Dynamical Systems Approach to Studying Resilience in Older Adults

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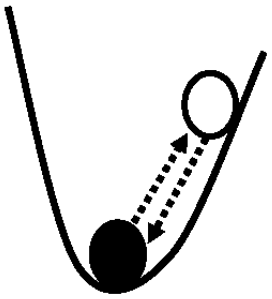
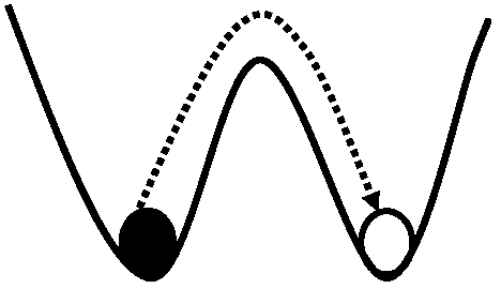
Inter-Related Properties of a Physiological System

- Stability/homeostasis
- Robustness
- Resilience



Stable System

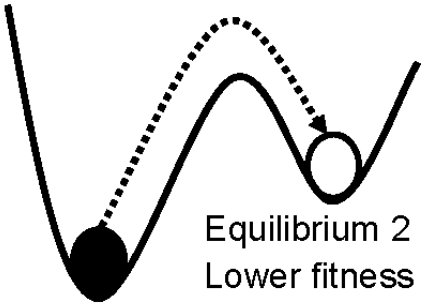
A. HOMEOSTASIS / STABILITY



Equilibrium 1
Baseline fitness

Equilibrium 2
Same level of fitness

B. ROBUST



Equilibrium 1
Baseline fitness

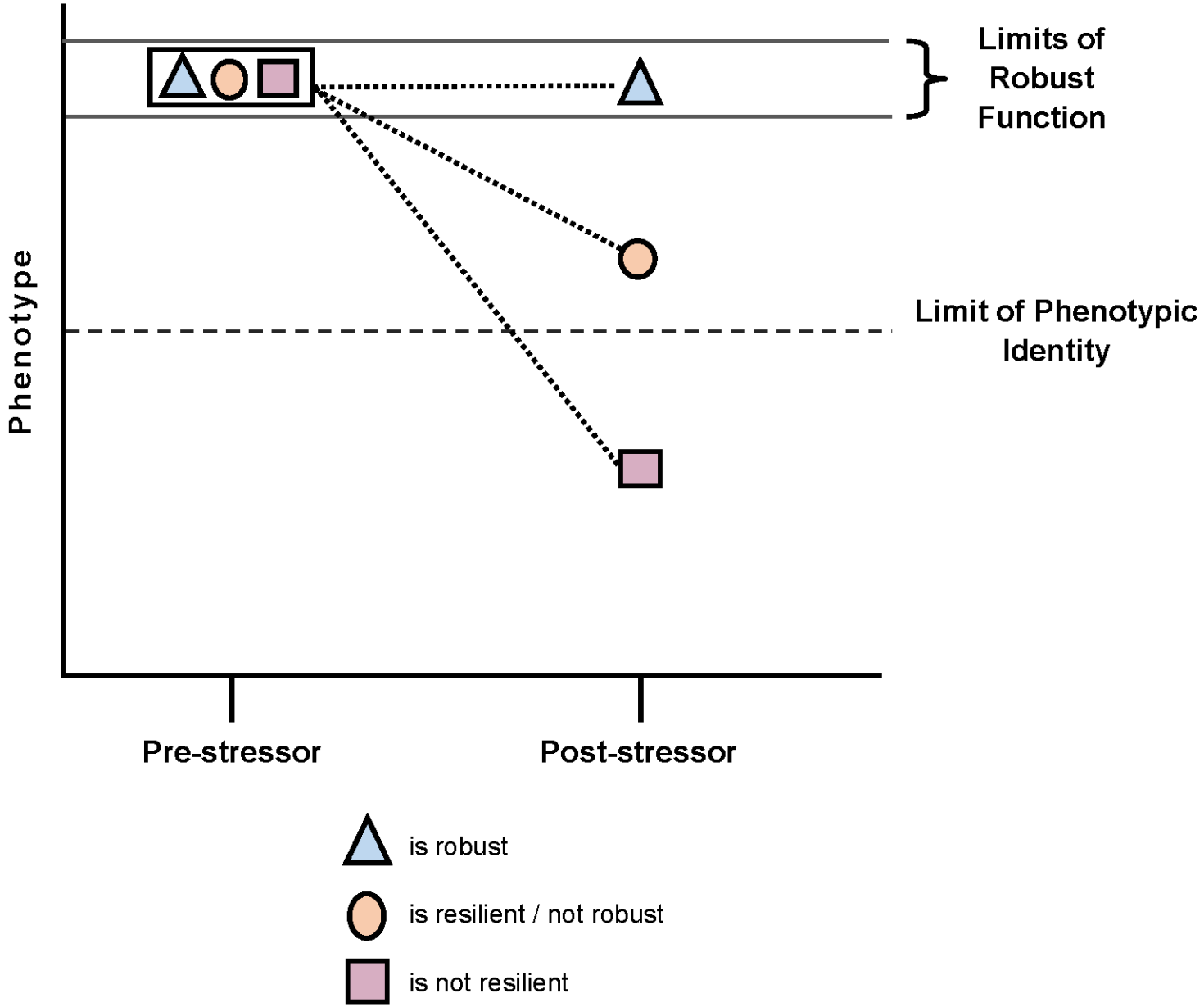
Equilibrium 2
Lower fitness but maintains phenotypic identity

