Measuring Aging:
How will we know when interventions work?

AFAR Grantee Conference
New York, New York
October 1, 2007

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

Parsing my title

1) Is "aging" a stand alone entity?

2) What is it?

3) Does it vary meaningfully between people?

4) Can we measure it? How?

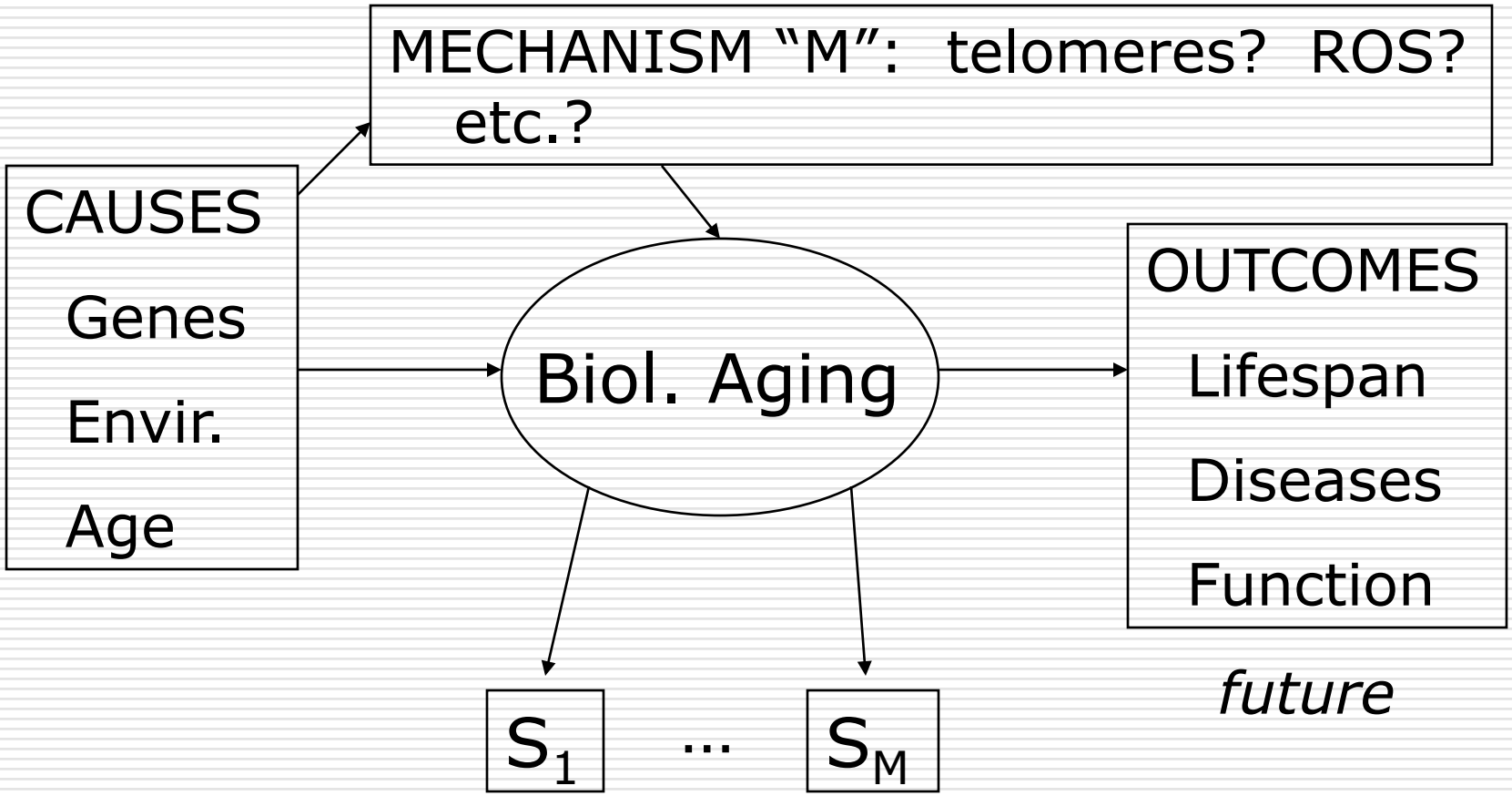
5) Can we intervene upon it? How?

6) How can we know if an intervention is effective at slowing aging?

