On the Next Generation of Frailty Measures: Unification of Physiologic and Clinical Manifestations

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Gerontological Society of America
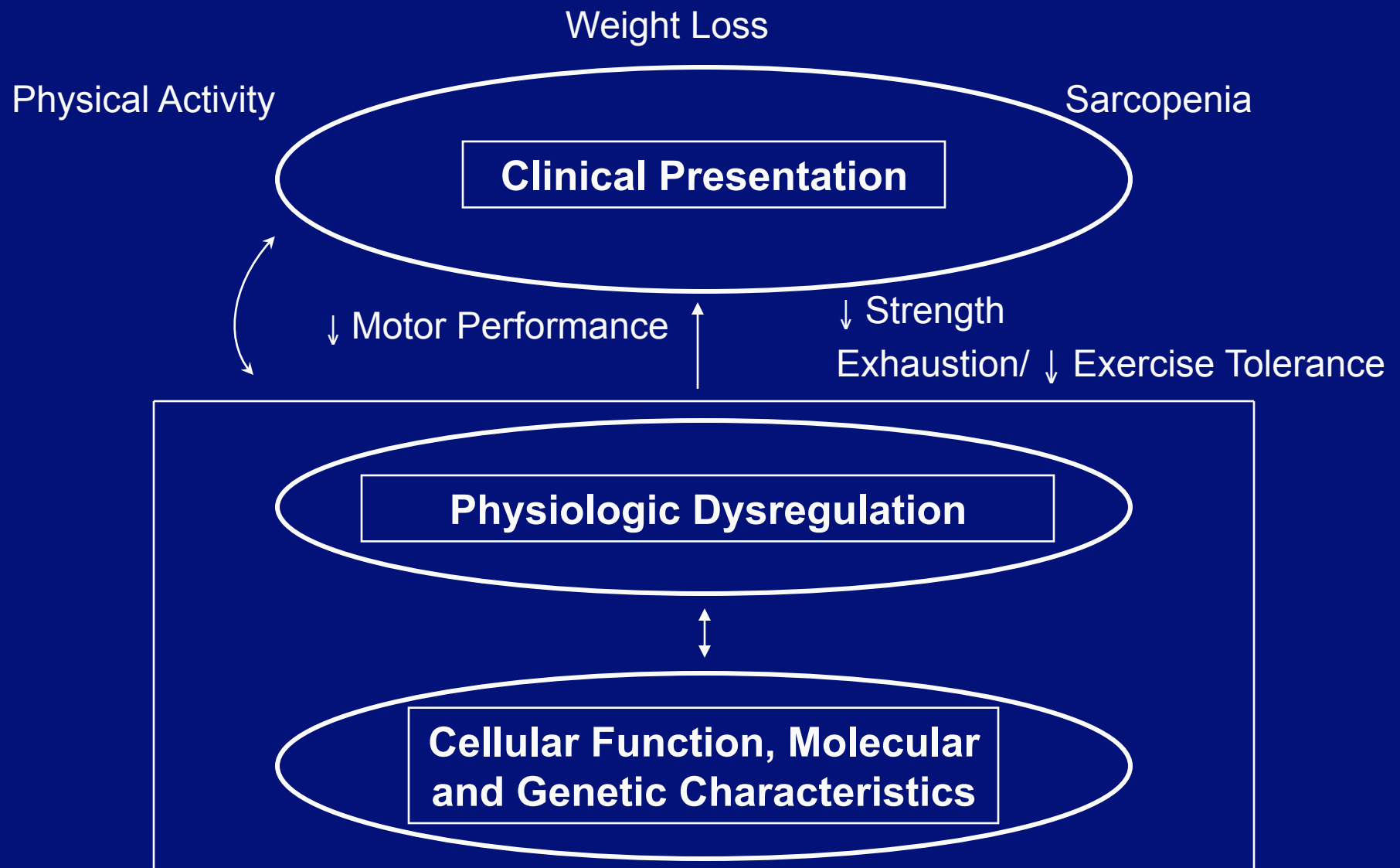**Washington, DC**
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Conceptual model for frailty

