Latent Class Measurement of Frailty and Dysregulation in Older Adults

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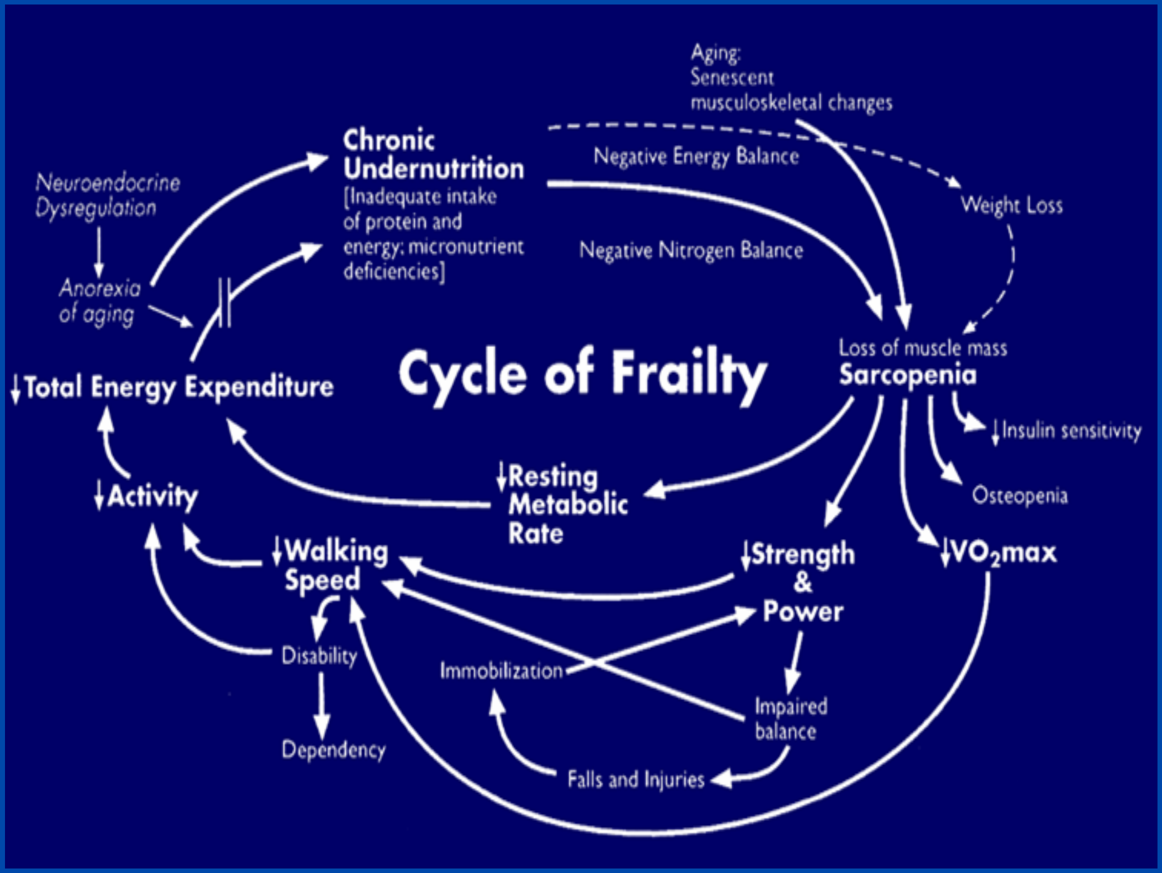
Outline

