A comparison of statistical methods for improving rare event classification in medicine

Thesis Defense

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Outline

Imbalanced Learning Problem

- When one outcome class greatly outnumbers the other, the outcome is
- said to be imbalanced
- Developing a classification model for imbalanced data results in over
- learning the majority class and under learning the minority class, and
- subsequently in low sensitivity and high specificity

  Need to improve predictive performance

  Many examples in medicine: rare diseases, rare adverse reactions to medications, etc.

Aims

- Improve predictive performance for imbalanced dataset
- Utilizing measures of sensitivity, specificity, accuracy, and ROC analysis to evaluate performance
- Compare two methods to handle imbalance
  - Informed probability cutpoints for predicted probabilities
  - Sampling techniques to balance datasets
- Evaluate these methods in two clinical data sets and in a simulation study

Methods

- Split data into training and test sets using a 2/3:1/3
- temporal split
- Create balanced datasets through sampling on training
- set
- Fit model to sampled data
  Get predicted probabilities on the hold-out test data
  Optimize probability cutoff for outcome

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Model

Cross-validated lasso regression - Least Absolute Shrinkage and Selection Operator

- Lasso:
    - Shrinks estimates by penalizing size of coefficients
    - Performs variable selection by shrinking some to 0

$$\hat{\beta}_{lasso} = argmin \sum_{j=1}^{N}(y_i - \beta_0 - \sum_{j=1}^{p} x_{ij}\beta_j)^2$$

subject to $\sum_{j=1}^{p} |\beta_j| \leq t$ where t is the tuning parameter.

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Cross Validation

- Cross validation:
  - Find the best "tuning parameter" for model selection which determines amount of shrinkage of estimates
  - Split data into k parts and then train on each of those except one, which is held out for testing
  - Then pick the tuning measure that minimizes error
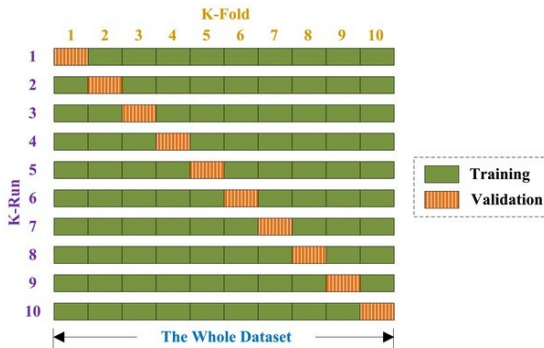
Advantages and Disadvantages of Lasso

- Advantages:
  - ▶ Lower variance of the predicted values
  - ▶ More accurate predictions
  - ▶ Reduces the number of predictors

- Disadvantages:
  - ▶ Biased coefficients, inference not same as logistic regression
  - ▶ No standard errors or p-values out of the model
    When two or more independent variables are highly
    correlated, lasso arbitrarily chooses only one to keep

ROC & Cutoff Probabilities

ROC (with pROC package):

- Receiver Operating Characteristics
- ROC curve plots sensitivity vs 1-specificity
- Each point on curve corresponds to a decision cutoff for classification
- Youden's J statistic represents the furthest upper left corner or "max" on curve
- Area under the curve (AUC) should be maximized

ROC Curve
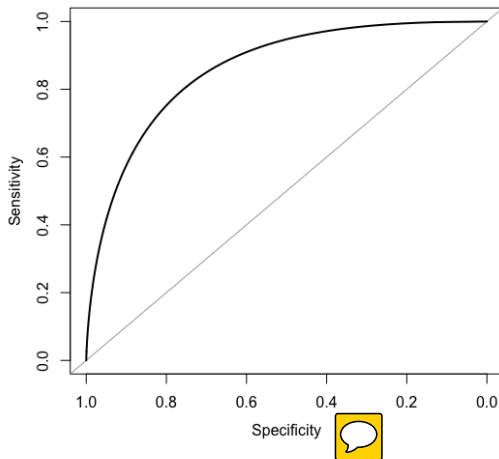
Figure 2: ROC Curve

Confusion Matrix

Correctly identify those w/ outcome:

