Geronmetrics: Leading the Next Generation of Discovery in Aging

Karen Bandeen-Roche, Ph.D.
Departments of Biostatistics, Medicine & Nursing
Johns Hopkins University

Gerontology Brown Bag
Miami University
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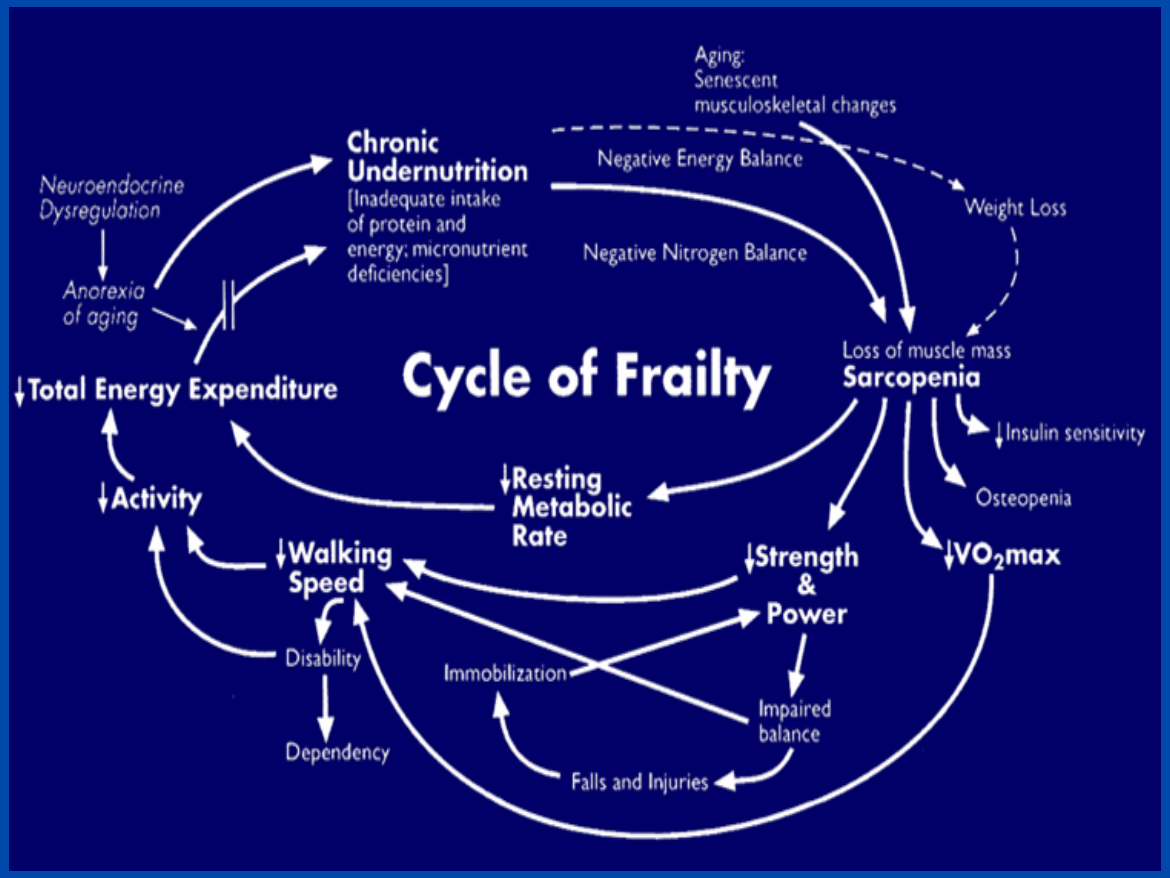
Introduction
Whither "geronmetrics"?