- 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

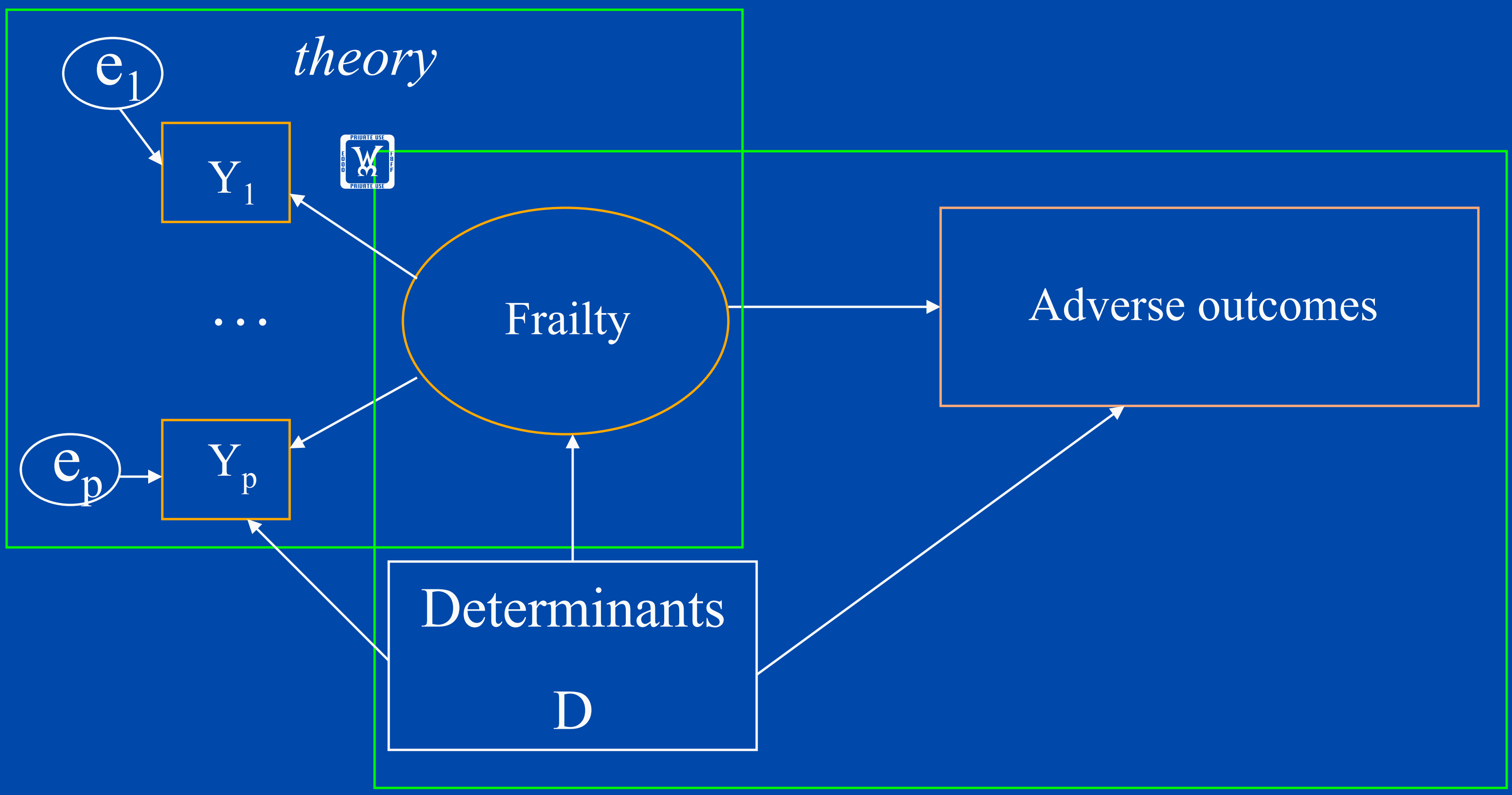


Fried et al., J Gerontol 2001; Bandeen-Roche et al., J Gerontol, 2006

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



Model

- **Generic**

Kernel

Mixing

- **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 t 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

- <u>Sensitivity</u>: 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

- **<u>Data source</u>**: 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

Criterion	2-Class Model		3-Class Model		
	CL. 1 NON-FRAIL	CL. 2 FRAIL	CL. 1 ROBUST	CL. 2 INTERMED.	CL. 3 FRAIL
Weight Loss	.073	.26	.072	.11	.54
Weakness	.088	.51	.029	.26	.77
Slowness	.15	.70	.004	.45	.85
Low Physical Activity	.078	.51	.000	.28	.70
Exhaustion	.061	.34	.027	.16	.56
Class Prevalence (%)	73.3	26.7	39.2	53.6	7.2

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?