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

Correctly identify those w/o outcome:

$$Specificity = \frac{TN}{TN + FP}$$

Correctly identify either group:

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

Predicted class

		P	N
Actual Class	P	True Positives (TP)	False Negatives (FN)
	N	False Positives (FP)	True Negatives (TN)

First Approach

No Sampling, Optimize Cut-off:

- Use original unsampled data and get predictions from the lasso model
  - Predictions return probability between 0 and 1 for each observation
- Use 0.5 standard probability cutoff to compare
- Find "best" probability cutoff
  - Youden's Index

Second Approach

Sampling:

- Create sampled data sets that are balanced
    - ▶ Down sample
    - ▶ Up sample
    - ▶ SMOTE

- Predict and use Youden's Index as cutoff

Down Sampling

- Under-sample majority to equal minority
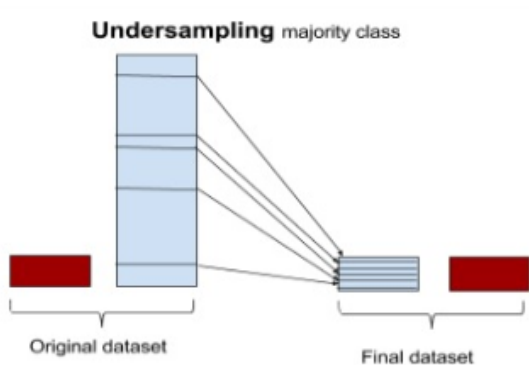
Figure 3: Down sample

Up Sampling

- Over-sample minority to equal majority

Oversampling minority class

Original dataset

Final dataset
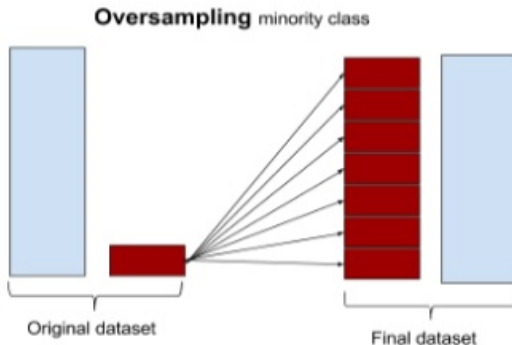
Figure 4: Up sample

SMOTE

- Synthetic Minority Over-sampling Technique
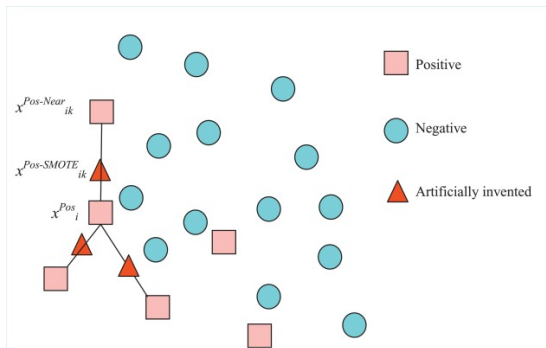
Figure 5: SMOTE

Models

- Model 1: No Sampling
  - 0.5 cutoff
  - Youden's Index
- Model 2: Down Sampling
  - Youden's Index
- Model 3: Up Sampling
  - Youden's Index
- Model 4: SMOTE
  - Youden's Index

Case Studies

We used these methods on two case studies to see how results may differ between two real world examples with rare outcomes.

- Case Study 1: Predicting chronic opioid therapy in hospitalized patients (5%)
- Case Study 2: Predicting surgical site infections in hospitalized patients (3.4%)

Case Study 1

- Data from Denver Health electronic health records (EHR)
- Definition of Chronic Opioid Therapy (COT) one year following the index hospital discharge:

Receipt of $\geq$ 90-day supply of opioids with $<$ 30-day gap in supply over a 180-day period or receipt of $\geq$ 10 opioid prescriptions over one year.