- "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

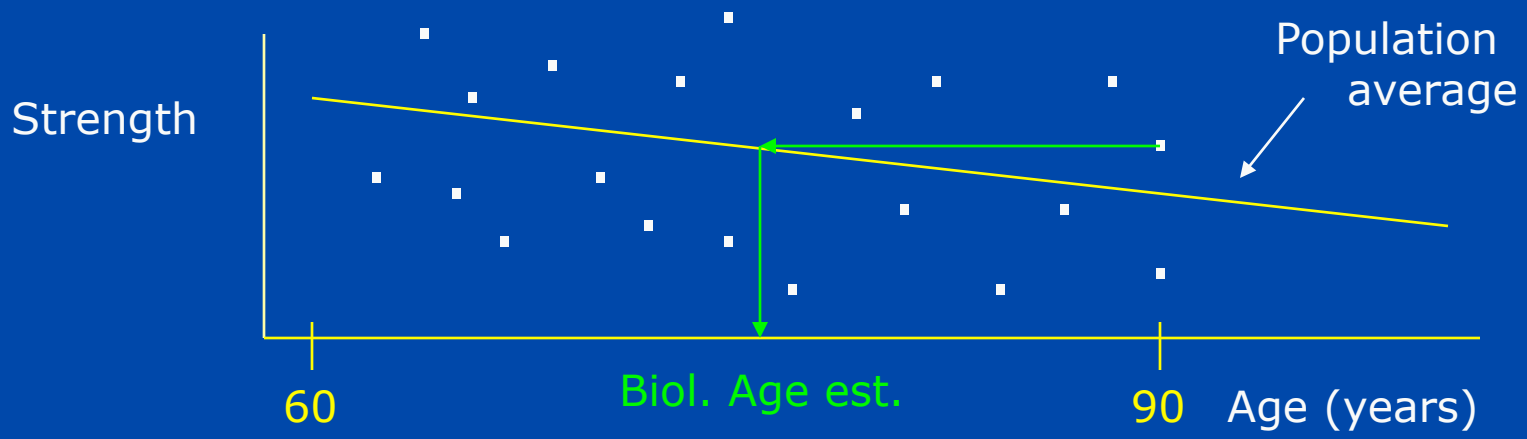
Outline

- Big picture: Biological aging
  - Four measurement paradigms
  - Partner: Alliance on Aging Research
- Application: Pro-inflammation
  - Component underlying frailty
  - Data: InCHIANTI (*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

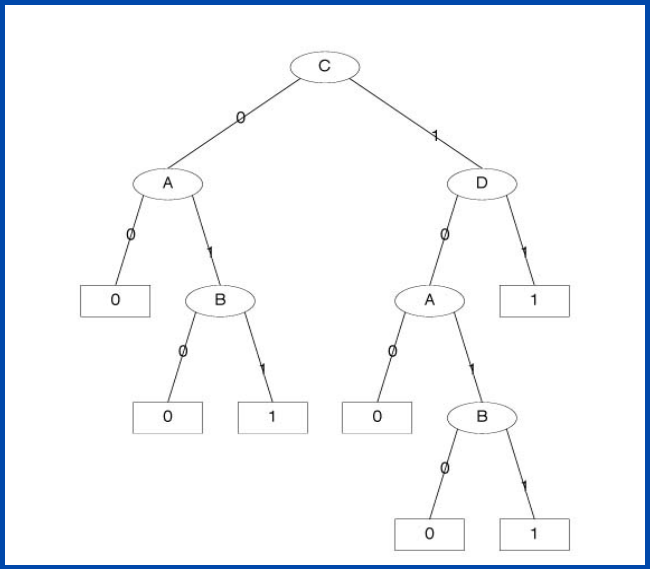
Identifying Biological Aging
Paradigm #1: Age-Relatedness



- 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)

