

Biost 518

Applied Biostatistics II

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Lecture 9: Regression Based Prediction

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Lecture Outline

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- General Setting
- Prediction of Summary Measures
 - Necessary Assumptions for Inference
 - Special cases
 - Means, Geometric Means, Odds, Probabilities, Rates, Hazard Ratios, Survival probabilities
- Prediction of Individual Observations
 - Necessary Assumptions for Inferences
 - Special cases
 - Continuous measurements, binary measurements, count measurements

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Setting for Predictions

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General Classification

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- Clustering of observations
- Clustering of variables
- Quantification of distributions
- Comparing distributions
- Prediction of individual observations

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1. Cluster Analysis

.....

- Focus is on identifying similar groups of observations
 - Divide a population into subgroups based on patterns of similar measurements
 - Univariate, multivariate
 - Known or unknown number of clusters
 - (All variables treated symmetrically: No delineation between outcomes and groups)

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2. Clustering Variables

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- Identifying hidden variables indicating groups that tend to have similar measurements of some outcome
 - Interest in some particular outcome measurement
 - Predictors that imprecisely measure some abstract quality
 - Desire to find patterns in predictors that more precisely reflect the abstract quality

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3. Quantifying Distributions

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- Focus is on distributions of measurements within a population
 - Scientific questions about tendencies for specific measurements within a population
 - Point estimates of summary measures
 - Interval estimates of summary measures
 - Quantifying uncertainty
 - Decisions about hypothesized values
 - May desire estimates within subgroups
 - E.g., estimates by sex, age, race

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Example: Estimation of Median

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- Statistical Tasks
 - Sample of patients newly diagnosed with stage II breast cancer
 - Follow for survival time (may be censored)
 - Statistical analysis
 - Best estimate of the median survival (K-M?)
 - Quantify uncertainty in that estimate
 - Compare to some clinically important time range (e.g., 10 years)

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4. Comparing Distributions

.....

- Comparing distributions of measurements across populations
 - 4a. Identifying groups that have different distributions of some measurement
 - 4b. Quantifying differences in the distribution of some measurement across predefined groups (effects or associations)
 - 4c. Quantifying differences in effects across subgroups (interactions or effect modification)

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4a. Identifying Groups

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- Identifying groups that have different distributions of some measurement
 - Focus is on some particular outcome measurement
 - Identify groups based on other measurements
 - E.g., quantifying distributions within subgroups
 - E.g., stepwise regression models
 - (cf: Cluster analysis where all measurements are treated symmetrically)

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Example: Identifying Groups

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- Statistical Tasks
 - Sample subjects to measure risk factors and disease prevalence
 - Cohort study
 - Case-control study
 - Statistical analysis
 - Stepwise model building
 - (Rank most interesting variables by p value?)

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5. Prediction

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- Focus is on individual measurements
 - Point prediction:
 - Best single estimate for the measurement that would be obtained on a future individual
 - Continuous measurements
 - Binary measurements (discrimination)
 - Interval prediction:
 - Range of measurements that might reasonably be observed for a future individual

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Example: Continuous Prediction

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- Creatinine clearance
 - Creatinine
 - Breakdown product of creatine
 - Removed by the kidneys by filtration
 - Little secretion, reabsorption
 - Measure of renal function
 - Amount of creatinine cleared by the kidneys in 24 hours

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Example: Continuous Prediction

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- Problem:
 - Need to collect urine output (and blood creatinine) for 24 hours
- Goal:
 - Find blood, urine measures that can be obtained instantly, yet still provide an accurate estimate of a patient's creatinine clearance

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Example: Continuous Prediction

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- Statistical Tasks:
 - Training sample
 - Measure true creatinine clearance
 - Measure sex, age, weight, height, creatinine
 - Statistical analysis
 - Regression model that uses other variables to predict creatinine clearance
 - Quantify accuracy of predictive model
 - (Mean squared error?)