C. RESILIENT / NOT ROBUST

Equilibrium 1
Baseline fitness

Equilibrium 2
Significantly lower fitness and loss of phenotypic identity

D. NOT RESILIENT


Limits of Robust Function
Limit of Phenotypic Identity
Phenotype
Pre-stressor
Post-stressor
is robust
is resilient / not robust
is not resilient

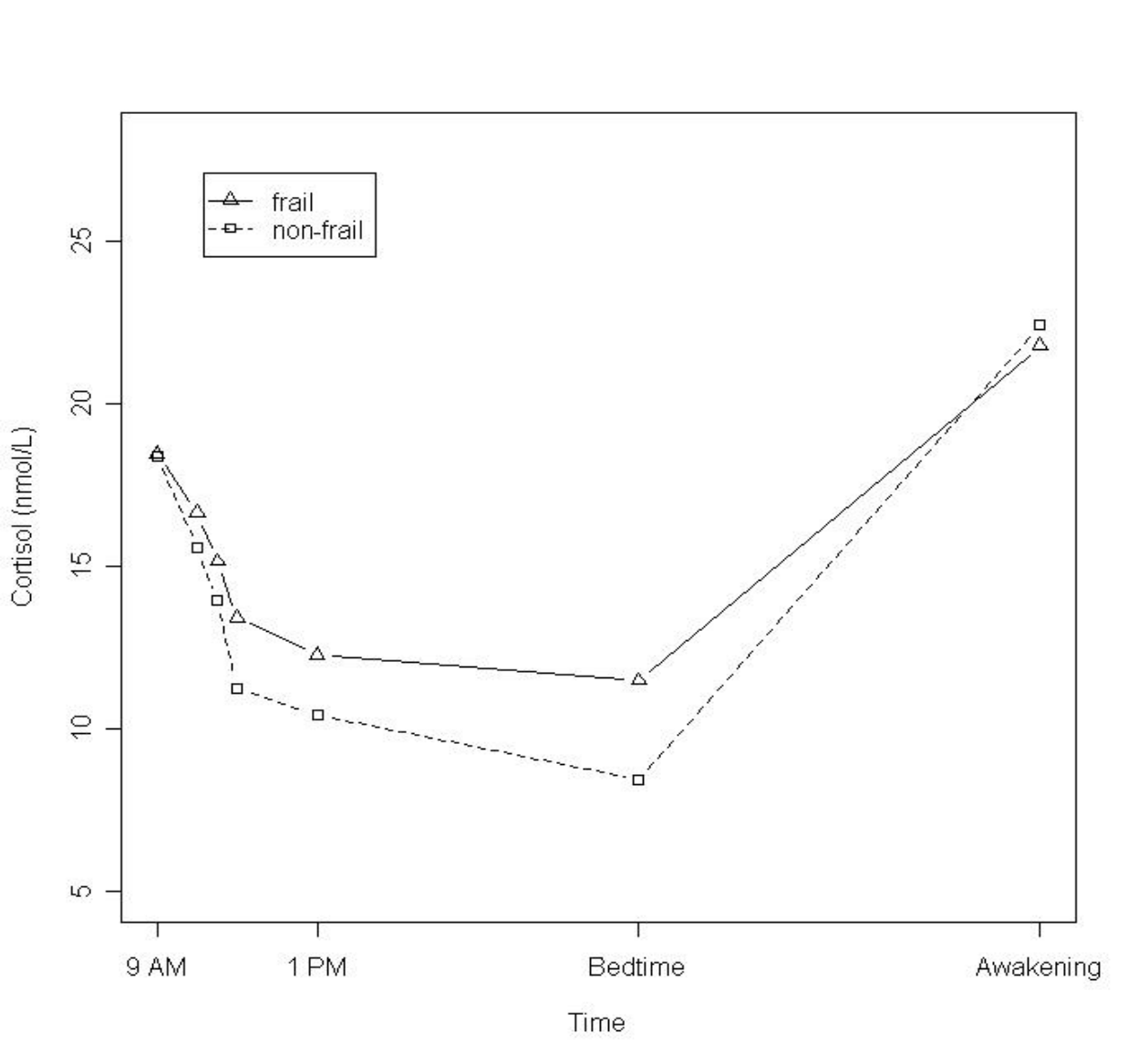
How is Frailty Related to These Concepts?

- Is it lack of robustness?
- Is it lack of resilience
- Is it something else?
- Note: robustness and resilience are w.r.t. a particular system and stimulus, whereas frailty is generally viewed as a “global” dysregulation

Dynamical Systems Approach

- Dynamical system: states of system change with time
- Autonomous and non-autonomous
- Autonomous (no external force)
  - diurnal cycles (e.g. cortisol rhythm)
  - longitudinal trajectories (e.g. biomarkers)
- Non-autonomous – a stimulus/stressor ks present