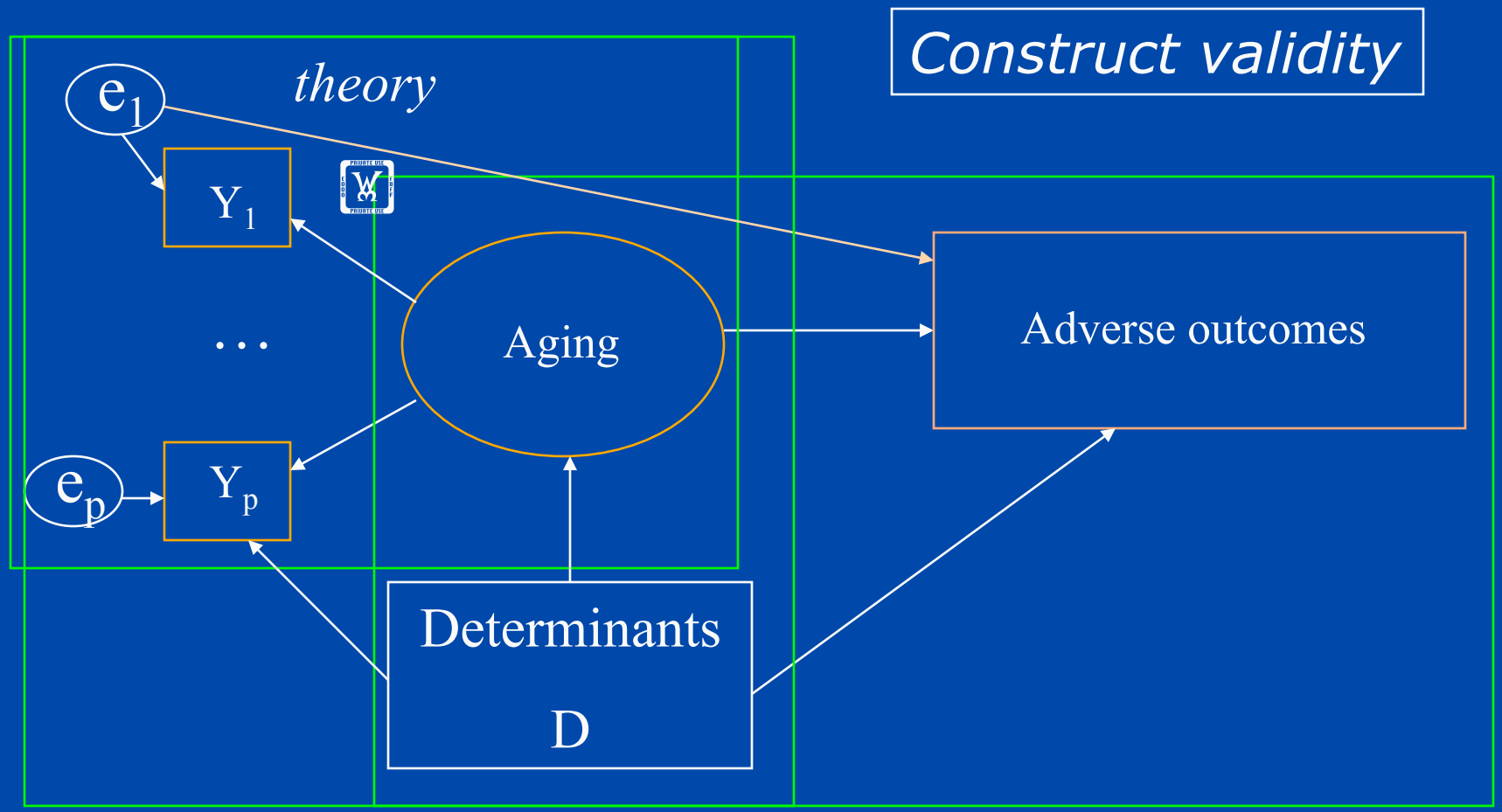


- Methods: Neural networks, regression trees, logic regression, etc.

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



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"