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Example: Discrimination

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- Diagnosis of prostate cancer
 - Use other measurements to predict whether a particular patient might have prostate cancer
 - Demographic: Age, race, (sex)
 - Clinical: Symptoms
 - Biological: Prostate specific antigen (PSA)
 - Goal is a diagnosis for each patient

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Example: Discrimination

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- Statistical Tasks:
 - Training sample
 - “Gold standard” diagnosis
 - Measure age, race, PSA
 - Statistical analysis
 - Regression model that uses other variables to predict prostate cancer diagnosis
 - Quantify accuracy of predictive model
 - ROC curve analysis
 - » Sensitivity vs 1 – Specificity
 - » True Positives vs False Positives

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Example: Interval Prediction

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- Determining normal range for PSA
 - Identify the range of PSA values that would be expected in the 95% most typical healthy males
 - Age, race specific values

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Example: Interval Prediction

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- Statistical Tasks:
 - Training sample
 - Measure age, race, PSA
 - Statistical analysis
 - Regression model that uses other variables to define prediction interval
 - (Mean plus/minus 2 SD?)
 - (Confidence interval for quantiles?)
 - Quantify accuracy of predictive model
 - (Coverage probabilities?)

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Regression Based Inference

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- Estimation of summary measures
 - Point, interval estimates within groups
 - Tests hypotheses about absolute measurements
- Inference about associations
 - First order trends in summary measures across groups
 - Point, interval estimates of contrasts across groups
 - Tests hypotheses about relative measurements
- Inference about individual predictions
 - Point, interval estimates

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So far: Inference for Associations

.....

- Necessary assumptions for classical regressions (no robust SE)
 - Independence of response measurements
 - Appropriate within group variance
 - Linear regression: Equal variance across groups
 - Other regressions: Appropriate mean-variance relationship
 - » Hence, some dependence on model fit
 - Sufficiently large sample size for asymptotic normal distribution of estimates to be a good approximation

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So far: Inference for Associations

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- Necessary assumptions for first order trends using robust SE
 - Independence of response measurements across identified clusters
 - May have correlated response within identified clusters
 - (Robust SE accounts for heteroscedasticity in large samples)
 - Lack of “model fit” leads to conservative inference due to mixing systematic and random error
 - Sufficiently large sample size for asymptotic normal distribution of estimates to be a good approximation

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Now: Inference for Predictions

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- Additional assumptions for predictions
 - Estimation of summary measures within groups
 - We need to know that our regression model accurately describes the relationship between summary measures across groups
 - Prediction of individual observations
 - We need to know the shape of the distribution within each group

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Estimation (Prediction) of Summary Measures

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Examples

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- Estimate age, height, and sex specific mean (or geometric mean) FEV
 - Linear regression to obtain estimates and CI
- Estimate probability (or odds) of remaining in remission for 24 months by age, PSA
 - Logistic regression to obtain estimates and CI
- Estimate median time to liver failure in PBC patients by age, bilirubin, etc.
 - Proportional hazards regression for estimates (and CI?)

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Issues

.....

- Which statistic provides the best estimate?
 - Definition of best?
 - Consistent (correct with infinite sample size)
 - Precise (minimal variability, minimal squared error)
 - Answer: Common regression models provide the best estimate in a wide variety of settings
- Is best good enough in particular setting?
 - Answer: CI for the value of true summary measure for each group

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General Methods

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- Estimated summary measure involves a linear function of regression parameters
 - Linear, logistic, Poisson regression this is all that is needed
 - Proportional hazards regression also needs an estimate of the survival distribution in the reference group
 - We are not yet very good at putting confidence bounds on this part of the estimates

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Necessary Assumptions

.....

- Independence
 - (between clusters for robust SE)
- Variance appropriate to the model
 - (relaxed for robust SE)
- **Regression model accurately describes relationship of summary measures across groups**
- Sufficient sample sizes for asymptotic distributions to be a good approximation

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Obtaining Point Estimates

- Substitution of predictor values provides the estimate of the modeled transformation of the summary measure
 - Linear regression: mean
 - Linear regression on logs: log geometric mean
 - Logistic regression: log odds
 - Poisson regression: log rate
 - Proportional hazards: log hazard ratio applied to baseline survival estimate

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Obtaining Interval Estimates

- Under the appropriate assumptions, we can obtain standard errors for each such estimate
 - Notable exception: Proportional hazards
 - More work to be done to get interval estimates
 - We generally find a confidence interval for the transformed summary measure, and then back transform to obtain the desired quantity

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Stata Commands: Predict

- After performing any regression command, the Stata command “predict” will compute estimates and standard errors
 - `predict varname, [what]`
 - *varname* is the name of the variable where you want the predictions stored
 - *what* is an option specifying what you want computed
 - `xb` = linear prediction (works for all types)
 - `stdp` = SE of linear prediction (works for all types)
 - `p` = probability (works for logistic)