Premise

Aging is a distinct biological process that varies among individuals, is measurable, and can be beneficially altered

How to measure 'aging'?
A spectrum of possibilities



How to measure 'aging'?
Some opinions

- Best shot: Work the problem from both (all?) ends
- A milieu where 'interdisciplinary,' 'translation,' etc. have real meaning
- My contribution: working the problem from the 'phenotype' end

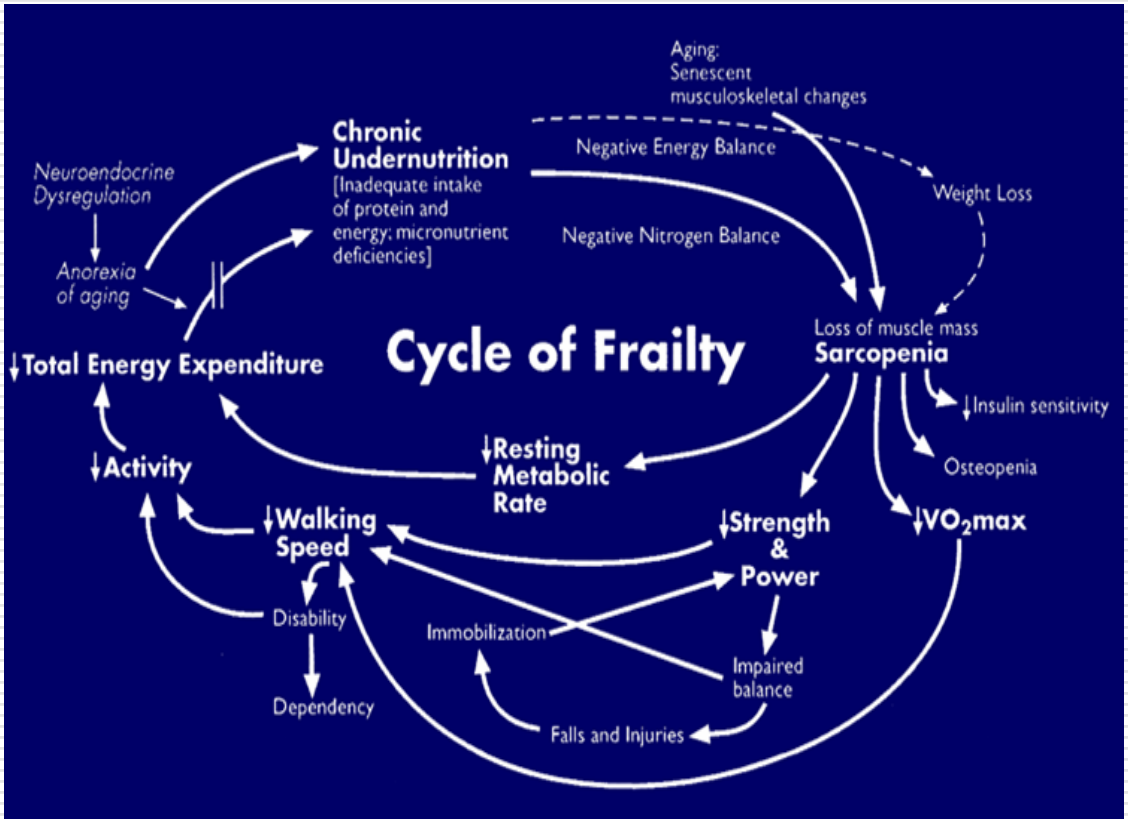
Outline

- Concepts, and a method, of measurement
- Application of the paradigm to constituents of ‘aging’
- Close-up view: Cause versus correlate?
- Strategy for ramping up from constituents to the whole

Complex health states in aging
Role of biomarkers in measurement

- 'Complex' = 'not directly measurable'
  - disability; systemic regulation; frailty; aging
  - measurement method: "geronmetrics"
  - a.k.a.: econometrics, psychometrics, biometrics
- Boring, no? *–NO!*
- Rather: essential to
  - Sensitivity for genetic, other discovery
  - Theory operationalization, testing
  - Specificity for genetic, other discovery
  - Correctly targeted, evaluated interventions

The Frailty Construct



Fried et al., J Gerontol 56:M146-56; Bandeen-Roche et al., J Gerontol, 61A:262-6

Measuring what we aim to measure
Validity

- Face : does it "look" like it should?
- Content : does it span what it should?
- Concurrent : does it co-occur as it should?
  - Special case: predictive
- Construct : does it behave as theorized?
  - Internal: are they distributed as theorized?
  - External: does it relate as theorized?

A method for measurement in aging: Latent Variable Modeling

What does 'latent' mean?

