

- Predictive Model Development & Assessment.
 - Defining error of prediction
 - Bias versus variance
 - ▷ AIC and BIC as criteria
 - Internal vs. External validation
- Accuracy Ideas for Survival Data.
 - ▷ ROC curves?
 - ▷ C index?
 - \triangleright Extension of R^2 ?

Example: Continuous Response

- Diagnostic classification often relies on the comparison of an observed measurement with "normal" or reference values.
 - > percent-predicted for FEV1
 - height & weight growth charts for children
- In such situations we desire a good <u>prediction</u> for an outcome, and typical ranges (e.g. 5th and 95th percentiles).
- As of (1999) there were no published reference percentiles for BMI (body mass index) for children between 0 and 36 months of age.
- The following data are a sample of data used by Heagerty & Pepe (1999) to create reference percentiles.
- The following data come from Group Health Cooperative based on subjects born between 1965 and 1971.



Prediction Error

One Statistical View:

- ▷ **Objective**: find a curve that is a function of age, f(age), that can be used as a prediction function for the mean BMI at each age, $E(Y \mid age)$ where Y denotes BMI.
- Specifically, suppose that we will use splines to estimate the function. Let p denote the number of splines that we are using for the function. Q: what value of p should we pick?
- Define: a curve will be judged in terms of its ability to create predictions that are "close" to real observations. We will choose the curve that is best in terms of minimizing our estimate of its error of prediction.
- Error In order to make progress we will need to choose some method for estimating the "error" of prediction.











Balancing Bias and Variance

- We have made progress: we have defined the error measurement that we want to use. We see that more flexible models won't necessarily lead to better predictions.
- Next:
 - If we can estimate the mean error for each possible f(x) form (e.g. number of splines used) then we simply choose the function that's best.
 - ▷ **Q**: How to estimate the error?
- Validation:
 - ▷ Apply your prediction, $\hat{f}(age_i)$, to some "new" data (so-called "validation" data, or "test" data).
 - Somehow use the data you have to estimate the out-of-sample error.

External Validation

- If you have some external test data (or have saved some data for validation) then the job is easy – just compute the possible prediction functions, apply them to the test data, and calculate their error.
- Example: For the BMI data we have 100 observations that we use to create prediction functions, and then apply the prediction function to the new data (50 observations). We measure:

$$\texttt{mean error} = \frac{1}{N^{\texttt{new}}} \sum_{j} \left[Y_j^{\texttt{new}} - \widehat{f}(\texttt{age}_j) \right]^2$$

• We show the square root of this mean average as rMPE.





Validation

• Q: Why not just estimate the error of prediction based on the data you used to develop the prediction function:

$$\texttt{mean within} - \texttt{error} = \frac{1}{N^{\texttt{old}}} \sum_i \left[Y_i^{\texttt{old}} - \widehat{f}(\texttt{age}_i)\right]^2$$

- A: Because this estimate is too optimistic you've used the data <u>both</u> to estimate the model, and to evaluate how well the model performs.
- Second, you will always decrease the within-sample error by adding more predictors, or more flexibility to your curve, f(x).
- However, the optimism is proportional to 1/N, so with large sample sizes the optimism may be small.



Within-sample Estimates of Prediction Error

• Cross Validation: CV works by leaving points (Y_i, X_i) out one at a time, and estimating the function f(x) based on the remaining N-1 points. This is an attempt to mimic the use of training and test samples for prediction. The CV estimate is then:

$$\mathtt{CV} = \frac{1}{N} \sum_{i} \left[Y_i - \widehat{f}^{(-i)}(\mathtt{age}_i) \right]^2$$

- Here $\widehat{f}^{(-i)}(x)$ is the estimated function based on data removing observation *i*.
- Estimate: There is an estimate called C_p that estimates the prediction error based on theoretical calculations. This is given as

$$C_p = \texttt{MSE}(\widehat{\mathbf{f}}) + 2 \cdot p \cdot \frac{\sigma^2}{N}$$



Example: BMI Data

- The purple curve on the previous plot is for C_p .
- The green curve on the previous plot is for CV.
- Cross-validation methods (CV) provide an approximately unbiased estimate of the prediction error.
- Cross-validation methods also sometimes create K "blocks" of data (for example breaking the data into K=10 blocks) and then apply for each observation the fit obtained from data in the other K - 1 blocks of data). Block choice is another bias/variance trade-off where larger blocks lead to less variable estimates of error, but with more potential for bias.
- Stone (1977) showed that AIC and the leave-one-out cross-validation approach are asymptotically equivalent.



- Goal = good prediction.
- Define criterion for judging = error scale
- Job is now easy choose model / function that is estimated to provide the best prediction.
- Use external validation (test) data, or use the development data and cross-validation or C_p .
- Q: what about binary data, or survival data?

