Latent Class Measurement of Frailty and Dysregulation in Older Adults

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Joint Statistical Meetings
Seattle, Washington
August 9, 2006
Outline

• Frailty and dysregulation
• Latent variable paradigm for measurement; application
• A new idea
  – Aims to balancing potentially conflicting theoretical premises
  – Application
• Discussion
Introduction
The Frailty Construct

Fried et al., J Gerontol 2001; Bandeen-Roche et al., J Gerontol, 2006
Frailty: Scientific Aims

- Sensitivity and specificity: A measure tied explicitly to systemic dysregulation

- Validate theory that frailty is:
  - More than a marker of disease
  - More than severe disability
  - A syndrome: an “aggregate” of component parts
  - A result of vulnerability to stressors & loss of reserve

- Product: A target for interventions
  - Deliverable: A summary variable

- Generalization: “Geronmetrics”
Frailty Measurement
Latent Variable Paradigm

\[ Y_1 \]
\[ \ldots \]
\[ Y_p \]

Frailty

Determinants

\[ D \]

Adverse outcomes

theory
Model

Generic

Specific (Latent Class Reg.; Categorical U=j, \{1,...,J\})

Measurement assumptions: [Y_i|U_i,x_i]

- conditional independence, nondifferential measurement

> heterogeneity in criterion presentation unrelated to measured or unmeasured characteristics

> fundamentally identifying
In what sense is LCA a “measurement” model?

• Does it “discover” structure?

• It operationalizes theory
  – Science: Test if predictions borne out
  – Most frequent theory: Homogeneity

• Sensitivity: Do minor changes to theory greatly affect conclusions?
Latent Class Measurement

How to obtain “indices”? 

• Via **posterior probabilities** of class membership =

\[
\hat{F}_{U|Y,x}(u \mid y, x)
\]

• Then: exactly how?
  - “Modal”: by highest probability
  - “Pseudo-classes”: Randomize (*Bandeen-Roche et al.*, 1997; *Wang et al.*, 2005)
Latent Class Measurement Syndrome Validation Application

- **Data source:** Women’s Health and Aging Studies (WHAS; Guralnik et al., 1995; Fried et al., 2000)

- This analysis:
  - baseline cohort
  - n=740, age 70-79

- **Frailty:** Fried criteria (Y: Fried et al. 2001)
  - Exhaustion; grip strength; physical activity; walking speed; weight loss
Latent Class Measurement Syndrome Validation Application

- Criteria **manifestation is syndromic**
  
  "a group of signs and symptoms that occur together and characterize a particular abnormality" (Webster Medical Dictionary 2003)

- If criteria characterize syndrome:
  - At least two clinically homogeneous groups (if <2, no co-occurrence)
  - No subgrouping of symptoms (otherwise, more than one abnormality characterized)
### Conditional Probabilities of Meeting Criteria in Latent Frailty Classes

**WHAS**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>2-Class Model</th>
<th>3-Class Model</th>
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<tbody>
<tr>
<td></td>
<td>CL. 1 NON-FRAIL</td>
<td>CL. 2 FRAIL</td>
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<tr>
<td>Weight Loss</td>
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<td>.26</td>
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<td>Weakness</td>
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<td>Low Physical Activity</td>
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<td>Exhaustion</td>
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<tr>
<td>Class Prevalence (%)</td>
<td><strong>73.3</strong></td>
<td><strong>26.7</strong></td>
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</table>

*Bandeen-Roche et al., J. Gerontol Med Sci, 2006*
Rationale of the New Work

• Which deserves pre-eminence?
  – Internally validating assumptions
  – Externally validating assumptions?
    • e.g. close tie to systemic dysregulation
  – Some compromise?
Rationale of the New Work

• Which deserves pre-eminence?
  – Internally validating assumptions
  –Externally validating assumptions?
  – Some compromise?

• A model (LCR) including externally validating variables and fitting by ML already “is” a compromise
A representation theorem

- Consider "mixing" & "kernel" distributions: true posterior, model
A representation theorem

- $Y_i$ is equivalent in distribution to $Y^*$ constructed as

1) Generate $V_i^*$ from $F_{V|x}^*(v | x_i)$

2) Given $V_i^*$, generate $Y^*$ from $F_{Y|V,x}^*(y | V_i^*, x_i)$

- **Relevance:**
  - True for $\theta^* = \text{Huber (1967) limit of MLE (e.g.)}$
True vs. realized mixing models

Class 1 vs class 3

-0.5
-0.2
0.0
0.2
0.4

logit

True
MLE
Rationale of the New Work

• Which deserves pre-eminence?
  – Internally validating assumptions
  – Externally validating assumptions?
  – Some compromise?