Dynamics of Diurnal Cortisol

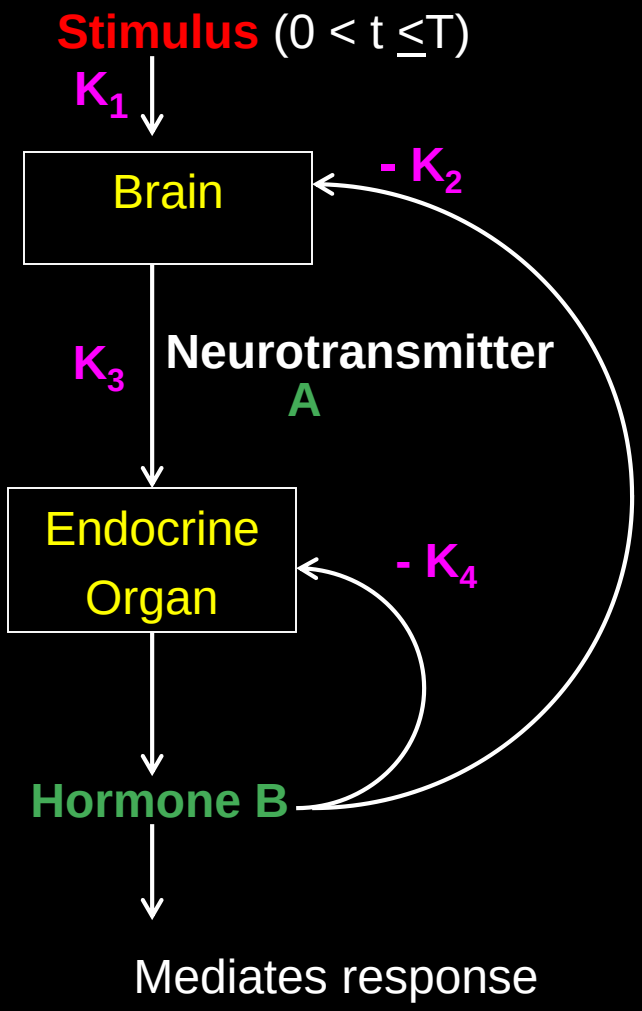


Varadhan et al. (JGMS 2007)

Stimulus-Response Paradigm

- Perturb the system with a finite stimulus and study its response (Varadhan, MAD 2008)
  - Response is classically biphasic, i.e. stimulation and recovery phases
  - Focus on magnitude and kinetics of response (e.g. characteristic time constants)

