA)
  - t-SNE
  - autoencoders
  - non-negative matrix factorization (NMF)
- hyperparameter optimization and AutoML

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