1. Present or potential but not evident or active: latent talent.

2. Pathology. In a dormant or hidden stage: a latent infection.

3. Biology. Undeveloped but capable of normal growth under the proper conditions: a latent bud.

4. Psychology. Present and accessible in the unconscious mind but not consciously expressed.

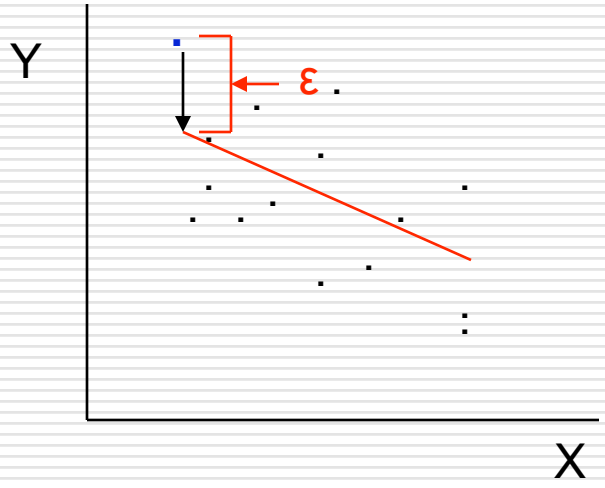
The American Heritage Dictionary of the English Language, Fourth Edition, 2000

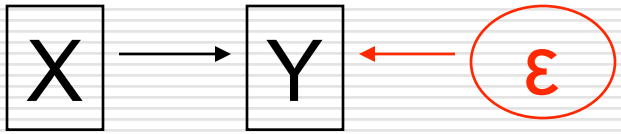
Underlying: not directly measurable. Existing in hidden form but capable of being measured indirectly by observables.