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

A representation theorem

- Consider “mixing” & “kernel” distributions:

posterior,
model

true

A representation theorem

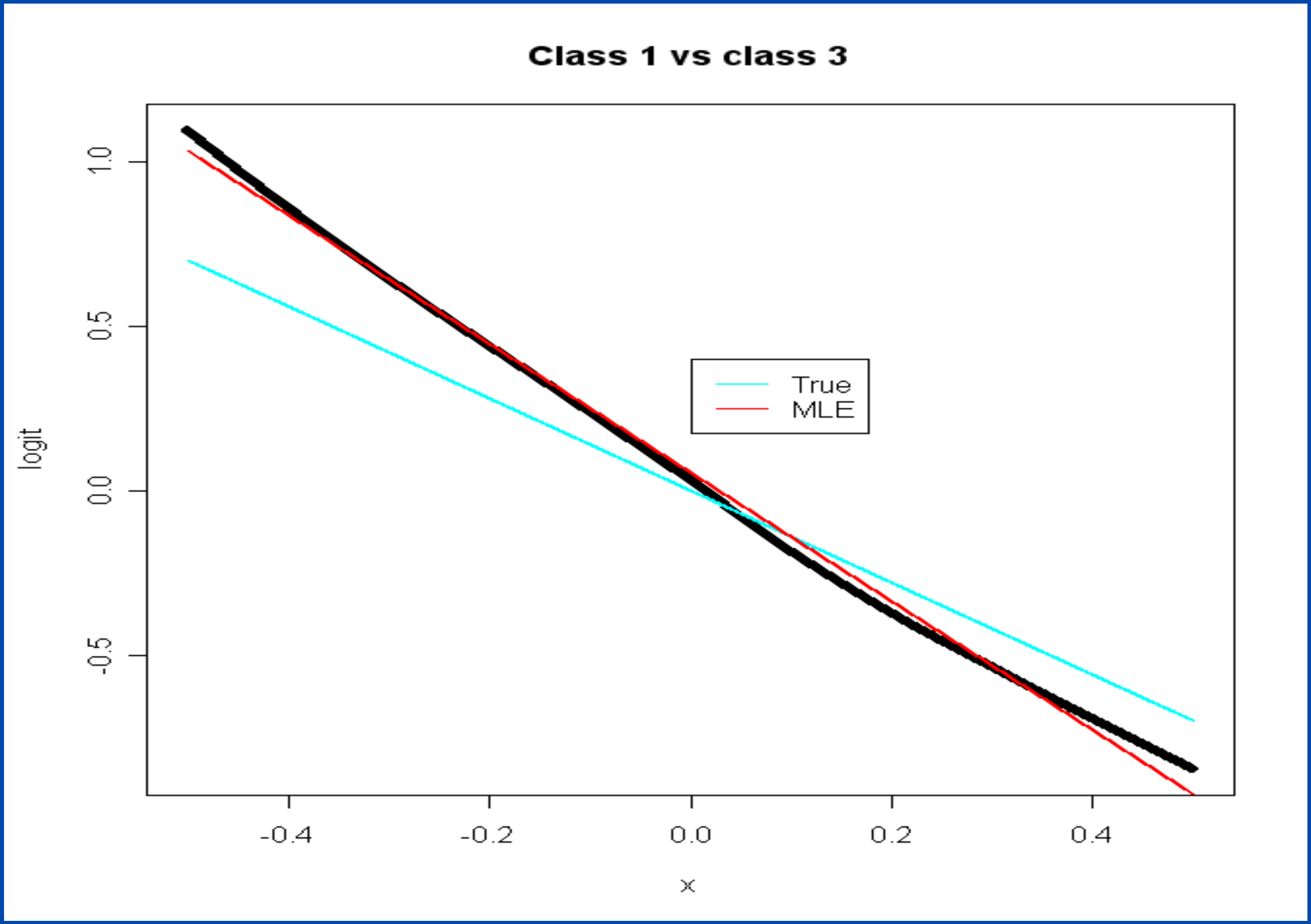
- Y_i is equivalent in distribution to Y^* constructed as

1) Generate V_i^* from $F^*_{V|x}(v \mid x_i)$

2) Given V_i^*, generate Y^* from $F^*_{Y|V,x}(y \mid V_i^*, x_i)$

- Relevance:
  - True for θ^* = Huber (1967) limit of MLE (e.g.)