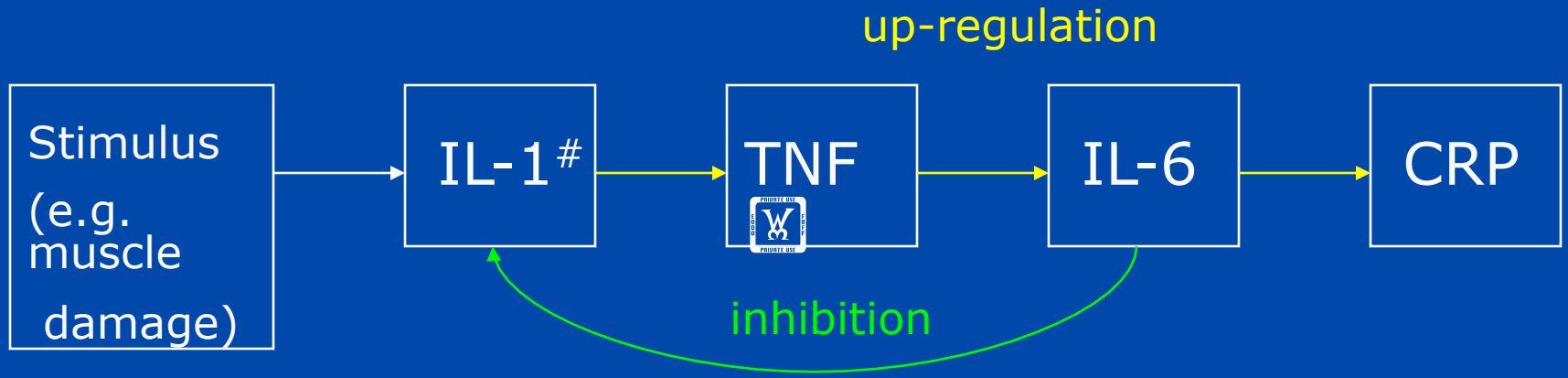
Identifying Biological Aging
Paradigm #4: Combinations

- 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: erythropoetin production / anemia (*Ershler, JAGS 51:S18-21*)