- Error Scale the previous presentation with the BMI data supposed that we have adopted a scale to measure the "distance" from the prediction to the data.
- Recall we used the likelihood (or partial likelihood) as a method for measuring how well a model "fits" data.

$$\log \mathcal{L}(\widehat{f}) = \sum_{i} \log \mathcal{L}(Y_i \mid \widehat{f}) = \sum_{i} \log P[Y_i \mid \widehat{f}]$$

- Here the model \hat{f} denotes the parameters for the model e.g. the regression coefficients, β_j , or as in the previous BMI example, the estimate of the prediction curve f(x).
- Since a higher value here reflects better agreement (prediction of Y_i) we can use -1 times this probability to denote error, or:

$$\texttt{error}_i = -2 \cdot \log \mathcal{L}(Y_i \mid \widehat{f})$$

- log Likelihood Error Scale provided we are willing to consider distance as measured by -2 times the probability of the observed data we can proceed to try and find a model that has the smallest error.
- Viewed another way, we seek a predictive model that when we take the model and calculate the probability of some new test (validation) data, the predictive model will assign high probability to this new data.
- **AIC**: the Akaike Information Criterion is a method that allows estimation of the expected prediction error:

$$E\left[-2 \cdot \log \mathcal{L}(Y_i^{\texttt{new}} \mid \widehat{f})\right] \approx -\frac{2}{N} E[\log \mathcal{L}(\widehat{f})] + \frac{2 \cdot p}{N}$$

• AIC – Using this idea, we can estimate the expected error, or more commonly presented as the total error where we don't divide by N:

$$\mathtt{AIC} = -2 \cdot \log \mathcal{L}(\widehat{f}) + 2 \cdot p$$

- Here $\log \mathcal{L}(\widehat{f})$ is the maximized log-likelihood using the model f which uses p parameters.
- Similar to before we can now search over models possibly non-nested models, or models with the same number of parameters, and judge them in terms of their predictive potential.
- Notice that similar to before, we see that as we add more parameters to the model the log *L* will increase (so -2 times it decreases) but we correct by "penalizing" for the number of parameters.

- Our previous criterion C_p is just AIC/N for the normal linear model.
- Summary:
 - \triangleright <u>If</u> we define **prediction** as our goal, and
 - If we accept log-likelihood units as a measure of how far/close we predict,
 - <u>Then</u> we can use AIC as a guide for identifying one or more candidate predictive models.

- The only task is to define the possible models that would be used for prediction, and then fit them all.
- Note: how many models possible with m predictors? If we consider only additive models where each variable is either in or out as a main effect then we have 2^m possible models.

▷
$$m = 10, 2^m = 1,024$$

▷
$$m = 20, 2^m = 1,048,576$$

- STATA has a function swaic that will sequentially add or delete predictors depending on whether they improve AIC.
- Note: we are taking an average of the error across all observations, and are therefore averaging over the covariate distribution in our sample. Will that generalize?

stset time, failure(status)

#delimit;

stcox

age logalb alkphos ascites logbil chol edema hepmeg plate logpro

sex

	sgot
	spiders
	stage
	treat
	trigly
	copper ;
#delimit	cr

swaic, m

Cox regression -- Breslow method for ties

No. of su Log likel	bjects = ihood = ·	28 466.6525	80 No 55	. of fai	lures =	112
_t	Haz. Ratio	o Std.	Err. z	P> z	[95% Conf.	Interval]
age	1.0271	0.0114	2.41	0.016	1.0050	1.0497
logalb	0.1151	0.1082	-2.30	0.021	0.0182	0.7264
alkphos	0.9999	0.0000	-0.06	0.951	0.9999	1.0000
ascites	1.2756	0.4912	0.63	0.527	0.5996	2.7135
logbil	2.1988	0.3483	4.97	0.000	1.6119	2.9995
chol	1.0001	0.0004	0.24	0.809	0.9992	1.0009
edema	1.8652	0.5380	2.16	0.031	1.0598	3.2828
hepmeg	0.9199	0.2340	-0.33	0.743	0.5586	1.5146

plate	I	1.0007	0.0011	0.63	0.532	0.9984	1.0030
logpro	I	10.7850	14.17989	1.81	0.070	0.8197	141.8928
sex	Ι	0.8436	0.2664	-0.54	0.590	0.4543	1.5666
sgot	Ι	1.0028	0.0020	1.38	0.166	0.9988	1.0067
spiders	Ι	1.0808	0.2576	0.33	0.744	0.6773	1.7246
stage		1.4187	0.2428	2.04	0.041	1.0143	1.9843
treat	Ι	0.9843	0.2080	-0.07	0.941	0.6504	1.4895
trigly	Ι	0.9979	0.0013	-1.59	0.112	0.9953	1.0004
copper		1.0015	0.0012	1.23	0.217	0.9990	1.0040