Ultimate Scientific Aims

- We argue that frailty is:
    - More than a marker of disease
    - More than severe disability
    - A *syndrome*: more than the component parts

- Aim: Advancement beyond progress made
    - Drilling down: from phenotype to etiology
    - Specificity: a measure tied explicitly to dysregulation
   - Product: a refined summary variable

Statistical Contribution to Achievement of Aims

- Long psychometric tradition
  - Validity, (reliability)
  - Framework: frailty as a latent variable
- Role of latent variable modeling?
  - Reveal underlying truth?
  - Operationalize theory?
  - Sensitivity analyses?
  - Commonality vs. uniqueness

Existence / Summary Paradigm
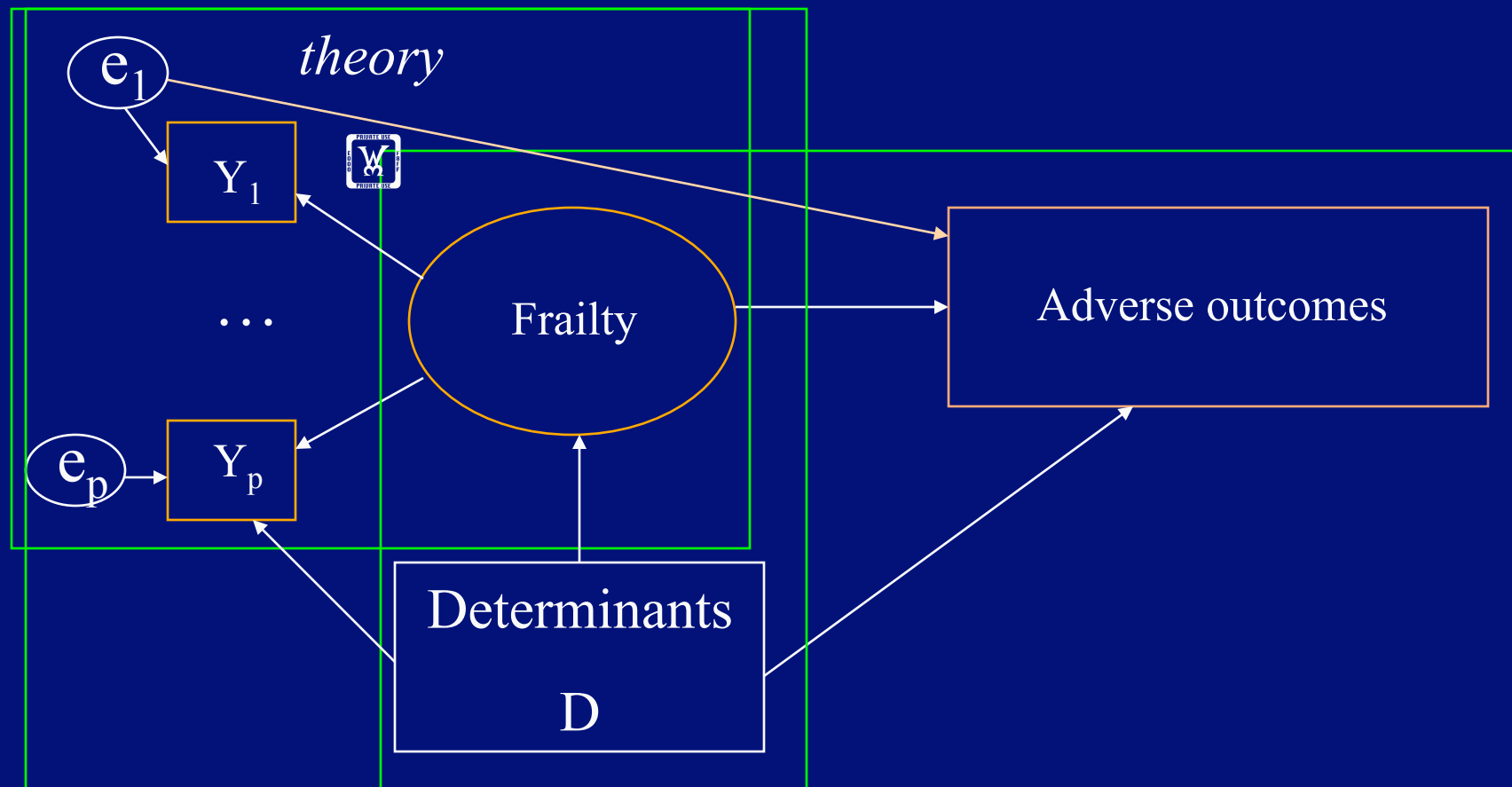
Conceptual framework
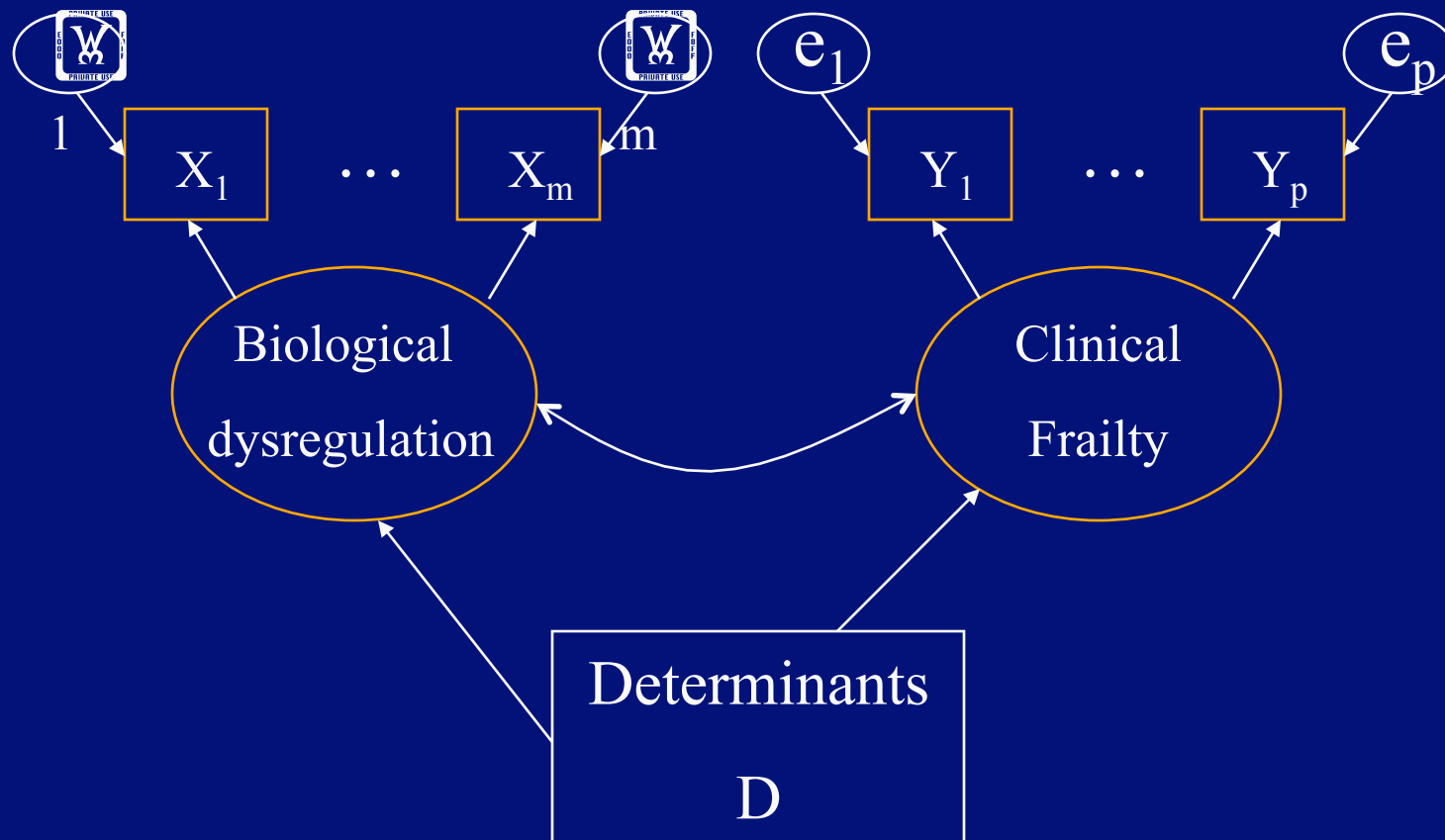
*Statistical methodology: SEM with latent variables (AMOS)*

