Geronometrics: Leading the Next Generation of Discovery in Aging

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Introduction
Whither “geronmetrics”?

• “Measurement of constructs in aging”
  – a.k.a.: econometrics, psychometrics, biometrics
  – e.g.: generalized inflammation; frailty; aging

• Boring, no?
  –NO!

• Rather: essential to
  – Sensitivity for genetic, other discovery
  – Theory operationalization, testing
  – Specificity for genetic, other discovery
  – Correctly targeted, evaluated interventions
Introduction
The Frailty Construct

Fried et al., J Gerontol 56:M146-56; Bandeen-Roche et al., J Gerontol, in press
Frailty: Scientific Aims

• Validate theory that frailty is:
  – More than a marker of disease
  – More than severe disability
  – A *syndrome*: more than component parts

• Specific Aims
  – Drilling down: from phenotype to etiology
  – Specificity: a measure tied explicitly to dysregulation
  – Product: a refined summary variable
Outline

• Big picture: Biological aging
  – Four measurement paradigms
  – Partner: Alliance on Aging Research

• Application: Pro-inflammation
  – Component underlying frailty
  – Data: InCHIANTTI (Ferrucci et al., JAGS, 48:1618-25)

• Etiological mechanisms: A few words
Biological Aging

• Hypothesis: Individual specificity
  – Seems manifestly true... however:
  – Identifiable? Less manifestly true?
  – Animal evidence: e.g. dog breeds

• Goal: Surrogate measurement via biomarkers
  – Alliance for Aging Research Initiative
  – Import: Research, interventions to slow aging

• Previous attempts: disappointing

• Guiding Principles
  – Multivariate validation
  – Differentiation from disease, other cofactors of aging
Identifying Biological Aging
Paradigm #1: Age-Relatedness

- Challenges
  - Age ≠ aging
  - Selection in studies: healthiest
  - Methodological: Multiple outcomes
  - Choice of measures: reliable; content-valid
Identifying Biological Aging Paradigm #2: Predictive Validity

- “Aging” = combination of aging-related variables that “best” predicts outcome(s)

- **Methods**: Neural networks, regression trees, logic regression, etc.
Identifying Biological Aging
Paradigm #2: Challenges

- Distinction between “aging-related variables” and “outcomes of aging”
- Agreement on “outcomes of aging”
- Methodological
  - Cross-validation
  - Multiple outcomes
Identifying Biological Aging
Paradigm #3: Latent Variables

Construct validity

theory

Aging

Adverse outcomes

Determinants

$Y_1$

$Y_p$

$D$

$e_1$

$e_p$
Identifying Biological Aging
Paradigm #3: Challenges

• Computing “measures” from model
  – Option 1: “Average” in domains (e.g. principal components)
  – Option 2: Prediction “from” model

• Impact of modeling assumptions
  – “local independence” (homogeneity)
  – “model fit” ≠ “unique discovery”
Identifying Biological Aging
Paradigm #4: Combinations

• Compromises between methods
  – Geek speak: penalization
  – Plainer: weighting for emphasis

• Example: Latent variable model with fit weighted to emphasize age-relatedness of “aging” (“D”)

• Nice science + statistics problem
Application: Pro-Inflammation

- Central role: cellular repair

- A hypothesis: dysregulation key in adverse aging
  - Muscle wasting (*Ferrucci et al., JAGS 50:1947-54; Cappola et al, J Clin Endocrinol Metab 88:2019-25*)
  - Receptor inhibition: erythropoietin production / anemia (*Ershler, JAGS 51:S18-21*)

Stimulus (e.g. muscle damage) → IL-1# → TNF → IL-6 → CRP

- Up-regulation
- Inhibition

# Difficult to measure. IL-1RA = proxy
Study: In CHIANTI

• **Aim**
  – Causes of decline in walking ability

• **Brief design**
  – Random sample ≥ 65 years (n=1270)
  – Enrichment for oldest-old, younger ages
  – Participation: > 90% in the primary sample

• **Data**
  – Home interview, blood draw, physical exam
  – So far: Two evaluations
Conceptual framework

