Bioinformatics and Biomarker Discovery
Part 1: Foundations

Limsoon Wong

9 September 2011

Themes of Bioinformatics

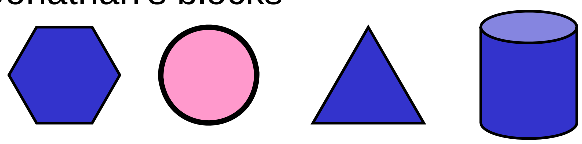
Bioinformatics =
  Data Mgmt +
  Knowledge Discovery +
  Sequence Analysis +
  Physical Modeling + ….

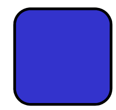
Knowledge Discovery =
  Statistics + Algorithms + Databases

Applications include diagnosis, prognosis, & treatment optimization, often thru biomarker discovery

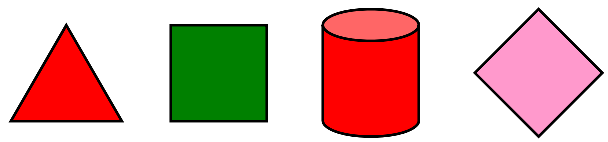
What is Knowledge Discovery?

Jonathan's blocks





Jessica's blocks



Whose block
is this?

Jonathan's rules : Blue or Circle
Jessica's rules : All the rest

What is Knowledge Discovery?

Question: Can you explain how?

Key Steps of Knowledge Discovery

- **Training data gathering**
- **Feature generation**
  - k-grams, colour, texture, domain know-how, ...
- **Feature selection**
  - Entropy, $\chi 2$, CFS, t-test, domain know-how...
- **Feature integration**
  - SVM, ANN, PCL, CART, C4.5, kNN, ...

What is Accuracy?

What is Accuracy?

	predicted as positive	predicted as negative
positive	TP	FN
negative	FP	TN

$$\text{Accuracy} = \frac{\text{No. of correct predictions}}{\text{No. of predictions}}$$

$$= \frac{TP + TN}{TP + TN + FP + FN}$$

Examples (Balanced Population)

classifier	TP	TN	FP	FN	Accuracy
A	25	25	25	25	50%
B	50	25	25	0	75%
C	25	50	0	25	75%
D	37	37	13	13	74%

- **Clearly, B, C, D are all better than A**
- **Is B better than C, D?**
- **Is C better than B, D?**
- **Is D better than B, C?**

Accuracy may not tell the whole story

Examples (Unbalanced Population)

classifier	TP	TN	FP	FN	Accuracy
A	25	75	75	25	50%
B	0	150	0	50	75%
C	50	0	150	0	25%
D	30	100	50	20	65%

- **Clearly, D is better than A**
- **Is B better than A, C, D?**

Exercise: What is B's Prediction strategy?

What is Sensitivity (aka Recall)?

	predicted as positive	predicted as negative
positive	TP	FN
negative	FP	TN

$$\underset{\text{wrt positives}}{\text{Sensitivity}} = \frac{\text{No. of correct positive predictions}}{\text{No. of positives}}$$

$$= \frac{TP}{TP + FN}$$

Sometimes sensitivity wrt negatives is termed **specificity**

What is Precision?

	predicted as positive	predicted as negative
positive	TP	FN
negative	FP	TN

$$\text{Precision}_{\text{wrt positives}} = \frac{\text{No. of correct positive predictions}}{\text{No. of positives predictions}} = \frac{TP}{TP + FP}$$

Unbalanced Population Revisited

classifier	TP	TN	FP	FN	Accuracy	Sensitivity	Precision
A	25	75	75	25	50%	50%	25%
B	0	150	0	50	75%	0%	ND
C	50	0	150	0	25%	100%	25%
D	30	100	50	20	65%	60%	38%

- **What are the sensitivity and precision of B and C?**
- **Is B better than A, C, D?**

Abstract Model of a Classifier

- **Given a test sample *S***
- **Compute scores *p(S), n(S)***
- **Predict *S* as negative if *p(S) / n(S)* < *t***
- **Predict *S* as positive if *p(S) / n(S)* ≥ *t***

t is the decision threshold of the classifier

changing *t* affects the recall and precision, and hence accuracy, of the classifier