Methods: Data
InCHIANTI (*Ferrucci et al., JAGS, 48:1618-25*)

- **Dysregulation: inflammation – 5 cytokines**
  - *IL-6, CRP, TNF-α, IL-1RA, IL-18*

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

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

Benefit # 1: Theory Infusion

- Central role: cellular repair

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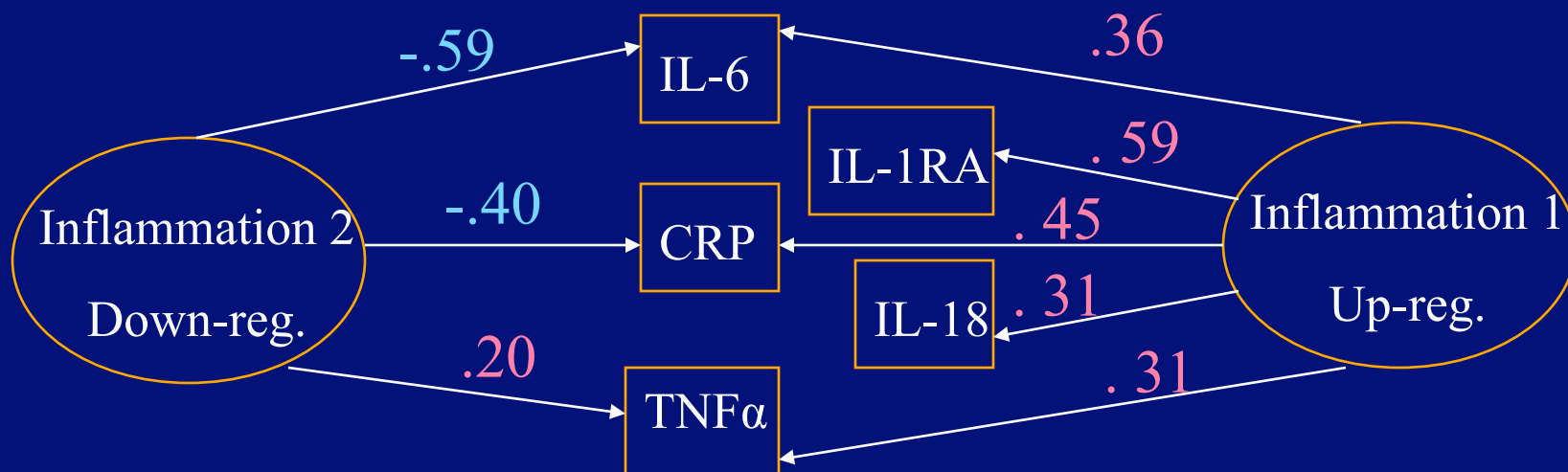 - Receptor inhibition: erythropoetin production / anemia *(Ershler, JAGS 51:S18-21)*