Stepwise Model Selection by AIC								
stcox regression.								
numbe	er of	obs = 2	80					
			Df	Chi2	P>Chi2	-2*11	Df Res	s. AIC
Null	Model	L				1114.80	280	1114.80
Step	1:	logbil	1 1	15.59	0.0000	999.21	279	1001.21
Step	2:	logalb	1	23.19	0.0000	976.02	278	980.02
Step	3:	age	1	15.56	0.0001	960.47	277	966.47
Step	4:	logpro	1	8.95	0.0028	951.52	276	959.52
Step	5:	copper	1	5.30	0.0213	946.21	275	956.21
Step	6:	stage	1	4.08	0.0435	942.14	274	954.14
Step	7:	edema	1	3.08	0.0792	939.06	273	953.06
Step	8:	trigly	1	2.68	0.1016	936.38	272	952.38

Step	9:	sgot	1	1.77	0.1832	934.60	271	952.60
Step	10:	ascites	1	0.37	0.5412	934.23	270	954.23
Step	11:	plate	1	0.38	0.5374	933.85	269	955.85
Step	12:	sex	1	0.25	0.6175	933.60	268	957.60
Step	13:	spiders	1	0.12	0.7258	933.48	267	959.48
Step	14:	hepmeg	1	0.10	0.7467	933.37	266	961.37
Step	15:	chol	1	0.06	0.8066	933.31	265	963.31
Step	16:	treat	1	0.00	0.9437	933.31	264	965.31
Step	17:	alkphos	1	0.00	0.9510	933.31	263	967.31

No. of s Log like	ub li	jects = hood =	2 -468.187	80 73	No. of	failures =	= 112
t]	Haz. Rat:	io Std. Er	r. z	P> z	[95% Conf.	Interval]
logbil logalb		2.400 0.090	0.3104 0.0737	6.77 -2.94	0.000	1.8631 0.0181	3.0933 0.4478
age		1.025	0.0097	2.69	0.007	1.0069	1.0450
Logpro copper		8.572 1.002	10.7273 0.0010	1.72 2.18	0.086	0.7379	99.5967 1.0042
stage		1.334	0.1907	2.02	0.044	1.0079	1.7654
trigly		0.998	0.4333	-1.55	0.122	0.9958	1.0004

- This model with the minimum AIC includes the (5) "Mayo model" variables (logbil, logpro, logalb, edema, age) and (3) additional variables.
- Some of the additional variables were not allowed as part of the Mayo model subset since they were not routinely or easily available.
- Here we have used m = 17 candidate covariates, leading to: $2^{17} = 131,072$ possible additive models.
- Notice that AIC includes trigly even though the variable doesn't achieve nominal 0.05 significance.

- This is due to the fact that AIC will include a variable (with 1 df) provided the likelihood increases enough to compensate for the penalty.
- This implies the likelihood ratio must be at least 2.0 for AIC to add.
- The critical value for a 1 df LR test is 3.86. An LR test with value 2.0 corresponds to a p-value of 0.1573.
- Caution: the inference associated with the model displayed does not account for the fact that model selection was done. We only display those covariates that have p-values (approx) less than 0.15. How to interpret the p-value given that we only see it if it's less than 0.15?

A Related Idea: BIC (* = extra)

- Bayesian Information Criterion (BIC) is similar to AIC but motivated from a different perspective.
- Assume we have a set of m = 1, 2, ..., M models that we assume all have an equal probability of being the "true" model.
- After analysis of the data we can then update our probabilities, and the model with the smallest BIC is the model with the highest probability of being the correct model.
- Define:

$$\mathtt{BIC} = -2 \cdot \log \mathcal{L}(\widehat{f}) + \log(N) \cdot p$$

• Rather than a penalty of $2 \cdot p$ used for AIC, this criterion uses a penalty of $\log(N) \cdot p$, and therefore will favor more parsimonious models.



Components of Accuracy

• Calibration

- ▷ Bias does observed match predicted?
- Evaluated graphically and formally.

• Discrimination

- Does prediction separate subjects with different risks?
- Evaluated qualitatively based on K-M plots.
- For binary outcomes we have standard concepts of classification error, and associated discrimination summaries.