True vs. realized mixing models



Rationale of the New Work

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- 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 $F^{*}_{V|x}(v\,|\,x_i)$:

$$f^{*}_{V|x}(v|x_i) = f_{V|x}(v|x_i)\int \frac{f_{\eta|v,x}(\eta|v,x_i;\lambda)}{f_{\eta|x}(\eta|x_i;\lambda)}\,dG_{\eta|x}(\eta|x_i).$$

Factor by which f*, f differ at x_i

- Idea 1: Right penalty yields f* = f

Simulation study
Three-class model

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

Class 1	Class 2	Class 3
.15	.85	.85
.15	.85	.85
.15	.85	.85
.15	.13	.85
.15	.13	.85

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: $f^*_{V|x}(v \mid x_i, \theta)$, $f_{V|x}(v \mid x_i, \theta)$ quite different

- Measure: Kullback-Leibler distance

KL Distance: f*, f
Scenario 1, n=2000

$\hat{\beta}_{12}$ \ $\hat{\beta}_{22}$	-3.4	-3.3	-3.2	-3.1	-3.0	-2.9	-2.8	-2.7	-2.6	-2.5	-2.4	-2.3	-2.2
-2.0	4.99	4.76	4.76	4.86	4.89	5.15	5.26	5.42	6.23	6.34	6.93	7.59	7.99
-1.9	4.58	4.28	4.40	4.57	4.19	4.42	4.62	5.09	5.15	5.62	6.03	6.91	7.31
-1.8	4.52	4.36	4.18	4.07	3.88	3.96	4.22	4.26	4.55	5.09	5.52	5.96	6.58
-1.7	4.30	4.05	3.90	3.64	3.85	3.71	3.73	4.05	4.35	4.46	4.92	5.33	5.77
-1.6	4.56	4.21	3.80	3.62	3.52	3.54	3.67	3.69	3.88	4.07	4.36	4.88	5.46
-1.5	4.67	4.11	3.88	3.70	3.56	3.41	3.46	3.42	3.75	3.74	4.28	4.52	4.85
-1.4	4.87	4.39	3.91	3.84	3.62	3.27	3.62	3.40	3.69	3.68	3.70	4.03	4.52
-1.3	5.25	4.73	4.50	4.16	3.86	3.54	3.45	3.46	3.39	3.52	3.78	4.12	4.43
-1.2	5.58	4.99	4.76	4.47	4.16	3.81	3.70	3.60	3.75	3.74	3.85	4.25	4.30
-1.1	6.25	6.05	5.26	4.90	4.55	4.14	4.20	4.03	4.01	3.94	3.91	4.45	4.28