Bandeen-Roche K, Synthesis, 2006

The Simplest Latent Variable

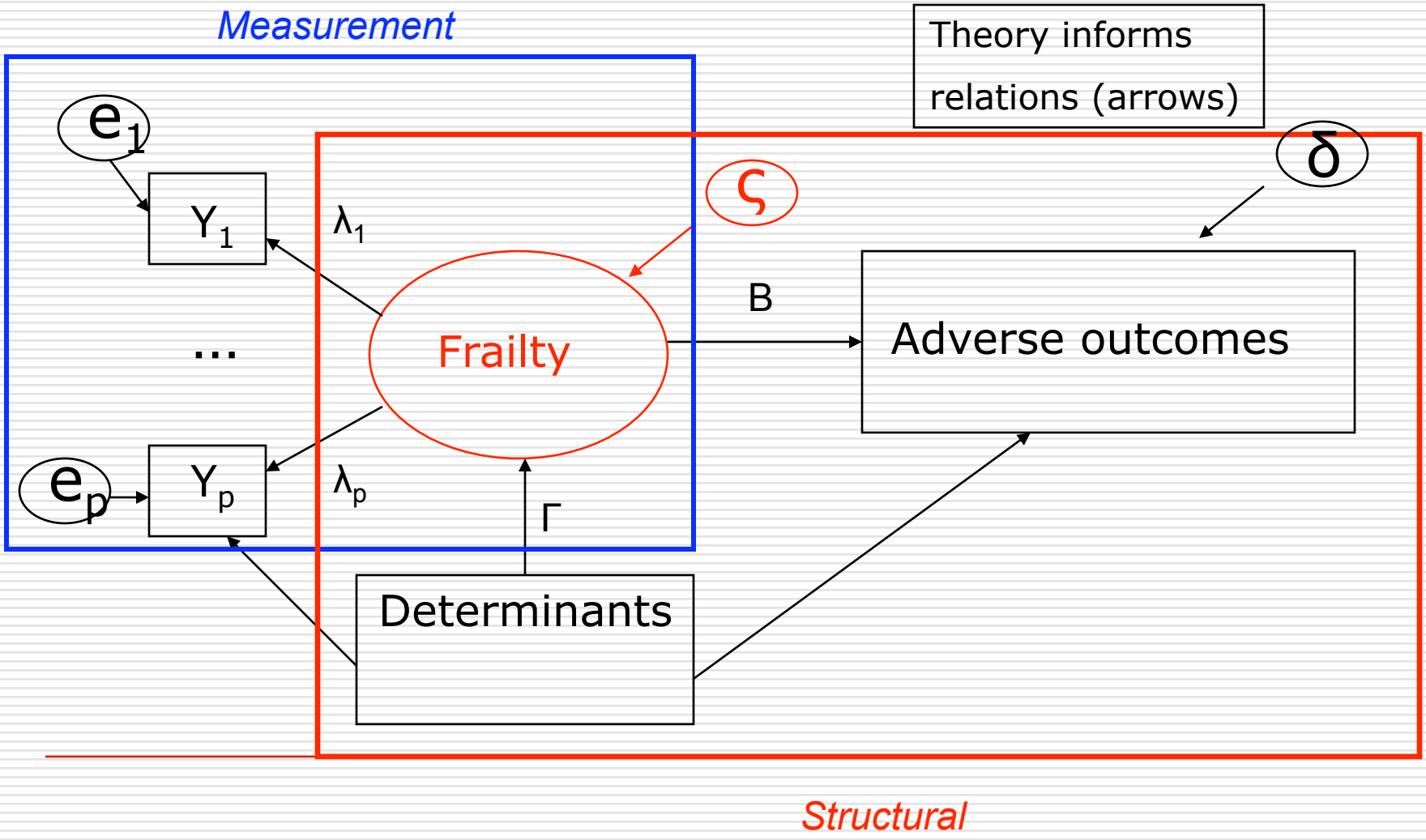
Ordinary Linear Regression Residual





$$Y = \beta_0 + \beta_1 X + \varepsilon$$

Frailty
Latent Variable Illustration



LATENT VARIABLE MODEL

Linear structural equations model with latent variables (LISREL):

Y_{ij} = outcome (j th measurement per person i; f railty indicator)
$\underline{x}_{ij}$ = covariates (corresponds to j th measurement, person i; risk f actor)

$\underline{\lambda}_j$ = loading ("coef f ient"; relates LV to j th measurement)
$\underline{\eta}_i$ = latent variables, person i; f railty statuses
ε_{ij} = observed response residual (error)
$\underline{\varsigma}_i$ = latent response residuals (error; specif ied distribution)

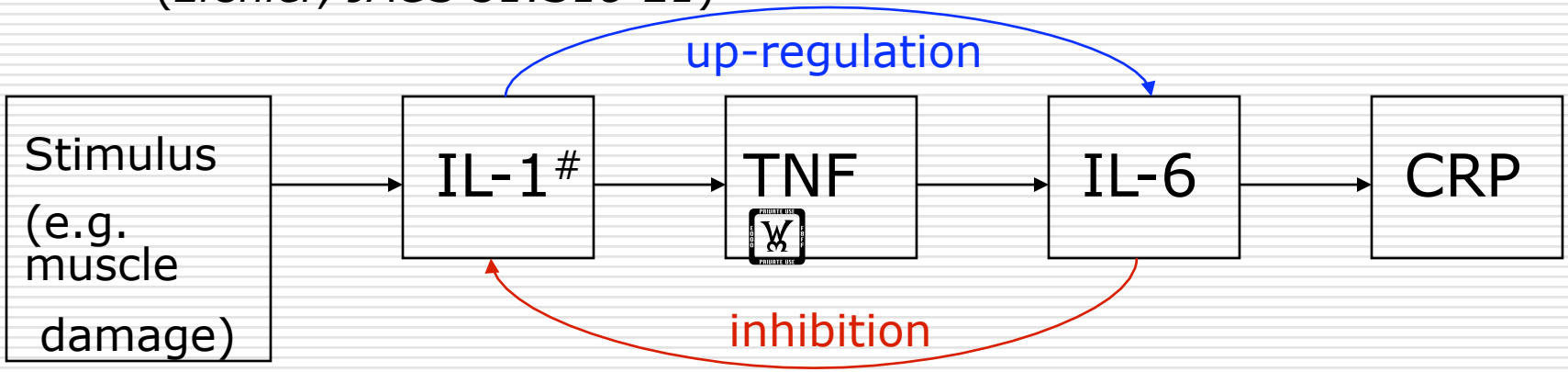
$$\underline{Y}_{ij} = \underline{\lambda}_{ij}^{T}\underline{\eta}_i + \varepsilon_{ij} \quad \text{(measurement model)}$$

$$\underline{\eta}_i = B\underline{\eta}_i + \Gamma\underline{x}_i + \underline{\varsigma}_i \quad \text{(structural model)}$$

Measurement of an aging constituent: 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

Measurement of pro-inflammation
A strategy using population data

- Model to characterize serum cytokine concentrations
  - Cons: time scale; target & functional specificity
  - Pros: serum concentrations may reflect local, generalized inflammatory regulatory activity
  - Question: Can we gather enough signal to determine the state of activation of the regulatory system & how it might be modulated?