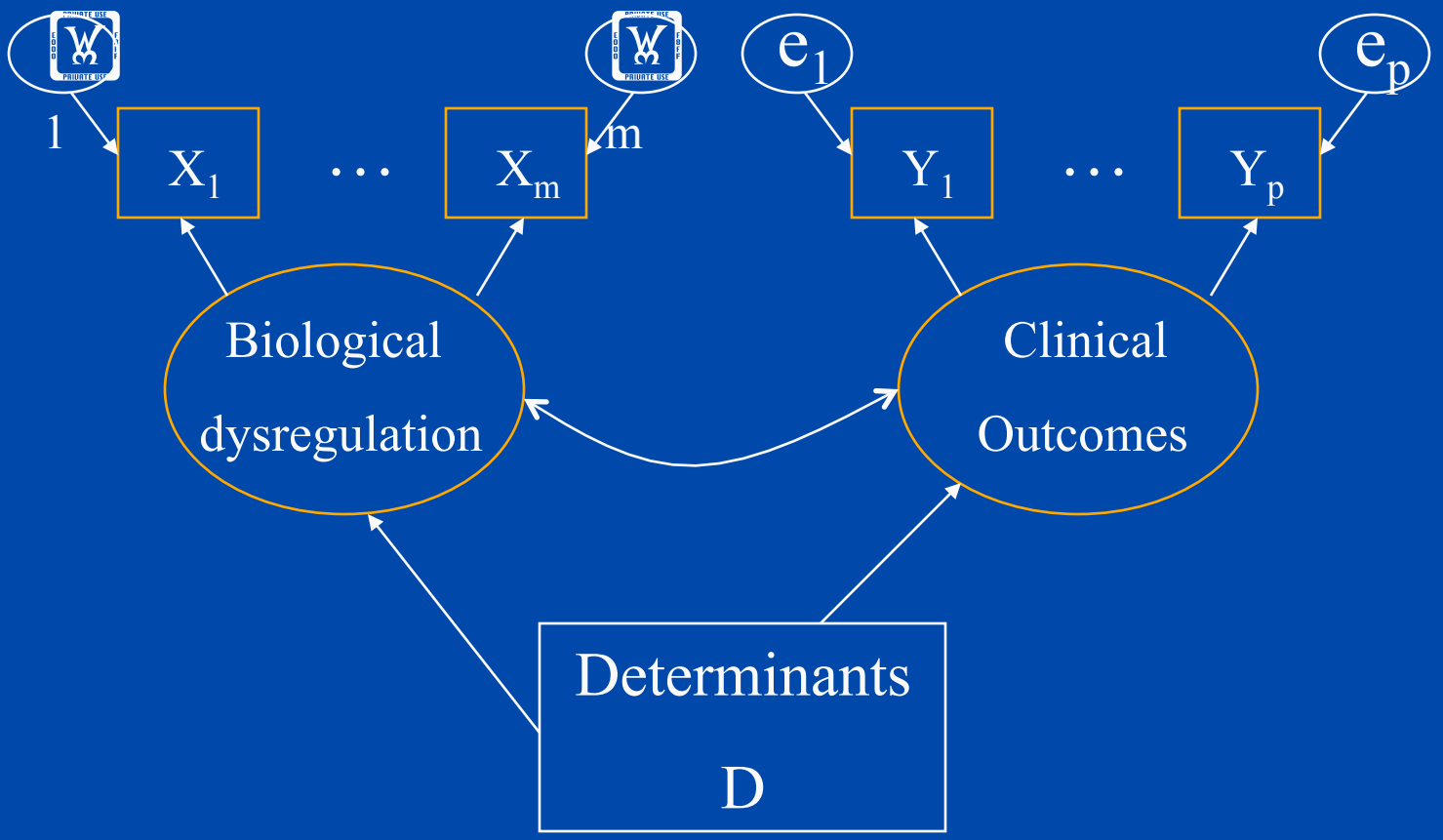


Difficult to measure. IL-1RA = proxy

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



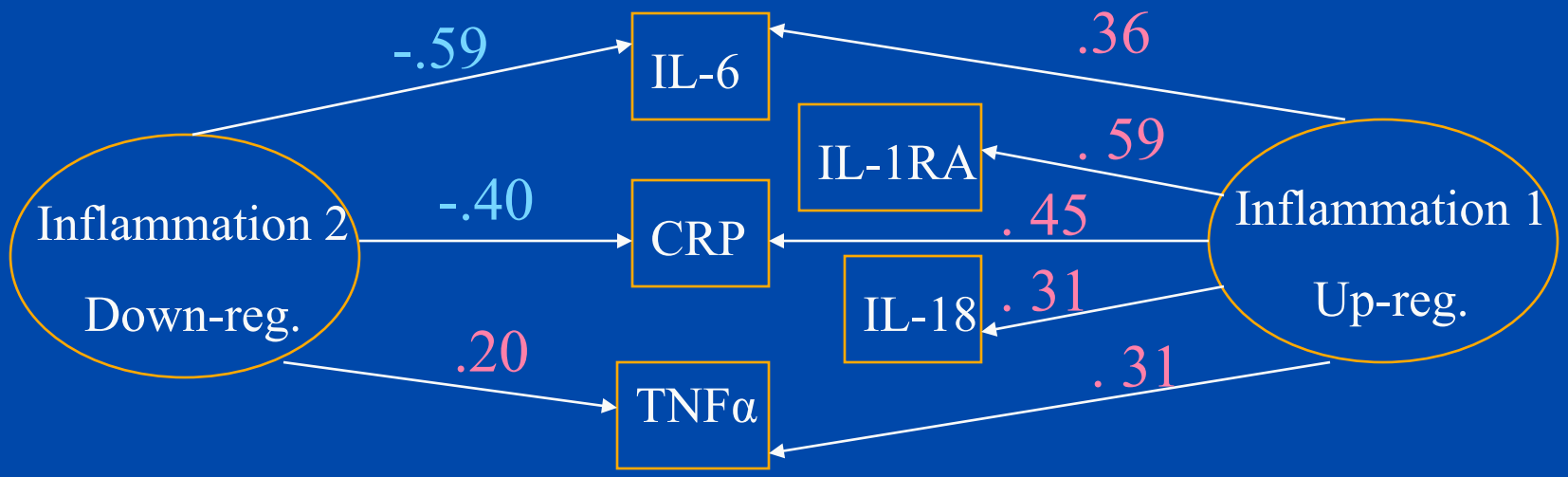
Statistical methodology: SEM with latent variables (AMOS)

Observed variables

- Inflammation – 5 cytokines
  - *IL-6, CRP, TNF-a, 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