True

ML

KL Distance: f*, f

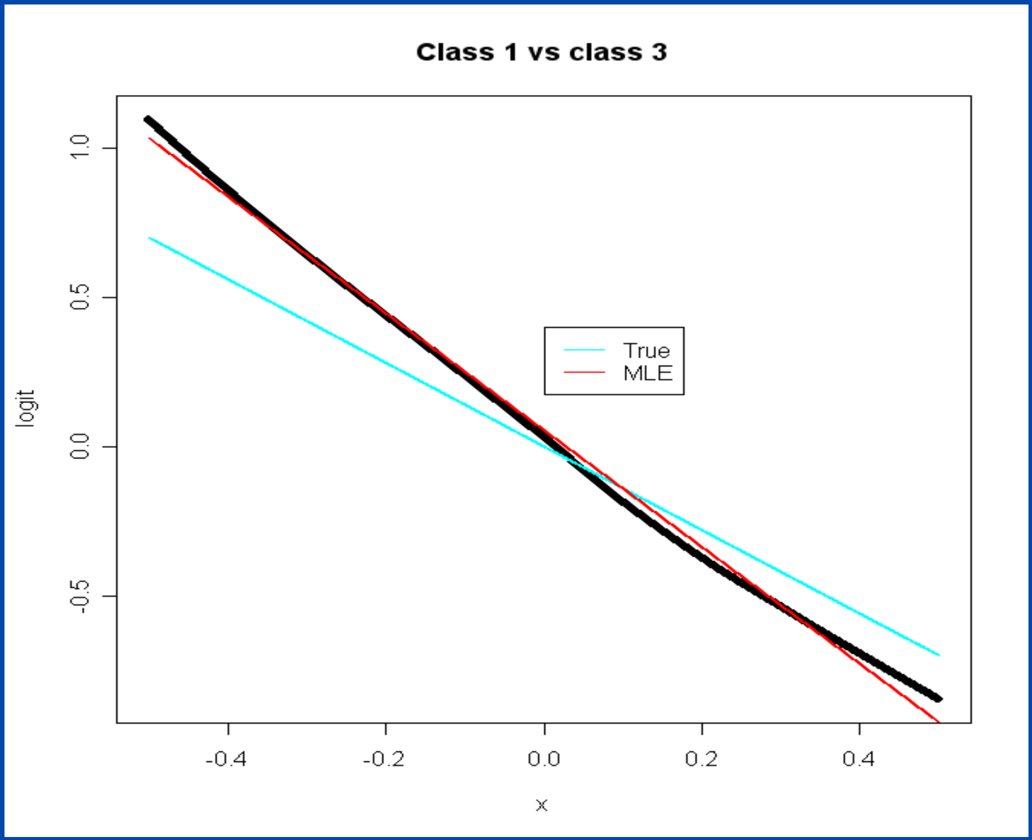
Scenario 2, n=2000

$\hat{\beta}_{12}$ \ $\hat{\beta}_{22}$	-3.8	-3.7	-3.6	-3.5	-3.4	-3.3	-3.2	-3.1	-3.0	-2.9	-2.8	-2.7	-2.6
-2.4	4.03	4.37	4.63	5.05	5.39	5.93	6.35	7.17	8.00	8.76	9.36	10.40	11.74
-2.3	3.79	3.87	4.10	4.59	4.93	5.14	5.84	6.38	6.76	7.79	8.55	9.46	10.50
-2.2	3.48	3.63	3.90	3.98	4.27	4.60	5.20	5.76	6.17	7.01	7.78	8.26	9.65
-2.1	3.31	3.17	3.47	3.51	3.95	4.25	4.69	5.04	5.64	6.34	7.01	8.09	9.07
-2.0	3.19	3.29	3.41	3.33	3.70	3.94	4.34	4.60	5.10	5.62	6.70	7.24	8.02
-1.9	3.17	3.09	3.19	3.27	3.39	3.64	3.99	4.25	4.93	5.40	6.17	6.90	7.37
-1.8	3.31	3.24	3.22	3.26	3.35	3.63	3.98	4.35	4.75	5.12	5.34	6.40	7.00
-1.7	3.56	3.33	3.43	3.32	3.31	3.57	3.85	4.17	4.40	4.79	5.43	6.00	6.33
-1.6	3.83	3.77	3.60	3.69	3.68	3.62	3.80	4.19	4.65	4.87	5.38	6.21	6.62
-1.5	4.36	3.95	4.02	3.97	3.89	3.82	4.05	4.24	4.56	5.05	5.37	5.86	6.36
-1.4	4.90	4.69	4.43	4.28	4.34	4.46	4.35	4.65	4.88	5.11	5.41	5.99	6.49
-1.3	5.56	5.41	5.11	4.95	4.77	4.84	4.72	4.74	5.01	5.49	5.85	6.19	6.60
-1.2	6.41	5.97	5.87	5.59	5.37	5.17	5.33	5.18	5.52	5.96	6.08	6.31	6.99

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-α, IL-1RA, IL-18, IL-1B, TGF-β*
  - Here: concern = poorer inhibition
- **Frailty: Fried criteria (as before)**