Bandeen-Roche, Ferrucci, Walston, Huang & Semba, 2007

Population data: InCHIANTI

Ferrucci et al., JAGS, 48:1618-25, 2000

- **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
  - Here: baseline evaluation

Measurement of Pro-Inflammation
Surrogate measures, validators

- **Inflammation –7 cytokines/acute phase prot.**

  IL-1b, IL-1RA, TNF-α, IL-6, CRP, IL-18, TGF-β

- **Health consequences**
  - **Mobility – z-score average**

    Usual & rapid speed; muscle power; range of motion; neurological intactness
  - **Frailty – criteria of Fried et al., 2001**

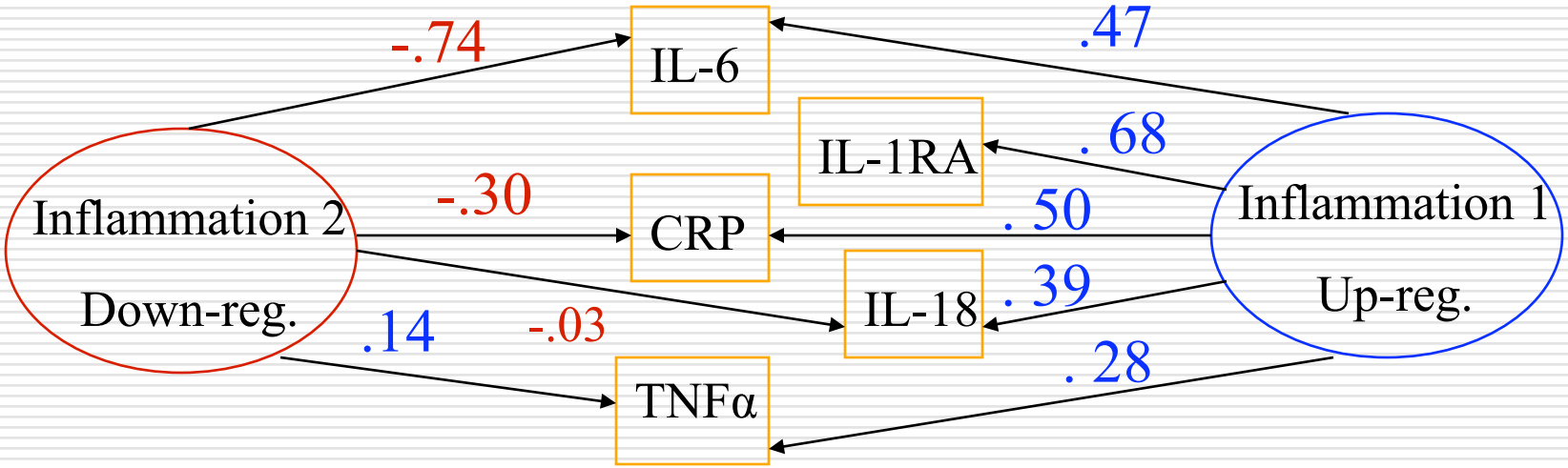
    Weight loss, exhaustion, low physical activity, weakness, slowness