- 27,705 patients where 5% developed COT within a year
- 35 explanatory variables
  - ▸ Ex: age, race, history of chronic pain, discharge diagnosis

Case Study 1: Results

Table 1: Results for Chronic Opioid Therapy

Model	Threshold	Sensitivity	Specificity	NPV	PPV	Accuracy	AUC	Covariates
Unsampled 0.5	0.5	8	99	96	35	96	86	31
Unsampled	0.043	85	73	99	12	73	86	31
Down sampled	0.401	85	73	99	12	74	86	34
Up sampled	0.399	85	74	99	12	74	87	34
SMOTE	0.472	74	84	99	17	84	86	33

ROC Plot
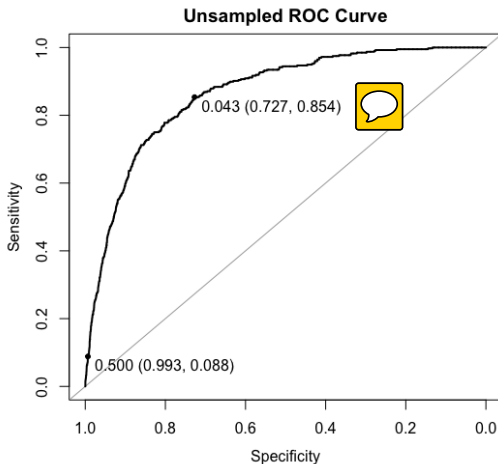
Figure 6: ROC for Original Data: Youden's Index and 0.5 cutoffs

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Case Study 2

- Need to identify post-operative complications to supplement manual chart review by nurses
- Surgical site infections (SSI) are the most common postoperative
- complication
- >50% of SSIs occur after patient discharge
  Data from 6,840 patients at the University of Colorado Hospital from
- 2013-2016
  136 independent variables were all binary indicators
  ▶ Ex: Antibiotic prescriptions, procedure codes, ICD-9 codes
  >

Case Study 2: Results

Table 2: Results for Surgical Site Infections

Model	Threshold	Sensitivity	Specificity	NPV	PPV	Accuracy	AUC	Covariates
Unsampled 0.5	0.50	0	0	0	0	0	0	0
Unsampled	0.04	80	90	99	24	90	89	35
Down sampled	0.48	82	87	99	20	87	89	20
Up sampled	0.45	79	91	99	24	90	89	123
SMOTE	0.15	89	79	99	14	80	88	88

Simulation Study

- We conducted a simulation study to look at how the methods performed at a greater range of prevalences
- We chose 3%, 5%, 10%, 20%, 40%, and 50% prevalences
- Goals:
  - ▸ Evaluate performance of methods described previously
  - ▸ Determine at what point it's no longer necessary to worry about imbalance

Simulation Methods

- Using the opioid independent variables, selected 10 of the strongest
- predictors to fit a logistic regression
- Generate simulated COT using coefficients from a logistic regression
  model fit to the observed COT
  Simulated the new outcome with a logistic distribution
  $$F(x) = \frac{e^z}{1 + e^z}$$

- Controlled prevalence by adjusting the intercept
- Implemented sampling and lasso regression with additional 15
  predictors (30 total) to get results

Simulation Results Part 1

Table 3: Results for 3, 5 and 10%

	Threshold	Sensitivity	Specificity	Accuracy	AUC	Coefficients
3%						
Unsampled 0.5	0.50	2	100	97	79	6
Unsampled	0.03	70	75	74	79	6
Down Sampled	0.49	70	74	74	78	9
Up Sampled	0.48	70	74	74	78	27
SMOTE	0.41	70	74	74	78	15
5%						
Unsampled 0.5	0.50	4	100	95	78	7
Unsampled	0.05	69	74	74	78	7
Down Sampled	0.49	69	74	74	78	9
Up Sampled	0.49	69	74	74	78	23
SMOTE	0.41	69	74	74	78	16
10%						
Unsampled 0.5	0.50	8	100	91	77	8
Unsampled	0.10	68	74	73	77	8
Down Sampled	0.49	68	74	73	77	9
Up Sampled	0.49	68	74	73	77	18
SMOTE	0.42	68	73	73	77	19