An Example

S	P(S)	N(S)	Actual Class	Predicted Class @ t = 3	Predicted Class @ t = 2
2	0.961252	0.038748	P	P	P
3	0.435302	0.564698	N	N	N
6	0.691596	0.308404	P	N	P
7	0.180885	0.819115	N	N	N
8	0.814909	0.185091	P	P	P
10	0.887220	0.112780	P	P	P
			accuracy	5 / 6	6/6
			recall	3 / 4	4/4
			precision	3 / 3	4/4

Recall that …
- **Predict *S* as negative if *p(S) / n(S)* < *t***
- **Predict *S* as positive if *p(S) / n(S)* ≥ *t***

Comparing Prediction Performance

- **Accuracy is the obvious measure**
  - But it conveys the right intuition only when the positive and negative populations are roughly equal in size

- **Recall and precision together form a better measure**
  - But what do you do when A has better recall than B and B has better precision than A?

So let us look at some alternate measures ….

Adjusted Accuracy

- **Weigh by the importance of the classes**

$$\text{Adjusted accuracy} = \alpha * \text{Sensitivity} + \beta * \text{Specificity}$$

where $\alpha + \beta = 1$

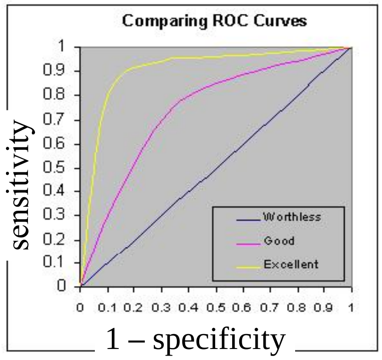
typically, $\alpha = \beta = 0.5$

classifier	TP	TN	FP	FN	Accuracy	Adj Accuracy
A	25	75	75	25	50%	50%
B	0	150	0	50	75%	50%
C	50	0	150	0	25%	50%
D	30	100	50	20	65%	63%

But people can't always agree on values for α, β

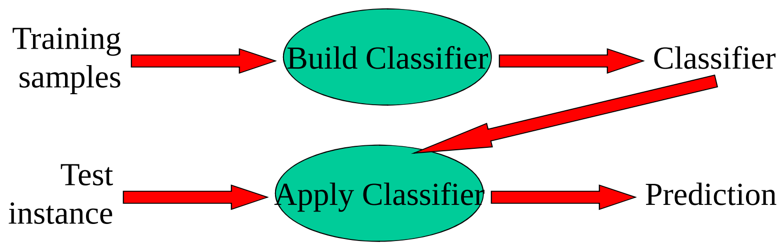
ROC Curves

- By changing t, we get a range of sensitivities and specificities of a classifier
- A predicts better than B if A has better sensitivities than B at most specificities
- Leads to ROC curve that plots sensitivity vs. (1 – specificity)
- Then the larger the area under the ROC curve, the better

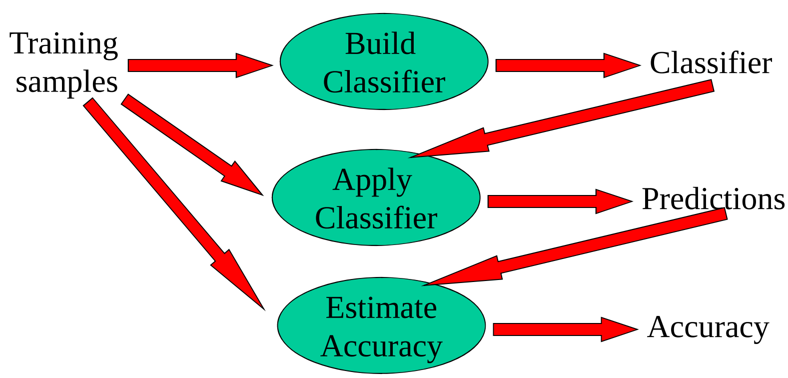


What is Cross Validation?

Construction of a Classifier



Estimate Accuracy: Wrong Way



Exercise: Why is this way of estimating accuracy wrong?

K-Nearest Neighbour Classifier (k-NN)

- Assume S is well approximated by its neighbours
- Then, given a sample S, find the k observations $S_1 \ldots S_k$ in the known data that are "closest" to it, and average their responses

$$p(S) = \sum_{S_i \in N_k(S) \cap D^P} 1 \qquad n(S) = \sum_{S_i \in N_k(S) \cap D^N} 1$$

where $N_k(S)$ is the neighbourhood of S defined by the k nearest samples to it.