Statistical methodology: SEM with latent variables (AMOS)
Observed variables

- **Inflammation** – 5 cytokines
  - *IL-6, CRP, TNF-α, IL-1RA, IL-18*

- **Mobility functioning** – Z-score average
  - *Usual & rapid speed; muscle power; range of motion; neurological intactness*

- **Frailty**: Fried et al., 2001 criteria
  - Exhaustion; grip strength; physical activity; walking speed; weight loss
  - Continuously measured versions

- **Analyses accounting for**: *age, gender*
Results

- LV method: measured = physiology + noise
  - Multivariate normal underlying variables, errors
  - Conditional independence of errors

<table>
<thead>
<tr>
<th>Inflammation 2</th>
<th>IL-6</th>
<th>CRP</th>
<th>IL-1RA</th>
<th>IL-18</th>
<th>Inflammation 1</th>
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<tbody>
<tr>
<td>Down-reg.</td>
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<td>Up-reg.</td>
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<td>-.59</td>
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Is there Value Added?  
In CHIANTI findings

- **YES!**

- Independent of age, sex, smoking, diseases:  
  Up-regulation associated with  
  - Worse mobility functioning [~ -.1 effect size]  
  - Heightened frailty prevalence [by ~ 30%]

- “Up-regulation” is specific, sensitive  
  - No individual cytokine adds to prediction  
  - Up-regulation affords superior prediction over individual cytokines
More on Specificity

Inflammation 1
Up-reg.

Inflammation 2
Down-reg.

Age

Clinical Frailty

Exh. Str. PA Spd.

Wt

.18
.14
.58
.37
.34
.35
.80
.04

.37
.34
.35
.80
.04

e_1 e_2 e_3 e_4 e_5
Etiological Mechanisms

- Holy grail?: What causes adverse aging?
  - Experimental data on humans: hard to come by
  - Observational, longitudinal data: central

- Cohort studies on aging abound
  - EPESE; CHS; HRS/ALIVE
  - Women’s Health and Aging Study (WHAS)
  - In CHIANTI

- How to utilize existing data to most nearly address causality?
Causal Models

• Three queries *(Pearl, 2000)*
  – Predictions
    • “Probabilistic causality” *(von Suppes, 1970)*
    • Is bad function probable among the inflamed?
  – Interventions / Experiments *(Bollen, 1989)*
    • Association, temporality, isolation
    • Does bad function follow inflammation?
  – Counterfactual
    • Does one’s function change if inflamed vs. not?
      • Neyman, 1923; Stalnaker, 1968; Lewis, 1973; Rubin, 1974; Robins 1986; Holland 1988
Toward “causal” inferences?

- **Propensity scoring** *(Rosenbaum/Rubin, 1983; Imai/Van Dyk, 2004)*
- **My work**: Implementation amid latent variables
- **Whichever causal method**: Assumptions

**Diagram**:

1. Inflammation → Mobility
2. Age, Gender, Smoking
3. Hx: CVD, Cancer, Diabetes
Propensity Score Model

- $I_1 \sim$ age, cancer hx, CVD hx
- $I_2 \sim$ age, gender, diabetes hx, smoking hx
Inflammation Effects (Summary 2)
Recap

- Presented: Frameworks for measurement
  - of complex geriatric health states
  - that incorporating biological knowledge
  - integrating causal inference methods

- Demonstration: Inflammation and adverse outcomes in In CHIANTI
Future Goals

• Extension across biological systems

• Cross-validation across populations

• Assessment of extent to which “associations” ↔ “mechanisms”

• Translation into interventions
Research needed

• Theory elicitation, incorporation

• Methods for synthesizing inferences across multiple data sets

• Best methods for deriving measures “M” for subsequent usage

• Surrogacy: “M” strongly relates to aging (A); treatment independent of M given A
Implications

- Refined understanding of aging states and their measurement
  - Integrating systems biology
  - Increasing sensitivity, specificity

- Heightened accuracy, precision for
  - Delineating etiology
  - Developing and targeting interventions