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Computing CI for Predictions

- Just use the usual formula
$$(\text{est}) \pm (\text{crit val}) * (\text{std err})$$
 - In linear regression, we usually use the t distribution to obtain CI
 - Stata: `(crit val) = invttail(df, $\alpha/2$)`
 - degrees of freedom = n minus number of regression parameters
 - In all other regressions, we would use the standard normal distribution
 - `(crit val) = invnorm(1- $\alpha/2$)` (1.96 for 95% CI)₂

Ex: Geom Mean FEV by ht, age

```
.....
regress logfev height age
Number of obs =      654
logfev |   Coef.   Std. Err.   t    P>|t|   [95% CI]
height |   .044    .002     26.71   0.000    .041    .047
age    |   .020    .003      6.23   0.000    .014    .026
_cons  |  -1.97    .078    -25.16   0.000   -2.12   -1.82

predict flogfev
predict sefit, stdp
g gmfev= exp(flogfev)
g gmlofev = exp(flogfev - invttail(651, .025) * sefit)
g gmhifev = exp(flogfev + invttail(651, .025) * sefit)
list gmfev gmlofev gmhifev if age==10 & height==66
      gmfev      gmlofev      gmhifev
330.   3.097021   3.038578   3.156588
```

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Ex: Odds Relapse by NadirPSA

```
.....
. logit relapse24 lognadir, robust
. predict lorel, xb
. predict selo, stdp
. g odds= exp(lorel)
. g oddslo= exp(lorel - 1.96 * selo)
. g oddshi= exp(lorel + 1.96 * selo)
. list odds oddslo oddshi if nadir==1
      odds      oddslo      oddshi
10.   .4911836   .2388794   1.009971
```

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Ex: Prob Relapse by NadirPSA

```
.....
. logit relapse24 lognadir, robust
. predict prel
. g prob = odds / (1+odds)
. g problo= oddslo / (1 + oddslo)
. g probhi= oddshi / (1 + oddshi)
. list prel prob problo probhi if nadir==1
      prel      prob      problo      probhi
10.   .3293918   .3293918   .192819   .5024805
```

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Prediction in PH Regression

- Recall that there is no intercept in PH models
 - Instead there is a “baseline hazard function” which is related to the survival function in the reference group
- Stata will allow prediction of baseline survival function in their “stcox” command
 - Specify option `basesurv(newvar)` in `stcox`
 - Then use `stcurve, survival at()`

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Stata Ex: Relapse in PSA Data

```

.....
. g relapse=0
. replace relapse=1 if inrem=="no"
. stset obstime relapse
. g lnadir= log(nadir)
. stcox lnadir ps, robust basesurv(bslnS)
No. of subjects = 48      Number of obs = 48
No. of failures = 34      Time at risk = 1408
                          Wald chi2(2) = 33.18
Log pseudolikelihood = -97.1      Prob > chi2 = 0.0000

```

	Robust					
	t	HR	SE	z	P> z	[95% C I]
lnadir	1.56	1.56	.124	5.66	0.000	1.34 1.83
ps	.960	.960	.0162	-2.41	0.016	.929 .992

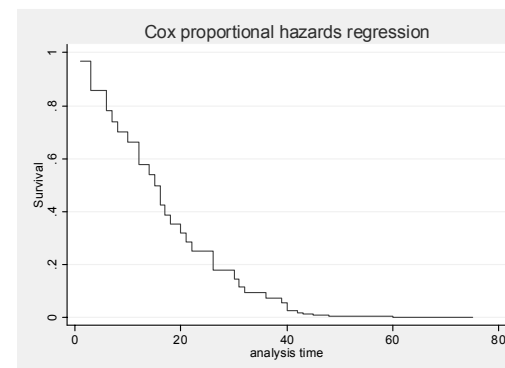
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Stata Ex: Predicted Survival

```

.....
. stcurve, survival at(lnadir=2 ps=70)

```



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Comments on PH Regression

- We can thus easily obtain estimated summary measures for any group based on semi-parametric PH assumption
 - Survival probabilities
 - Quantiles (median, etc.)
 - (Restricted mean (area under survival curve))
- We do not yet provide SE for those estimates

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Prediction (Forecast) of Individual Measurements