- **Confounders**

  Age, gender, history of: cancer, cardiovascular disease, diabetes, smoking

Results

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



IL-1b, TGF-β coefficients < .10

Is there Value Added?
InCHIANTI findings

- *YES!*

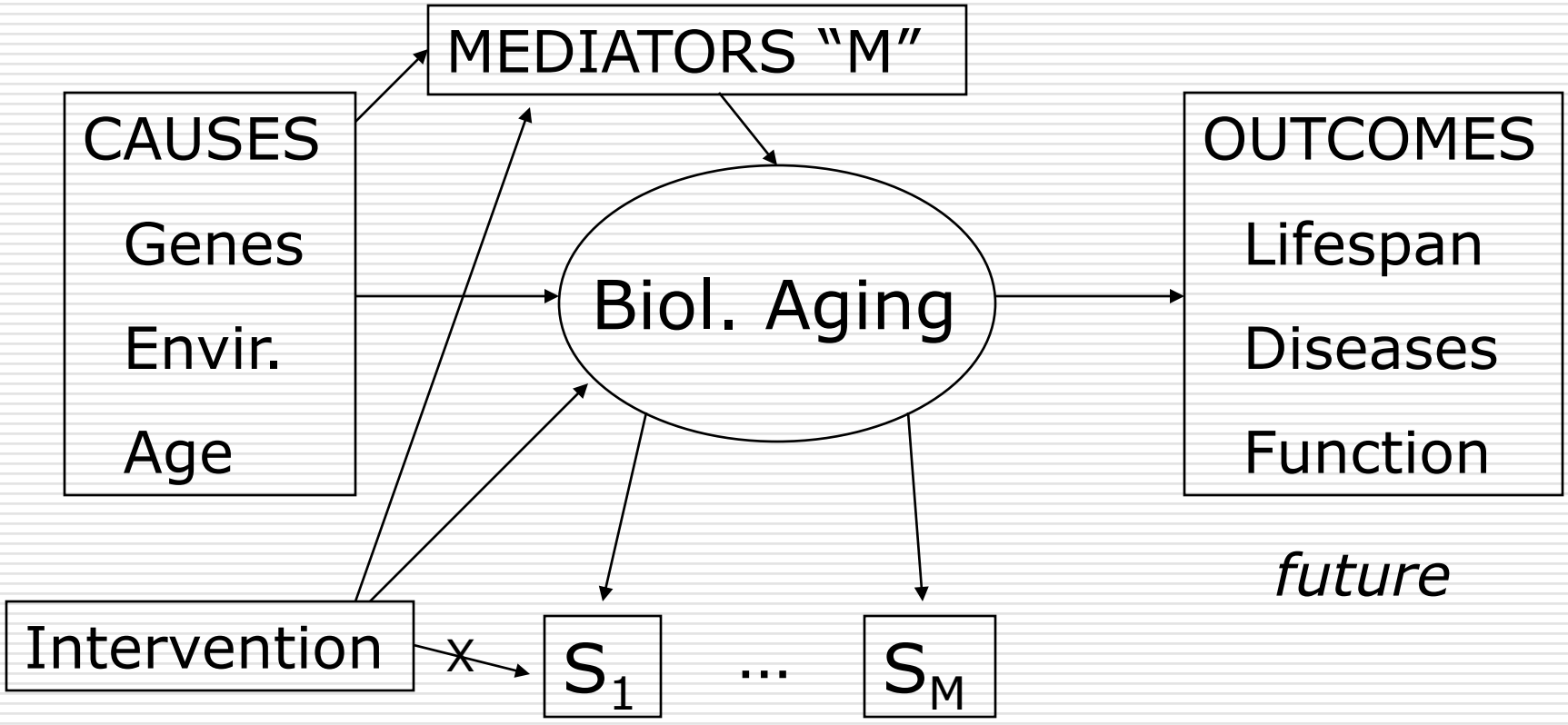
- Independent of age, sex, smoking, diseases:
  Up-regulation associated with
  - Worse mobility functioning *[~ -.1 effect size]*
  - Heightened frailty prevalence *[by ~ 30% odds]*

- "Up-regulation" is specific, sensitive for worse mobility
  - No individual cytokine adds to prediction
  - Up-regulation affords superior prediction over individual cytokines
  - Intriguing down-regulation specificity to frailty criteria of weight loss, weakness

A thorny, subsequent scientific issue:

How to ensure intervention upon ‘aging’ or ‘health,’ and not only its markers?

Symptoms, Causes, Consequences
Conceptual Framework



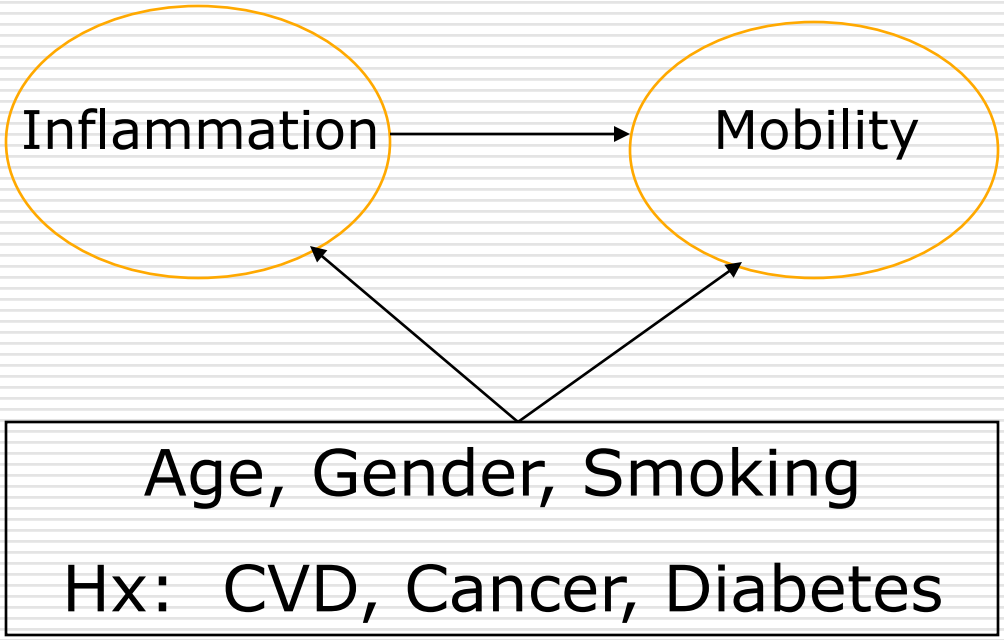
SURROGATES

How to tell whether a thing causes a subsequent thing?