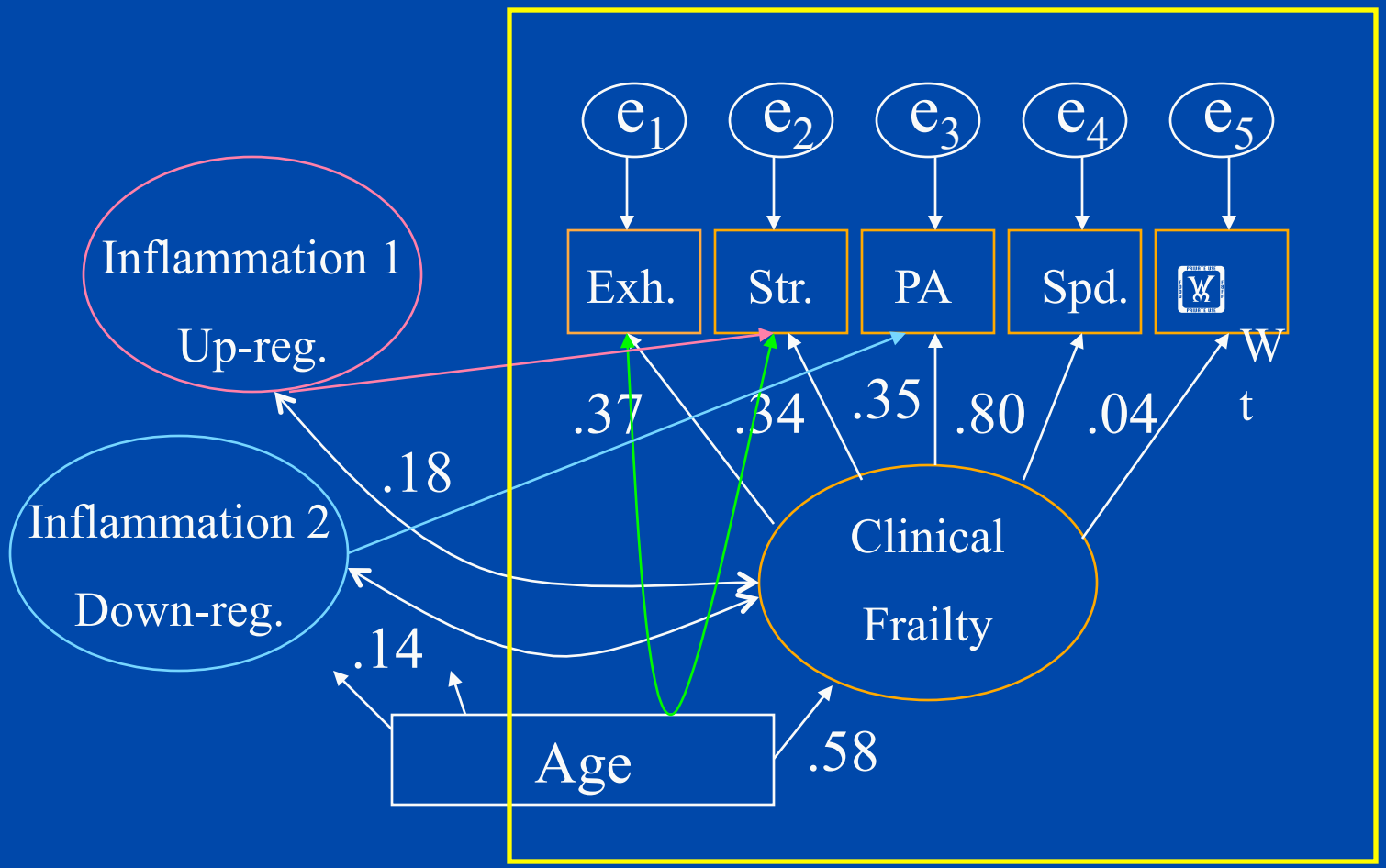
Is there Value Added?
In CHIANTI findings