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Examples

- Estimate “normal range” for FEV by age, height, and sex groups
 - Linear regression
- Estimate probability (or odds) of remaining in remission for 24 months by age, PSA
 - Logistic regression
- Estimate range of times to liver failure in PBC patients by age, bilirubin, etc.
 - Proportional hazards regression

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Issues

- Which statistic provides the best estimate?
 - Definition of best?
 - Consistent (correct with infinite sample size)
 - Precise (minimal variability, minimal squared error)
 - Answer: Common regression models provide the best estimate in a wide variety of settings
- How variable is “best” in particular setting?
 - Answer: Prediction (Stata: Forecast) interval for the value of individual observation in each group

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Necessary Assumptions

- Independence
 - (between identified clusters for robust SE)
- Variance appropriate to the model
 - (NOT relaxed for robust SE)
- Regression model accurately describes relationship of summary measures across groups
- **Shape of distribution same in each group**
- Sufficient sample sizes for asymptotic distributions to be a good approximation

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Comments

- These are strong assumptions
 - Consequently, we do not have many methods that provide robust inference
 - Robust SE will only work here for correlated response, not for heteroscedasticity
 - For the most part, precise methods have only been well developed for
 - Binary or Poisson variables
 - All we need is an estimate of the probability or rate
 - Normally distributed data

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Obtaining Point Estimates

.....

- Substitution of predictor values provides the estimate of the modeled transformation of the summary measure
 - Linear regression: mean
 - Linear regression on logs: log geometric mean
 - Logistic regression: log odds
 - Poisson regression: log rate
 - Proportional hazards: log hazard ratio applied to baseline survival estimate

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Obtaining Interval Estimates

.....

- Under the appropriate assumptions, we can obtain standard errors for each such estimated summary measure
 - Notable exception: Proportional hazards
 - More work to be done to get interval estimates
 - We generally find a confidence interval for the transformed summary measure, and then back transform to obtain the desired quantity
- THEN: Add in variability within group

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Statistical Software

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- No statistical package that I know of will provide prediction intervals except for normally distributed data
 - Even then, I do not think that they are behaving the way we want them to
 - Frequentist intervals describe behavior across repeated experiments, not within one experiment

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Prediction Intervals: Normal Data

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- Obtaining point estimates
 - The point prediction is typically the mean (or log geometric mean) from the regression model

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Obtaining Interval Estimates

- Under the appropriate assumptions, we can obtain standard errors for each such prediction
 - The standard error accounts for
 - Uncertainty in estimating the regression parameters
 - The within group standard deviation
 - Spread of data about the group specific means

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Stata Commands: Predict

- After performing any regression command, the Stata command “predict” will compute estimates and standard errors
 - `predict varname, [what]`
 - *varname* is the name of the variable where you want the predictions stored
 - *what* is an option specifying what you want computed
 - `stdf` = standard error of forecast (works for linear regression)

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Computing Prediction Intervals

- Just use the usual formula

$$(\text{est}) \pm (\text{crit val}) * (\text{std err})$$
 - In linear regression, we usually use the t distribution to obtain CI
 - Stata: `(crit val) = invttail(df, $\alpha/2$)`
 - degrees of freedom = n minus number of regression parameters

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Ex: Geom Mean FEV by ht, age

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Number of obs =      654
_____+-----+
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predict flogfev
predict sefore, stdf
g predfev= exp(flogfev)
g predlofev = exp(flogfev - invttail(651, .025) * sefore)
g predhifev = exp(flogfev + invttail(651, .025) * sefore)
list predfev predlofev predhifev if age==10 & height==66
      predfev   predlofev   predhifev
330.   3.097021   2.320911   4.132662
```

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Caveat

- This “forecast” or “prediction interval” assumes that the log FEV measurements are normally distributed
 - This is a pretty strong assumption

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Extensions

- I know how to get approximate intervals based on some slightly weaker semi-parametric assumptions
 - Uses nonparametric estimates of the error distribution
 - This would work for censored data as well
 - Most software packages will not do this

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Better Approaches

- It would be better to find nonparametric confidence intervals for
 - the 2.5th percentile
 - the 97.5th percentile

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But Still...

- All of these methods suffer from
 - Strong semiparametric assumptions
 - Multiple comparisons if more than one group
 - (But we do know how to get confidence bands)
 - Coverage probabilities defined across replicate experiments
 - On average (across experiments), 95% of observations will be within an interval
 - But in any given experiment, the intervals might truly cover less or more of the population

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