Frailty analysis: Results

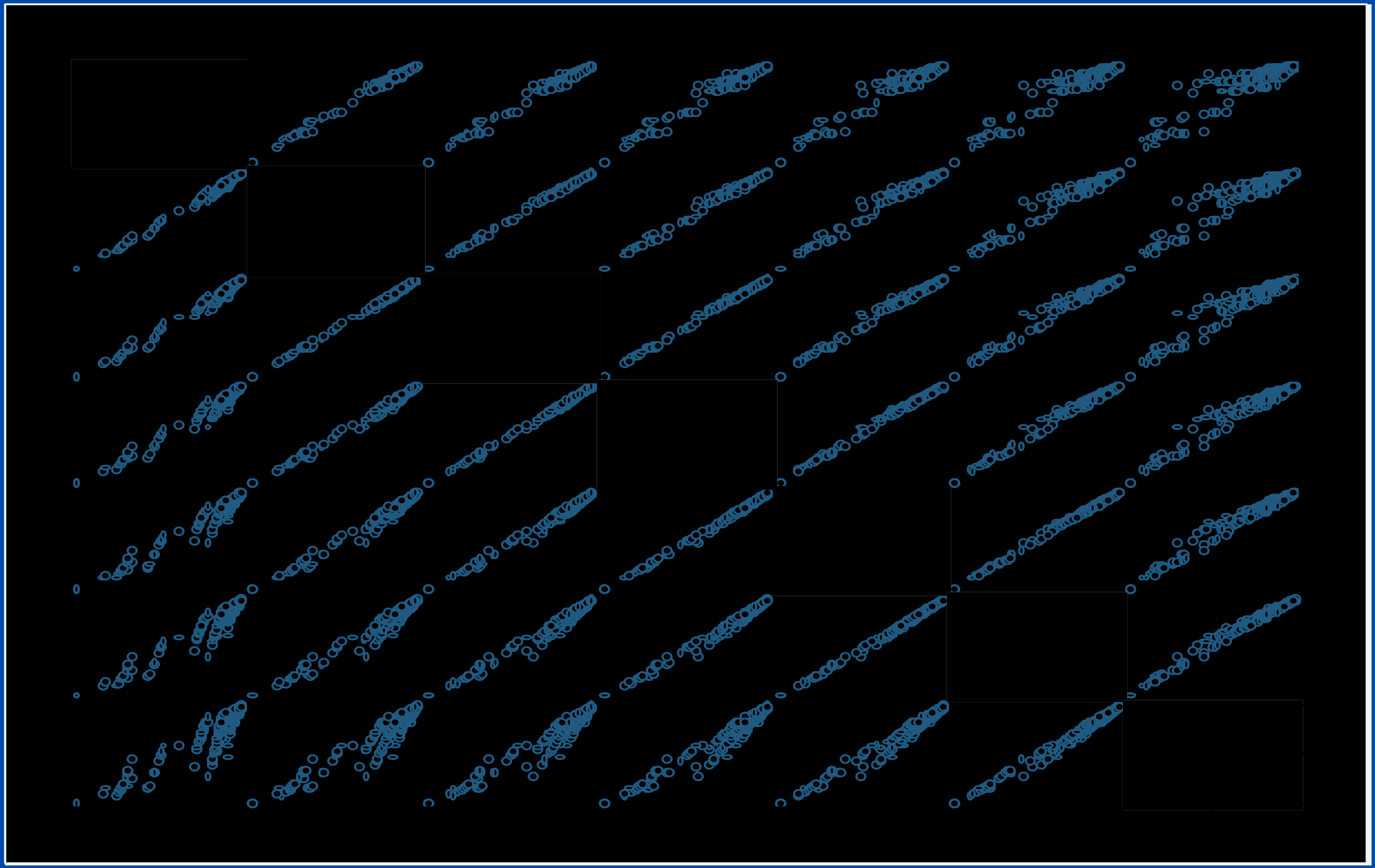
- Measurement model: 2 classes
  - Conditional probabilities similar to WHAS
  - Lower “frail” prevalence (15% vs. 27%)