- *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



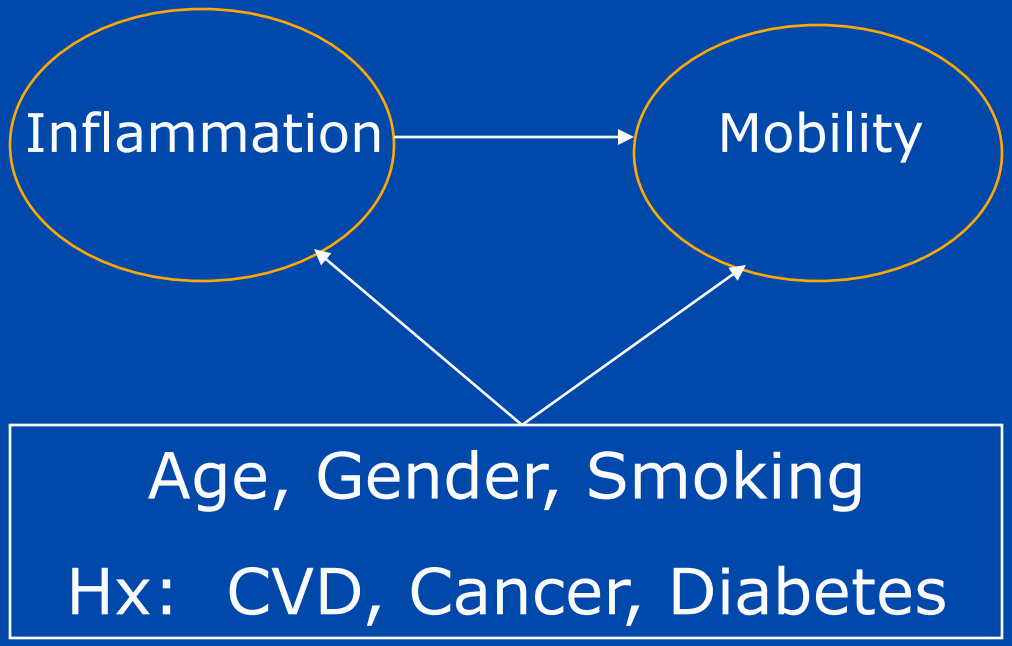
Etiological Mechanisms

- 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*

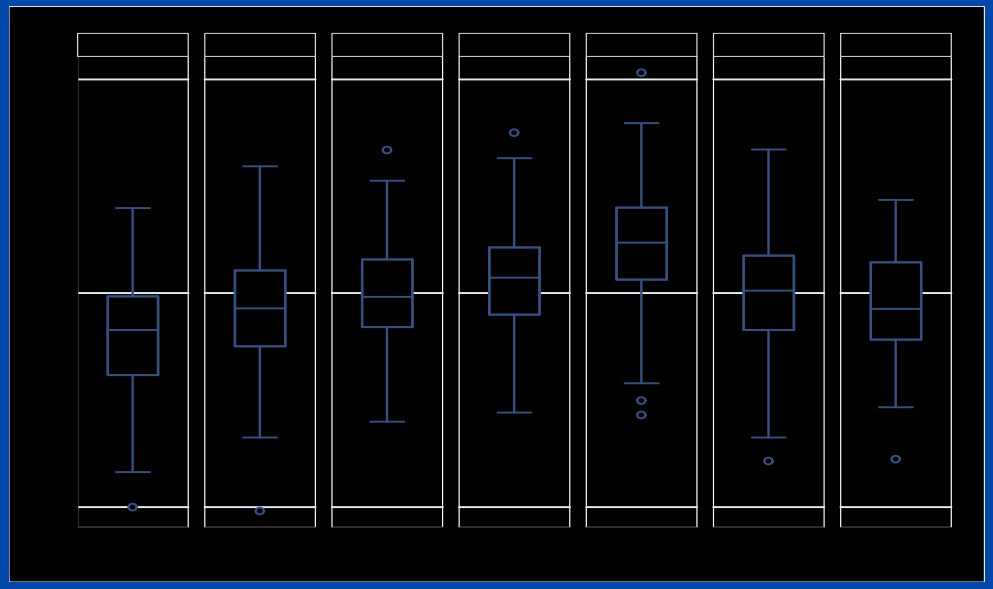
Toward "causal" inferences?