Assume distance between samples is Euclidean distance for now

Illustration of kNN (k=8)

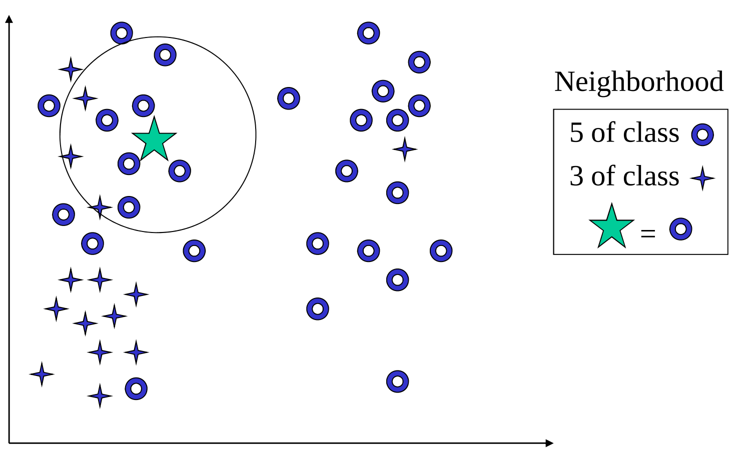
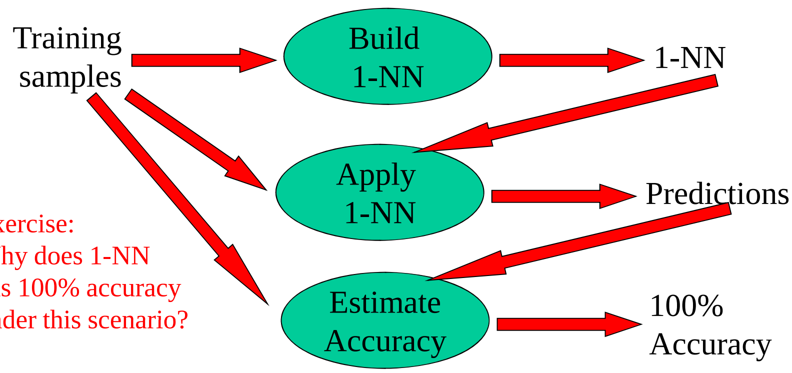


Image credit: Zaki

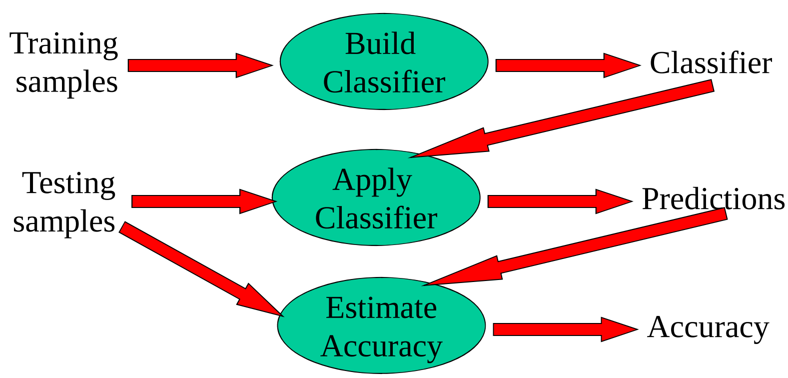
Estimate Accuracy: Wrong Way



Exercise:
Why does 1-NN
has 100% accuracy
under this scenario?

For sure k-NN (k = 1) has 100% accuracy in the "accuracy estimation" procedure above. But does this accuracy generalize to new test instances?