Does pro-inflammation cause bad mobility?

- 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*

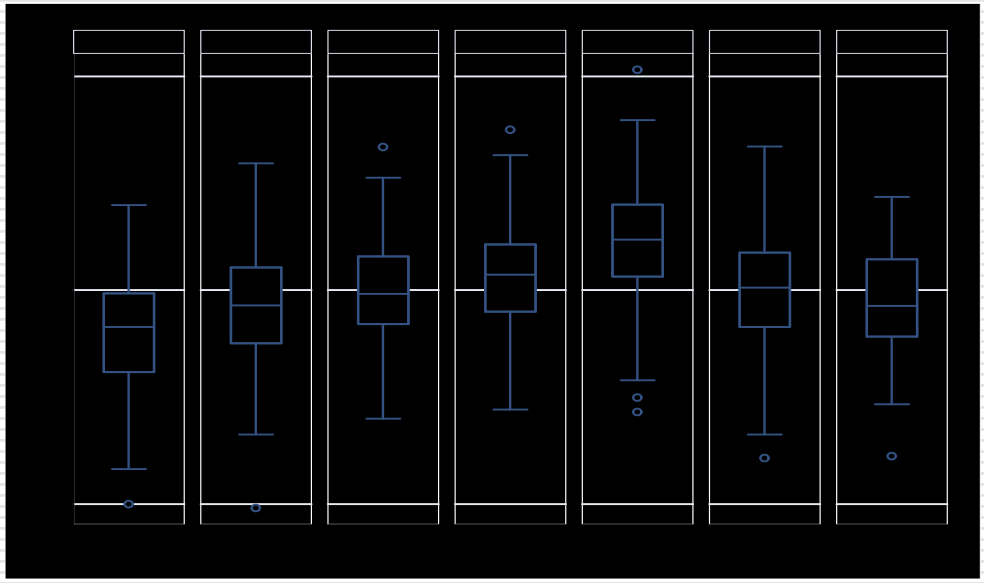
Toward "causal" inferences?



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

Propensity Score Model
Ages 20+

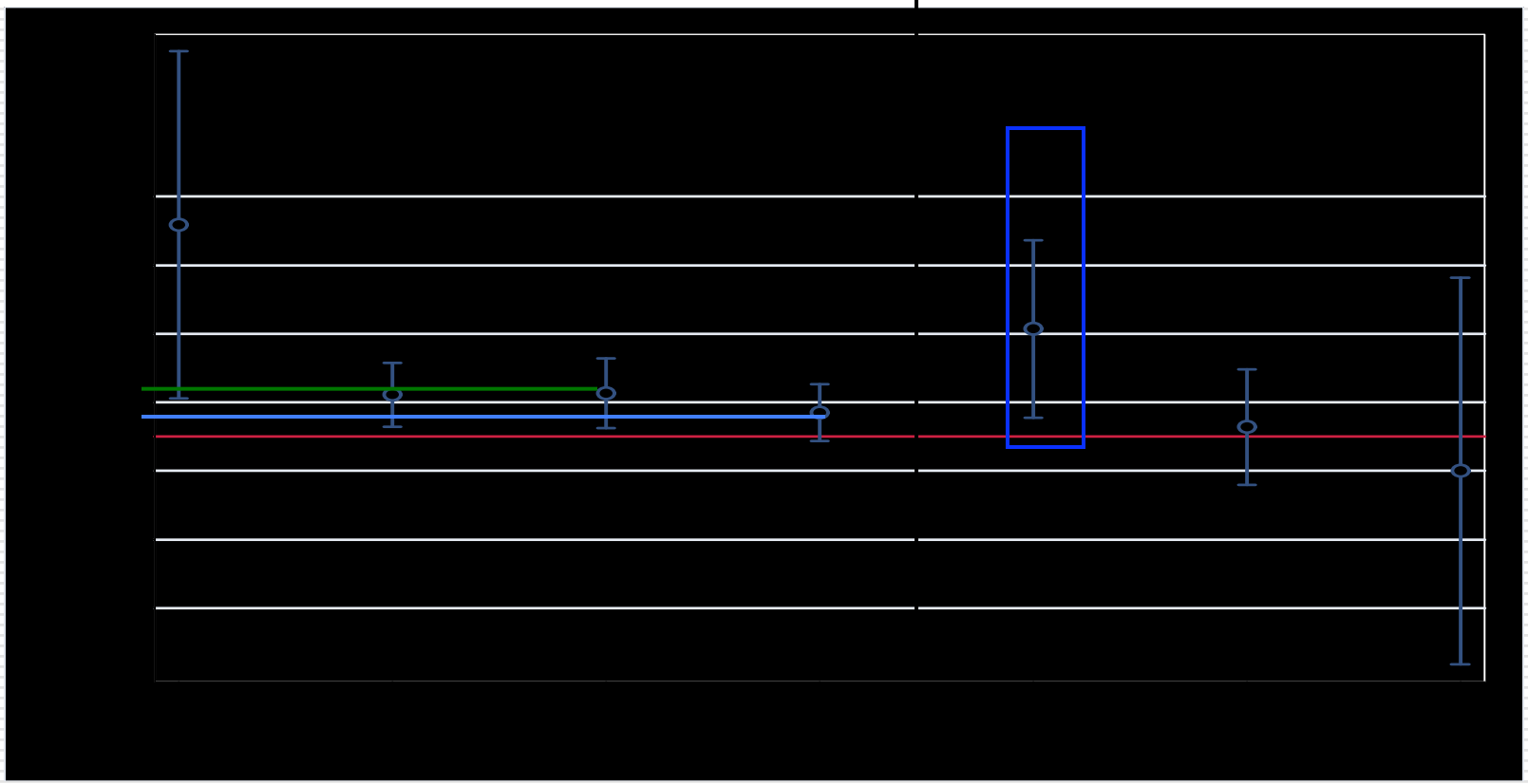
- I_1 ~ age, cancer hx, CVD hx
- I_2 ~ age, male, diabetes hx, smoking hx