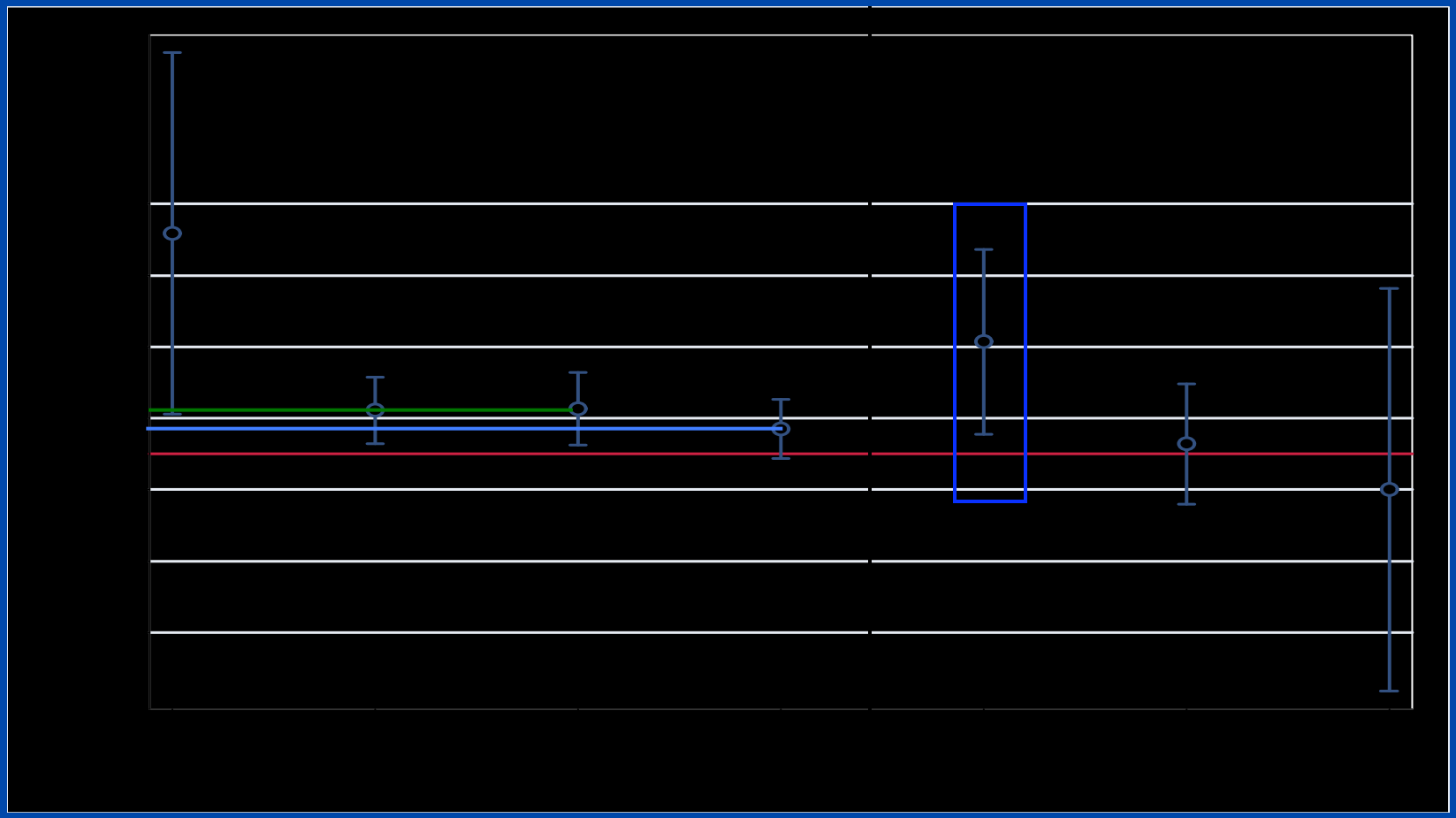
- Propensity scoring *(Rosenbaum/Rubin, 1983; Imai/Van Dyk, 2004)*
- My work: Implementation amid latent variables
- Whichever causal method: Assumptions

Propensity Score Model

- I_1 ~ age, cancer hx, CVD hx
- I_2 ~ age, gender, diabetes hx, smoking hx



Inflammation Effects (Summary 2)



raw adjusted PS-full PS-red. diab/sm young cancer

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