Estimate Accuracy: Right Way



Testing samples are NOT to be used during "Build Classifier"

Cross Validation

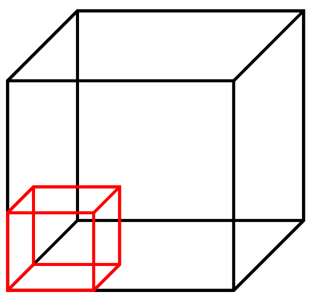
1.Test	2.Train	3.Train	4.Train	5.Train
1.Train	2.Test	3.Train	4.Train	5.Train
1.Train	2.Train	3.Test	4.Train	5.Train
1.Train	2.Train	3.Train	4.Test	5.Train
1.Train	2.Train	3.Train	4.Train	5.Test

- Divide samples into k roughly equal parts
- Each part has similar proportion of samples from different classes
- Use each part to test other parts

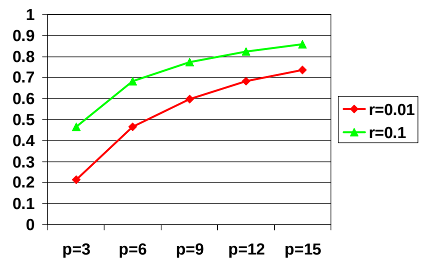
Curse of Dimensionality

Curse of Dimensionality

- How much of each dimension is needed to cover a proportion r of total sample space?



- Calculate by $e_p(r) = r^{1/p}$
- So, to cover 10% of a 15-D space, need to sample $(0.1)^{1/15}$ = 85% of each dimension!



Exercise: Why $\mathbf{e_p(r) = r^{1/p}}$?

Consequence of the Curse

- Suppose the number of samples given to us in the total sample space is fixed
- Let the dimension increase
- Then the distance of the k nearest neighbours of any point increases
- Then the k nearest neighbours are less and less useful for prediction, and can confuse the k-NN classifier (and other types of classifiers as well)

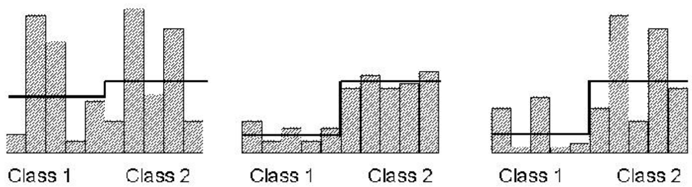
What is Feature Selection?

Tackling the Curse

- **Given a sample space of p dimensions**
- **It is possible that some dimensions are irrelevant**
- **Need to find ways to separate those dimensions (aka features) that are relevant (aka signals) from those that are irrelevant (aka noise)**

Signal Selection (Basic Idea)

- **Choose a feature w/ low intra-class distance**
- **Choose a feature w/ high inter-class distance**



Signal Selection (e.g., t-statistics)

The t-stats of a signal is defined as

$$t = \frac{|\mu_1 - \mu_2|}{\sqrt{(\sigma_1^2/n_1) + (\sigma_2^2/n_2)}}$$

where σ_i^2 is the variance of that signal in class i, μ_i is the mean of that signal in class i, and n_i is the size of class i.

Suggestion a modification to t-stats when n1 and n2 are small.

Self-fulfilling Oracle

- Construct artificial dataset with 100 samples, each with 100,000 randomly generated features and randomly assigned class labels
- Select 20 features with the best t-statistics (or other methods)
- Evaluate accuracy by cross validation using only the 20 selected features
- The resultant estimated accuracy can be ~90%
- But the true accuracy should be 50%, as the data were derived randomly

What Went Wrong?

- The 20 features were selected from the whole dataset
- Information in the held-out testing samples has thus been "leaked" to the training process
- The correct way is to re-select the 20 features at each fold; better still, use a totally new set of samples for testing

Concluding Remarks

What have we learned?

- **Methodology of data mining**
  - Feature generation, feature selection, feature integration
- **Evaluation of classifiers**
  - Accuracy, sensitivity, precision
  - Cross validation
- **Curse of dimensionality**
  - Feature selection concept
  - Self-fulfilling oracle

References

- John A. Swets, Measuring the accuracy of diagnostic systems, *Science* 240:1285--1293, June 1988
- Trevor Hastie et al., *The Elements of Statistical Learning: Data Mining, Inference, and Prediction*, Springer, 2001. Chapters 1, 7
- Lance D. Miller et al., Optimal gene expression analysis by microarrays, *Cancer Cell* 2:353--361, 2002
- David Hand et al., *Principles of Data Mining*, MIT Press, 2001
- Jinyan Li et al., Data Mining Techniques for the Practical Bioinformatician, *The Practical Bioinformatician*, Chapter 3, pages 35—70, WSPC, 2004