Simulations Results Part 2

Table 4: Results for 20, 40, and 50%

|	Threshold	Sensitivity	Specificity	Accuracy	AUC	Coefficients
20%						
Unsampled 0.5	0.50	21	97	82	76	8
Unsampled	0.20	66	73	72	76	8
Down Sampled	0.49	66	73	72	76	9
Up Sampled	0.49	66	73	72	76	13
SMOTE	0.42	66	72	71	75	23
40%						
Unsampled 0.5	0.50	49	84	70	74	9
Unsampled	0.39	66	71	69	74	9
Down Sampled	0.49	66	71	69	74	9
Up Sampled	0.49	65	71	69	74	10
SMOTE	0.41	64	71	68	73	28
50%						
Unsampled 0.5	0.50	63	72	68	73	9
Unsampled	0.49	63	72	68	73	9

Sensitivity and Specificty by Prevalence
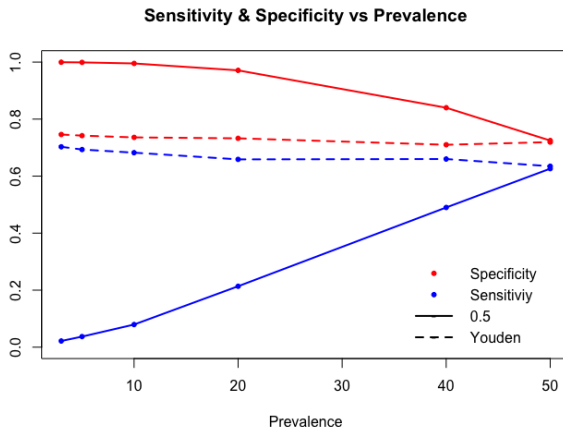
Figure 7: Comparing Youden's Index vs 0.5 cutoff results across prevalence

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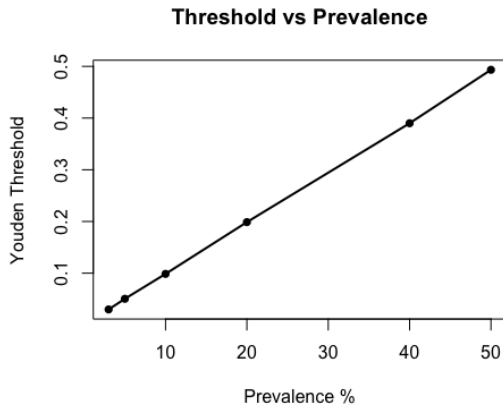
Threshold vs Prevalence

Figure 8: Youden's Index matches prevalence

Discussion

- Not much difference between Youden's + sampling vs. Youden's alone
- Over sampling and SMOTE selected highest number of variables
- Very often, threshold equals prevalence
- Sensitivity low even in less extreme imbalanced data for 0.5 cutoff
- Costs are unknown

Conclusion

I don't really see any value in sampling, but I'm not sure I should say that, or if I should still give some credit to sampling? (in one or two instances it had lower coefficients or slightly higher accuracy/AUC but it seems insignificant and variable to me)

- When costs are known, these approaches may be used with more intentional decision making
- Further Investigation:
- Choosing cutoff with training set rather than test set

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Funding??

Thank you for attending.

Case Study 1

- Design: Denver Health retrospective analysis electronic health record (EHR) data from 2008 to 2014.
- Patients: Hospitalized patients at an urban, safety-net hospital.
- Definition of Chronic Opioid Therapy (COT) one year following the index hospital discharge:

  Receipt of $\geq$ 90-day supply of opioids with $<$ 30-day gap in supply over a 180-day period or receipt of $\geq$ 10 opioid prescriptions over one year.

Case Study 1: Patient Population

- 27,705 patients
- Majority had incomes <185% of the Federal Poverty Level
- 70% were ethnic minorities
- 5% with COT
- Excluded Patients:
    - <15 or >85 years old
    - Those in prison, jail, or police custody
    - Those who died within one year following their index hospitalization
    - Patients with <2 healthcare visits to Denver Health three years preceding their index hospitalization
    - Undocumented persons receiving emergent hemodialysis
    - Obstetric patients

Case Study 2

Add more details on this case study here