Developing an Active Post-Market Surveillance System for Detecting Outlying Orthopedic Device Components

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Introduction

- Historically outlier detection initiated by clinical observation, adverse event reporting, or a manufacturer initiative
  - Harmful devices may go undetected
    - Rare events & lengthy observation windows
  - Disproportionate focus on identification of harmful devices vs. good devices
  - Unique effects of components (vs. confounded effects)
- More recent is data mining registry data
  - Can resolve some of these problems

Introduction

- Several components make up an orthopedic device
- Incorporating component model+attributes of a component significantly increases the dimensionality of the problem
  - Single femoral stem design, but based on clinical attributes may have many design subtypes

Statistical Modeling

- Multiple regression (Cox model)
  - As the number of predictors increases the method becomes problematic (e.g. non-Convergence)
- Best subset regression
  - Typically not feasible when p>30
- Stepwise regression
  - Selection of features that train well but don’t necessarily test well

Statistical Modeling

- Many registries implement a two-step approach
  - Step 1: Compare a component to a component group on incidence density (ID)
    - Conditional on meeting effect size (2x ID) , significance ($p<.05$), and sample size criteria (10 procedures or 75% revised w/ at least 2 revisions) proceed to Step 2
  - Step 2: adjustment for confounders (conditional Cox regression)
- In the presence of confounding approach may not be optimal
- No adjustment for use of other components
- Use of incidence density rate can be problematic because time is only considered cumulatively

Statistical Modeling

- Start with an adjusted (conditional) survival model
- Elastic Net[1]
  - Shrinks all variables effects
  - Shrinks some down to 0
    - Ideal for variable selection (outlier detection)
  - Can be used even when $\gg$.
  - Algorithm is very fast and therefore scalable

[1] Zou H, Hastie T (2005). Regularization and Variable Selection via the Elastic Net. Journal of the Royal Statistical Society B, 67(2), 301–320

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Elastic Net in Brief

- Simply constrained version of conventional regression models
- Constrain based on size of coefficients
- Consider Lasso for linear regression:

$$[\quad - (\quad + \quad + \cdots + \quad)] \quad \text{subject to } ||\beta|| \leq t$$

where $||\beta|| = |\quad| + \cdots + |\quad|$

Elastic Net in Brief

- Lasso:

$$|| \quad - . \quad || \quad + \lambda||\beta||$$

- Elastic Net:

$$|| \quad - . \quad || \quad + \lambda[(1-\alpha)||\beta|| \quad + \alpha||\beta|| \quad]$$

- Elastic net combines the penalties of Lasso and Ridge through α
  - When $\alpha = 1$ → Lasso   When $\alpha = 0$ → Ridge
  - Why combine the penalties?
  - Lasso does not do well with highly correlated variables (Ridge better)
  - Ridge doesn't shrink to 0 (Lasso does)
- Need to identify optimal values for λ and α
  - For each α (e.g., 0, .1, .2 … 1) search over 100 λ values
  - Final solution has α/ λ values that minimize cross validation error (10-fold)

Elastic Net in Brief

- Time to event[2] more complicated than linear regression
  - Start with a weighted partial likelihood to account for ties (Breslow)
  - Quadratic approximation of the log weighted partial likelihood (Taylor series expansion at current betas)
  - Solve by iterative penalized weighted least squares

[2]Simon et al. Regularization paths for Cox's proportional hazards model via coordinate descent. Journal of Statistical Software 2011; 39: 1-13

Methods

- Kaiser Permanente Total Joint Replacement Registry
- Only implants from one manufacturer
- N=1725 (THAs)
- Considered 4 general hip components: acetabular shell, insert, femoral head, stem
- Using ICOR/ISAR implant database
  - Combined model name with additional attributes

Methods

- Acetabular shell: intended cement, actual cement, fixation surface, material, surface coating
- Femoral head: size, material
- Insert: antioxidant, articulation, hood, material
- Stem: intended cement, actual cement, fixation surface, material, surface coating, neck connection, stem type
- Filled in missing values for attributes based on available catalogue information
  - Still some missing attributes
- 81 distinct components: 12 acetabular shells, 22 femoral heads, 36 stems, 11 inserts

Methods

- Outcome: time to first revision (removal of any component)
- Exposures of interest: 81 device components (dummy variables)
- Potential confounders: age, sex, race, diagnosis (osteoarthritis vs. other), bilateral patient (yes vs. no), body mass index (BMI), American Society of Anesthesiologists (ASA) score (<3 vs. ≥3), and diabetes (yes vs. no)
  - Missing data imputed (1 imputation) [3]
    - Imputation model: all confounders, event indicator, and Nelson-Aalen estimate of the cumulative baseline hazard[4]
    - Not much missing, ASA 7% all others less than 1%
  - All confounders forced into model with no penalty

[3] van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res. 2007; 16:219-42.

[4] White IR, Royston P. Imputing missing covariate values for the Cox model. Stat Med. 2009; 28: 1982-98.

Results

- Cross validation error minimized with alpha=.7 & lambda= 0.00063
- 25 components selected among 81
- Included the 25 components in a Cox regression

Results (Top variables)

Component	n	Avg. Comp.yrs	Max. Comp.yrs	Events	B	SE
Model= A| Intended Cement= Cementless| Fixation Surface= missing| Material= Titanium| Coating= HA| Neck Connection= Modular| Stem Type= NonModStem| Cement Used= uncemented	2	2.0	3.8	1	4.49	1.18
Model= B| Intended Cement= Cementless| Fixation Surface= missing| Material= Titanium| Coating= HA| Neck Connection= Modular| Stem Type= NonModStem| Cement Used=uncemented	62	2.9	4.6	29	3.75	0.39
Model= B| Intended Cement= Cementless| Fixation Surface= missing| Material= Titanium| Coating= HA| Neck Connection= Modular| Stem Type= NonModStem| Cement Used= missing	8	3.1	5	3	3.30	0.71
Model= C| Head Size= 36| Material= Alumina	64	7.3	11.6	1	-1.98	1.17

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Conclusion

- The effectiveness of these components would need to be subsequently evaluated more rigorously
  - Comparison of stems ensure balance on other components
  - Adjust for dependency among observations due to clustering
  - Adjust for cluster-level confounding
- Elastic Net is a useful tool for outlier detection
- Other options exist
  - Developing extensions of multivariate survival tree ensembles

Thank you.