ROC Curve

An ROC curve plots the True Positive Rate, TP(c), versus the False Positive Rate, FP(c) for all possible cutpoints, c:

$$\mathsf{FP}(\mathbf{c}) = P(M > \mathbf{c} \mid D = 0)$$

$$\mathsf{TP}(\mathbf{c}) = P(M > \mathbf{c} \mid D = 1)$$

ROC Curve : $[FP(c), TP(c)] \forall c$

 $\mathsf{ROC}(p)$: $[p = FP(\mathbf{c}^p), TP(\mathbf{c}^p)]$ for $p \in [0, 1]$































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ROC Curves

- "ROC plots provide a pure index of accuracy by demonstrating the limits of a test's ability to discriminate between alternative states of health over a complete spectrum of operating conditions" *Zweig and Campbell (1993)*
- 2. Compare different markers.
- 3. Compare sensitivity when controlling specificity.
- 4. AUC interpretation:

"For a randomly chosen case and control, the area under the ROC curve is the probability that the marker for the case is greater than the marker for the control."

5. AUC is a marker-outcome concordance summary (c-index).

Sensitivity and Specificity for Survival

Let T denote the survival time, and let D(t) denote the counting process for the uncensored outcome:

$$D(t) = 1(T \le t)$$

Possible definitions:

$$CASE(t) : \begin{cases} Cumulative D(t) = 1 \\ CONTROL(t) : \begin{cases} Dynamic D(t) = 0 \end{cases}$$



- Consider the 5-variable "Mayo model", and the 8-variable model identified using AIC.
- Consider classification of subjects according to their "model score" defined as $\hat{\beta}_1 \cdot X_1 + \hat{\beta}_2 \cdot X_2 \dots$
- Consider **Cases** to be subjects who die within 2-years.
- Consider **Controls** to be subjects who live beyond 2-years.
- **Q**: How well do the two models discriminate between the 2-year cases and controls?

```
****
**** consider 2-year survival
****
```

```
gen d2yr = (time <= 365*2)
```

```
*** check for censoring before 2-years
tab d2yr status
recode d2yr 1=. if status==0
```

```
****
```

```
**** ROC curves
*****
graph box score1, by(d2yr)
```

```
graph box score2, by(d2yr)
```

```
*** score 1 ***
logit d2yr score1
lsens, gensens( sens1 ) genspec( spec1 )
lroc
```

```
*** score 2 ***
```

```
logit d2yr score2
lsens, gensens( sens2 ) genspec( spec2 )
lroc
```

```
*** both ROC curves on one plot ***
gen FP1 = 1-spec1
gen TP1 = sens1
gen FP2 = 1-spec2
gen TP2 = sens2
```

sort FP1

graph twoway (connected TP1 FP1) (scatter TP2 FP2)











Example: VA ACQUIP Data

• Cox model with age only.

 $M_1 = \widehat{\beta}_1 X_1$ for validation data

- Cox model with age and score. $M_2 = \widehat{\beta}_2 X_2 \text{ for validation data}$
- Cox model with age and (PCS, MCS). $M_3 = \widehat{\beta}_3 X_3 \text{ for validation data}$
- Cox model with age, (PCS,MCS) and score. $M_4 = \widehat{\beta}_4 X_4 \text{ for validation data}$

Survival Model: VA ACQUIP Data

- 5,469 subjects used for model development of comorbidity index [SIC = Seattle Index of Comorbidity].
- 5,478 subjects used for model validation.
- AUC for model 3 = 0.71
- AUC for model 4 = 0.74, p < 0.005 for difference.
- See Fan et al. (2002) J. Clin Epi.









ROC for 2-year survival



1-specificity

Accuracy: Some other proposals

${\cal R}^2$ Generalizations

- Korn and Simon (1990)
- Schemper and Henderson (2000)
- O'Quigley and Xu (2001)

TP, FP, ROC Generalizations

- Etzioni et al. (1999); Slate and Turnbull (1999)
- Heagerty, Lumley, and Pepe (2000)

Concordance (c-index)

- Harrell et al. (1996)
- Heagerty & Zheng (2005)

R^2 : Schemper and Henderson (2000)

Idea:	$D(t) = 1(T \le t)$	with $E[D(t)] = 1 - S($	t)
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	Without Covariates	With Covariates
variance	S(t)[1-S(t)]	$S(t \mid X)[1 - S(t \mid X)]$
average (X)		$E_X \left\{ S(t \mid X) [1 - S(t \mid X)] \right\}$
average (T)	$\int_t S(t) [1 - S(t)] f(t) dt$	$\int_t E_X \left\{ S(t \mid X) [1 - S(t \mid X)] \right\} f(t) dt$
	\downarrow	\downarrow
	V_0	V_X

Proposal: $R^2 = (V_0 - V_X)/V_0$



• Uncommon to use R^2 for logistic regression / binary classification.



- Clear goal of **prediction** (how will this be used?)
- Need to define an "error" measurement scale
 - Distance for a continuous measurement
 - ▷ Classification errors for discrete
- Need to obtain honest estimates of error rates
 - ▷ Test data (external)
 - Cross-validation
- Computational problem of searching candidate models.