up-regulation

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

inhibition
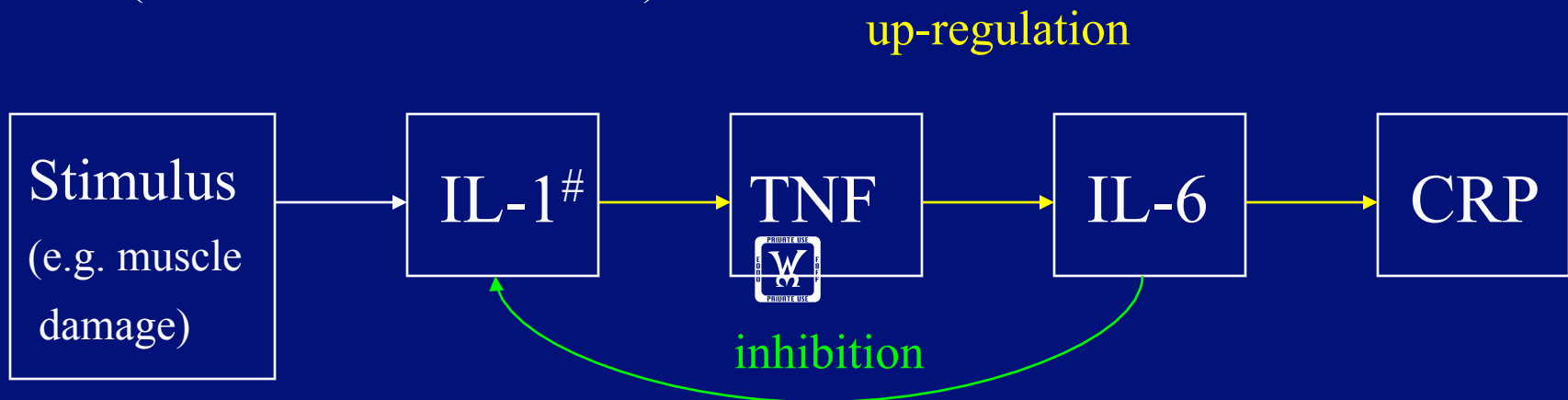
Difficult to measure. IL-1RA = proxy

