Bioinformatics and Biomarker Discovery Part 1: Foundations

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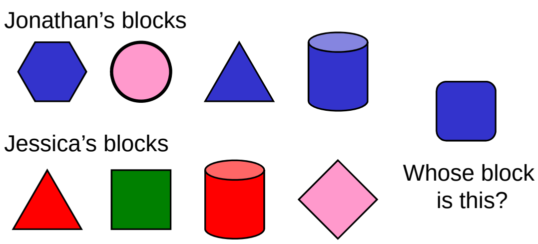
Themes of Bioinformatics

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 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

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

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

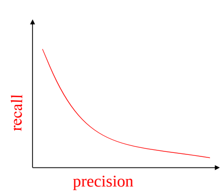
An Example

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***

Precision-Recall Trade-off

- **A predicts better than B if A has better recall and precision than B**
- **There is a trade-off between recall and precision**



- **In some applications, once you reach a satisfactory precision, you optimize for recall**
- **In some applications, once you reach a satisfactory recall, you optimize for precision**

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**

Adjusted accuracy = α * Sensitivity + β * Specificity

where $\alpha + \beta = 1$

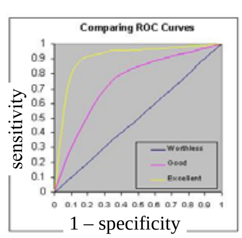
typically, $\alpha = \beta = 0.5$

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

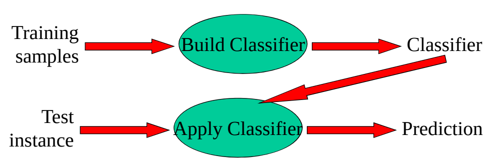
ROC Curves

- **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**

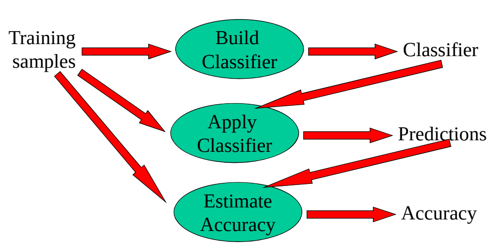


What is Cross Validation?

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)

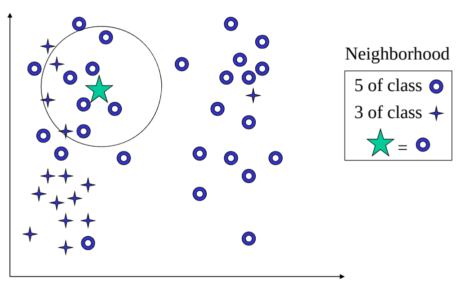
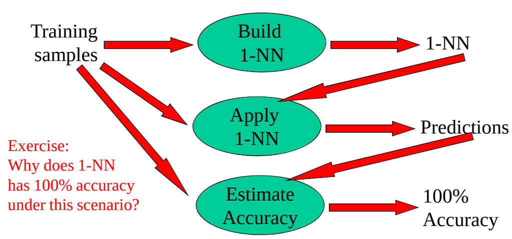


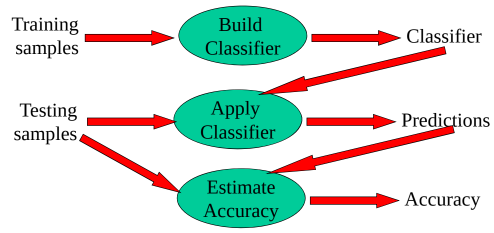
Image credit: Zaki

Estimate Accuracy: Wrong Way



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"

How Many Training and Testing Samples?

- **No fixed ratio between training and testing samples; but typically 2:1 ratio**
- **Proportion of instances of different classes in testing samples should be similar to proportion in training samples**

- **What if there are insufficient samples to reserve 1/3 for testing?**
- **Ans: Cross validation**

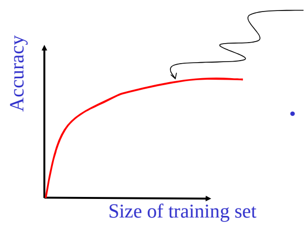
Cross Validation

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**

How Many Fold?

- **If samples are divided into k parts, we call this k-fold cross validation**

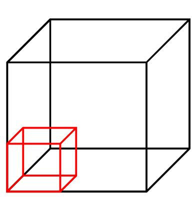


- **Choose k so that**
  - the k-fold cross validation accuracy does not change much from k-1 fold
  - each part within the k-fold cross validation has similar accuracy
- **k = 5 or 10 are popular choices for k**

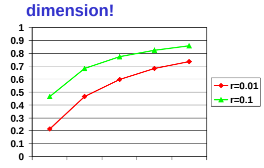
Curse of Dimensionality

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 $e_p(r) = r^{1/p}$?

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)

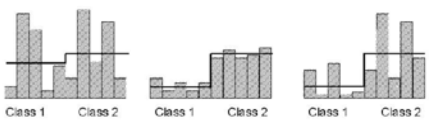
What is Feature Selection?

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

Confounding Factors

A True Story (Charig et al, 1986)

Treatment A	Treatment B
78% (273/350)	83% (289/350)

	Treatment A	Treatment B
Small Stones	*Group 1* 93% (81/87)	*Group 2* 87% (234/270)
Large Stones	*Group 3* 73% (192/263)	*Group 4* 69% (55/80)
Both	78% (273/350)	83% (289/350)

- Treatment B seems more effective than Treatment A for kidney stone
- Now Treatment A seems more effective than Treatment B
- Case of Simpson Paradox: But we won't know this if we don't capture stone size info

A Made-Up Example

param	class	sex
100	alive	m
99	alive	m
98	alive	m
95	alive	m
90	alive	m
71	dead	m
80	dead	m
85	dead	m
73	dead	m
75	dead	m
71	alive	f
75	alive	f
73	alive	f
76	alive	f
72	alive	f
60	dead	f
65	dead	f
62	dead	f
63	dead	f
64	dead	f

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

Any Questions?

Acknowledgements

- **The first two slides were shown to me 10+ years ago by Tan Ah Hwee**

References

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