I_2 (down regulation), by prop. scores

Inflammation Effects (Summary 2)

Ages 20+



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

Summary

- A paradigm for aging measurement from the "phenotype" end
  - Principles: validity
  - Conceptual framework: latent variables
  - Methodology: latent variable modeling
- Reasoning and analysis to distinguish "causes" from "correlates"
- Role, power of quantitative science in biomarker development

Implication
Measuring 'aging' via biomarkers

- Important
  - Basic research: Does "aging" vary in humans?
  - Translation: An intervention target
- Timely
- Underway: Alliance for Aging Research Panel
  - Leading aging researchers, policy makers
  - Biomarkers of Aging Initiative

Biological Aging in Humans
Validity of the premise?

Aging is a distinct biological process that varies among individuals, is measurable, and can be beneficially altered

Biological Aging in Humans
Validity of the premise?

- Face validity
  - Inter-individual variation: between, within species
  - Alterable: caloric restriction, etc.
- Construct elements
  - Multiple concurrent derangements
  - Coincident (nonlinear) decline over time
  - System-, cause-specific

Plan: Biomarkers of Aging
Step 1: Biomarker prioritization

- **Person-level**: Lifespan; disease; performance: status, rate of decline; QOL; physical activity; vital capacity
- **Integrative functions**: reaction time; wound healing
- **Organ-level**: disease signs—sensory, bone, CVD; strength; memory; mood outcomes; glucose intolerance
- **"Biological" markers**: DNA damage; oxidative stress; lipid peroxidation; glycation; immune; fibrinogen; gene / protein expression; neuroendocrine markers
- **Goals:**
  - Validity – Interdisciplinary Science
  - Measurement quality – reliability; age-association; change

Plan: Biomarkers of Aging
Subsequent steps

- Step 2: Assemblage of **multiple**, high quality, population-based, longitudinal, **human studies**
- Step 3: **Data analysis** development, conduct
  - Infusion of construct theory into models
  - Concurrent validation as well
- Step 4: **Proof of principle**
  - Candidate indices, cross-validation
  - Utility of the whole vs. the parts; causally
- Step 5: **Dissemination**, refinement, translation

Acknowledgments

- Hopkins Colleagues

  Linda Fried, Ron Brookmeyer, Paulo Chaves, Yi Huang, Richard Semba, Jeremy Walston, Qian-Li Xue, Scott Zeger

- Colleagues outside of Hopkins

  Luigi Ferrucci, Jack Guralnik, Don Ingram, Richard Miller, Scott Pletcher

- Funding / Institutional Support

  Johns Hopkins Older Americans Independence Center, National Institute on Aging

- Alliance for Aging Research