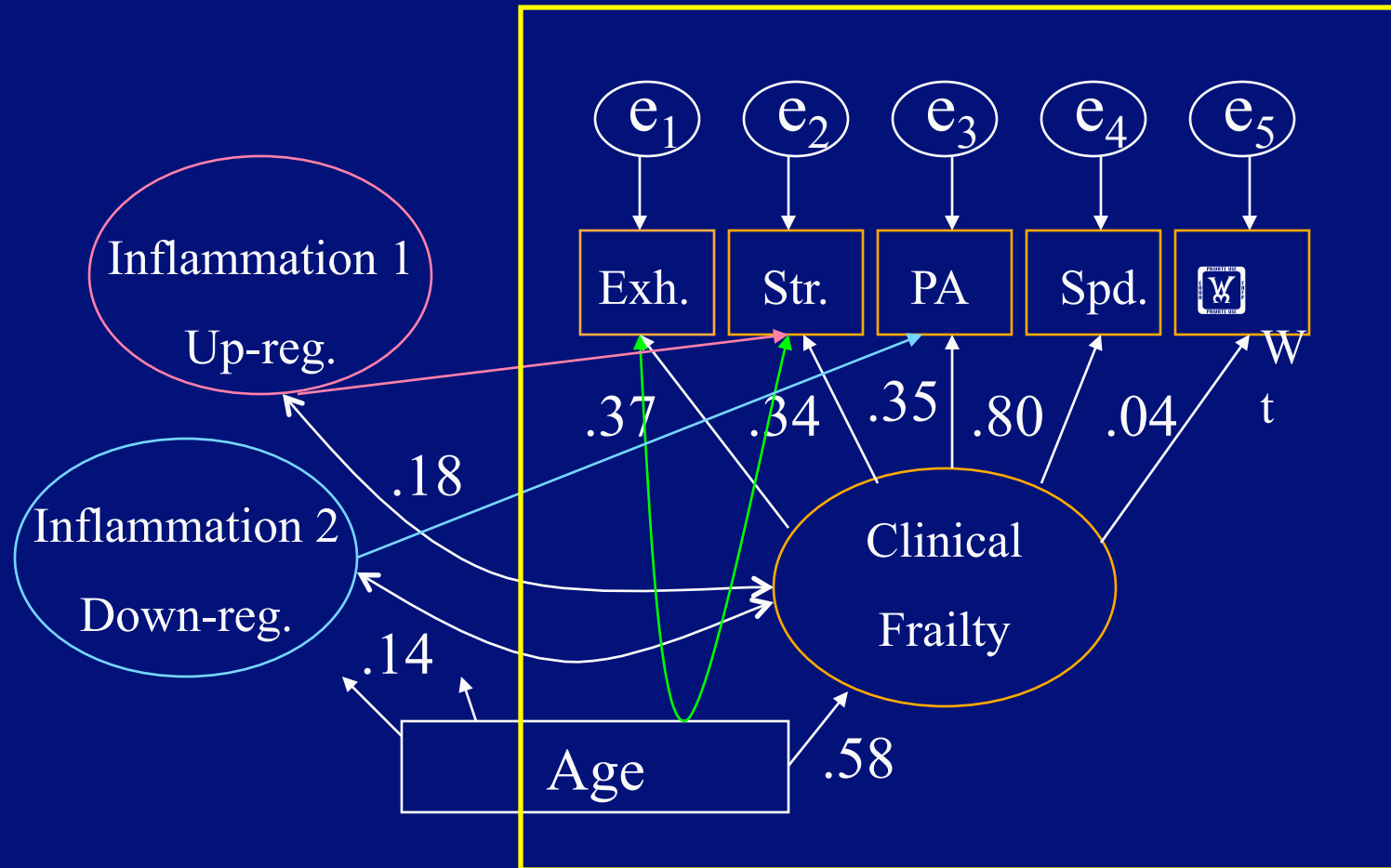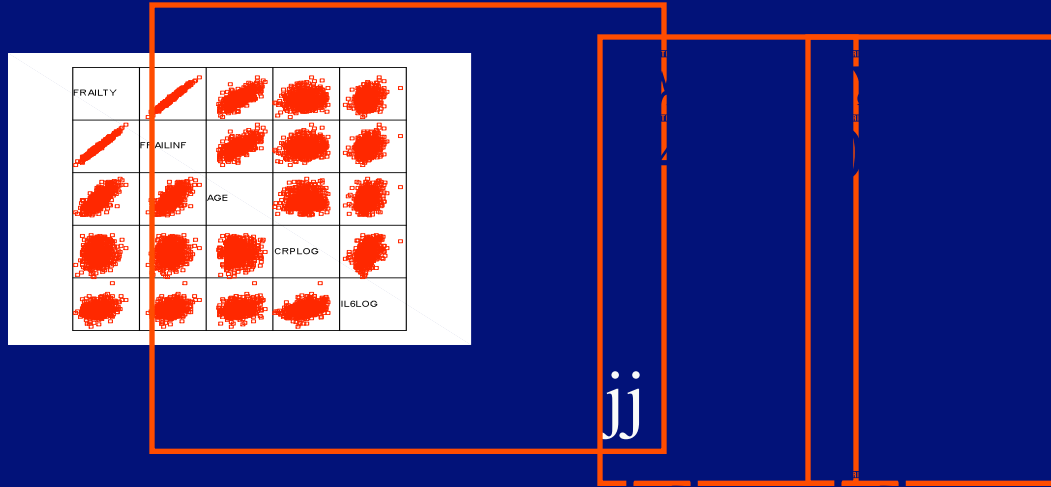# Theory infusion
Construct Definition

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

Benefit 2: Specificity

Benefit 3: Variable Refinement

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Discussion

- Demonstrated: A framework for
  - Incorporating bio-regulation into frailty measurement
  - Distinguishing risk factor effects on frailty (i) status; (ii) measurement
  - Refining frailty characterization
- Needed:
  - More explicit incorporation of theory in models
  - Best methods for deriving measures from models
  - Performance comparison

Implications

- Refined understanding of frailty and its measurement
  - Integrating systems biology
  - Increasing specificity

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