• Proposal: Allow stronger (or weaker) compromise than ML via “penalized” fitting
Implementing penalization

- **On LCR kernel**: Houseman, Coull & Betensky, *BMCS* online early

- **On LCR mixing distribution**: Sheppard et al., Session 320

- **Key questions**
  - Form of the penalty
  - Different purpose than usual?
  - What is the objective function?
One empirical lead

Deciding the extent of penalization

- Notice the form of $F_{V|x}^*(v|x_i)$:

- Idea 1: Right penalty yields $f^* = f$
Simulation study
Three-class model

- Small: 100 reps; single $x \sim \text{Unif}(-.5,.5)$
- Multiple $n$: Here, $n=2000$
- Poly Log Reg: $\beta_{01} = \beta_{02} = 0; \beta_{12} = -1.4; \beta_{12} = -2.8$
- Measurement:

<table>
<thead>
<tr>
<th>Class 1</th>
<th>Class 2</th>
<th>Class 3</th>
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Simulation study
Three-class model

• Two scenarios (among more)
  – Frank LCR
  – Differential measurement: last two items have increased log(odds = 1) per unit x of 1.4 within each class

• Premise: $f_{v|x}(v|\theta, x_i)$, $f_{v|x}(v|\theta, x_i)$ quite different

• Measure: Kullback-Leibler distance
KL Distance: $f^*, f$

Scenario 1, $n=2000$

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<th>$\hat{\beta}_{22}$</th>
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KL Distance: $f^*, f$

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**ML**

**True**
Simulation Study

Empirical support for “penalty”?  

- Average conditional probability estimates amazingly stable
- Distinction: $Y|V^*,x$
Frailty analysis: Data
InCHIANTI (Ferrucci et al., JAGS, 48:1618-25)

- **Aim**: Causes of walking decline

- **Brief design**
  - Random sample ≥ 65 years (n=1270)
  - Enrichment for oldest-old, younger ages
  - Participation: > 90% in the primary sample
  - Home interview, blood draw, physical exam

- **Dysregulation: inflammation – 7 cytokines**
  - $IL-6$, $CRP$, $TNF-\alpha$, $IL-1RA$, $IL-18$, $IL-1B$, $TGF-\beta$
  - Here: concern = poorer inhibition

- **Frailty**: Fried criteria (as before)
Frailty analysis: Results

• Measurement model: 2 classes
  – Conditional probabilities similar to WHAS
  – Lower “frail” prevalence (15% vs. 27%)

• Regression model
  – 1 SD worse inhibition index associated with 35% reduction in non-frail odds (z ~ 3)
  – Regression coefficient on original index scale: 3.00

• Next: Vary regression coefficients in increments of +/- 0.5, up to +/- 2.0
Frailty analysis: Results
Posterior probs. from different fits
Frailty analysis: Results
Posterior probs. non-frail, different fits
Frailty analysis: Results
Age-adjusted relation to mobility

<table>
<thead>
<tr>
<th>Frailty fit: inflamm. slope</th>
<th>Mobility slope (frail vs non)</th>
<th>SE</th>
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<td>ML + 2.0</td>
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Recap

• Presented: Frameworks for measurement
  – of complex geriatric health states
  – incorporating biological knowledge

• Demonstrations
  – Frailty in WHAS
  – Frailty and inflammatory dysregulation in In CHIANTI
Rationale for the proposal

• vs looser internal validation criteria?
  – estimability

• vs Bayesian approach
  – depends on degree of empiricism
  – if balance by “consensus”—Bayesian

• Allows some distrust of the data
Research needed

- Theory elicitation, incorporation
- Methodology freeing measurement model estimation to “move” with “penalty”
  - Rotation?
  - Penalty on conditional probabilities
- Compromise of latent variable, predictive approaches
- Best index derivation
Implications

• Refined understanding of aging states and their measurement
  – Integrating biology
  – Increasing sensitivity, specificity

• Heightened accuracy, precision for
  – Delineating etiology
  – Developing and targeting interventions
Acknowledgments

• Hopkins Colleagues
  Linda Fried, Ron Brookmeyer, Yi Huang, Jeannie-Marie Leoutsakos, Jeremy Walston, Qian-Li Xue, Scott Zeger

• Colleagues outside of Hopkins
  Luigi Ferrucci, Jack Guralnik, Don Ingram, Richard Miller

• Funding / Institutional Support
  Johns Hopkins Older Americans Independence Center, National Institute on Aging, Alliance for Aging Research