- 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

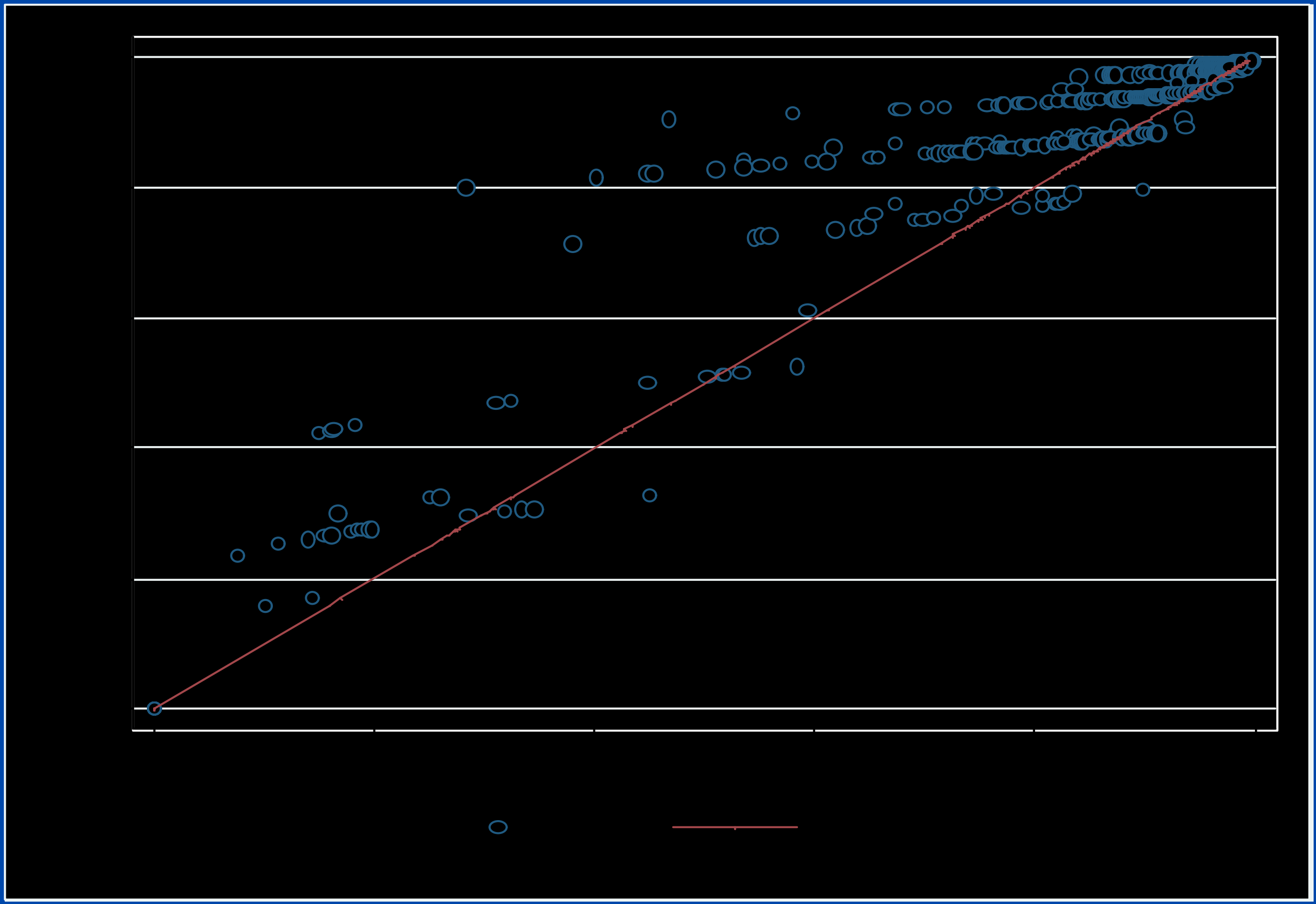
Frailty analysis: Results

Posterior probs. from different fits



Frailty analysis: Results

Posterior probs. non-frail, different fits



Frailty analysis: Results

Age-adjusted relation to mobility

Frailty fit: inflam. slope	Mobility slope (frail vs non)	SE
ML – 2.0	-1.1	.089
ML – 1.0	-1.0	.087
ML – 0.5	-1.0	.086
ML	-0.99	.085
ML + 0.5	-0.93	.085
ML + 1.0	-0.92	.085
ML + 2.0	-0.82	.083

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

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