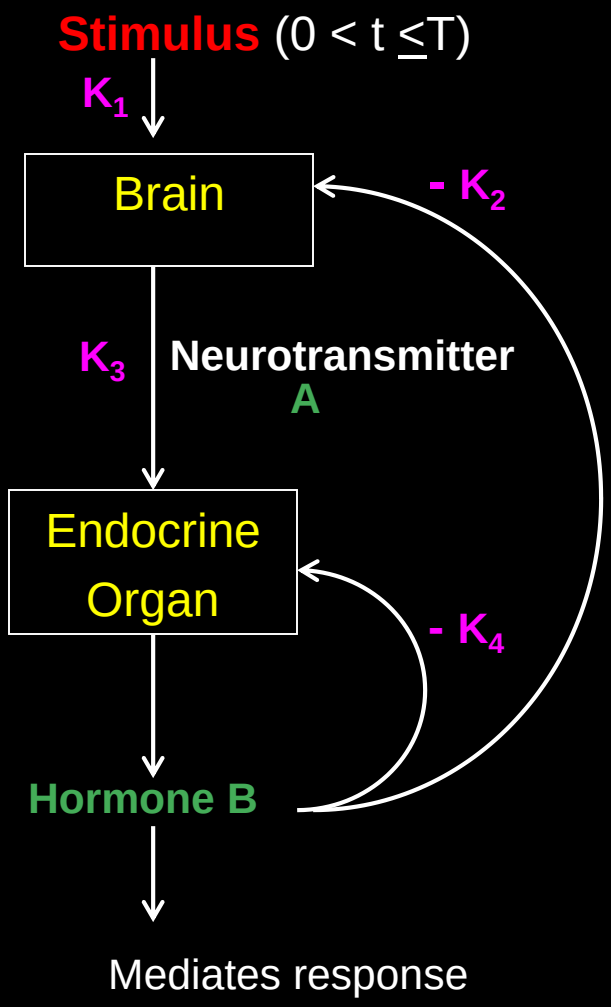
A Specific Example

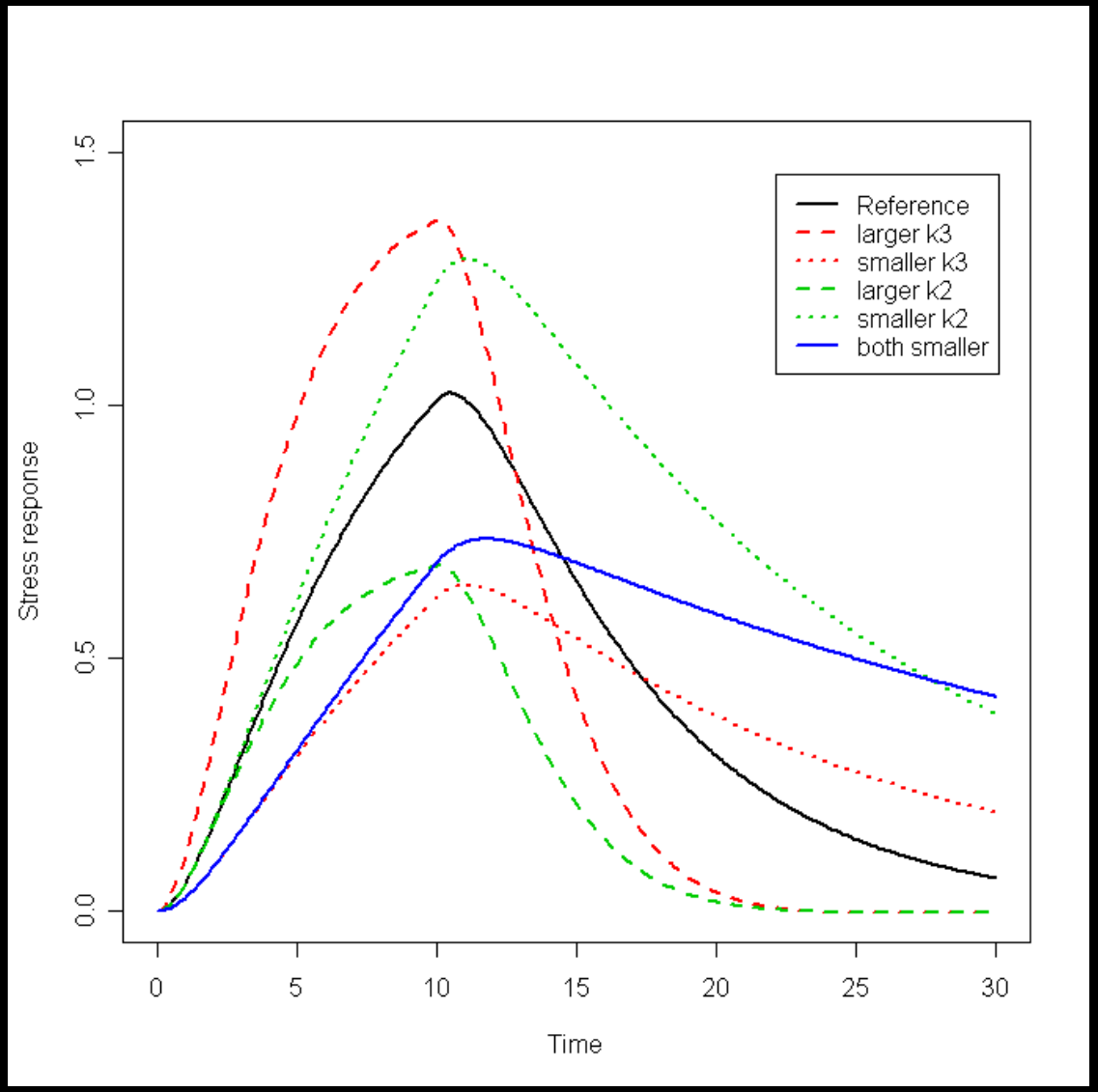


$$\frac{dA}{dt} = k_1 I\{0 < t \le T) - k_2 B$$

$$\frac{dB}{dt} = k_3 A - k_4 B$$

$$A(0) = B(0) = 0$$


Stimulus (0 < t ≤T)
K1
Brain
- K2
K3
Neurotransmitter
A
Endocrine
Organ
- K4
Hormone B
Mediates response


Reference
larger k3
smaller k3
larger k2
smaller k2
both smaller
Stress response
0.0
0.5
1.0
1.5
0
5
10
15
20
25
30
Time

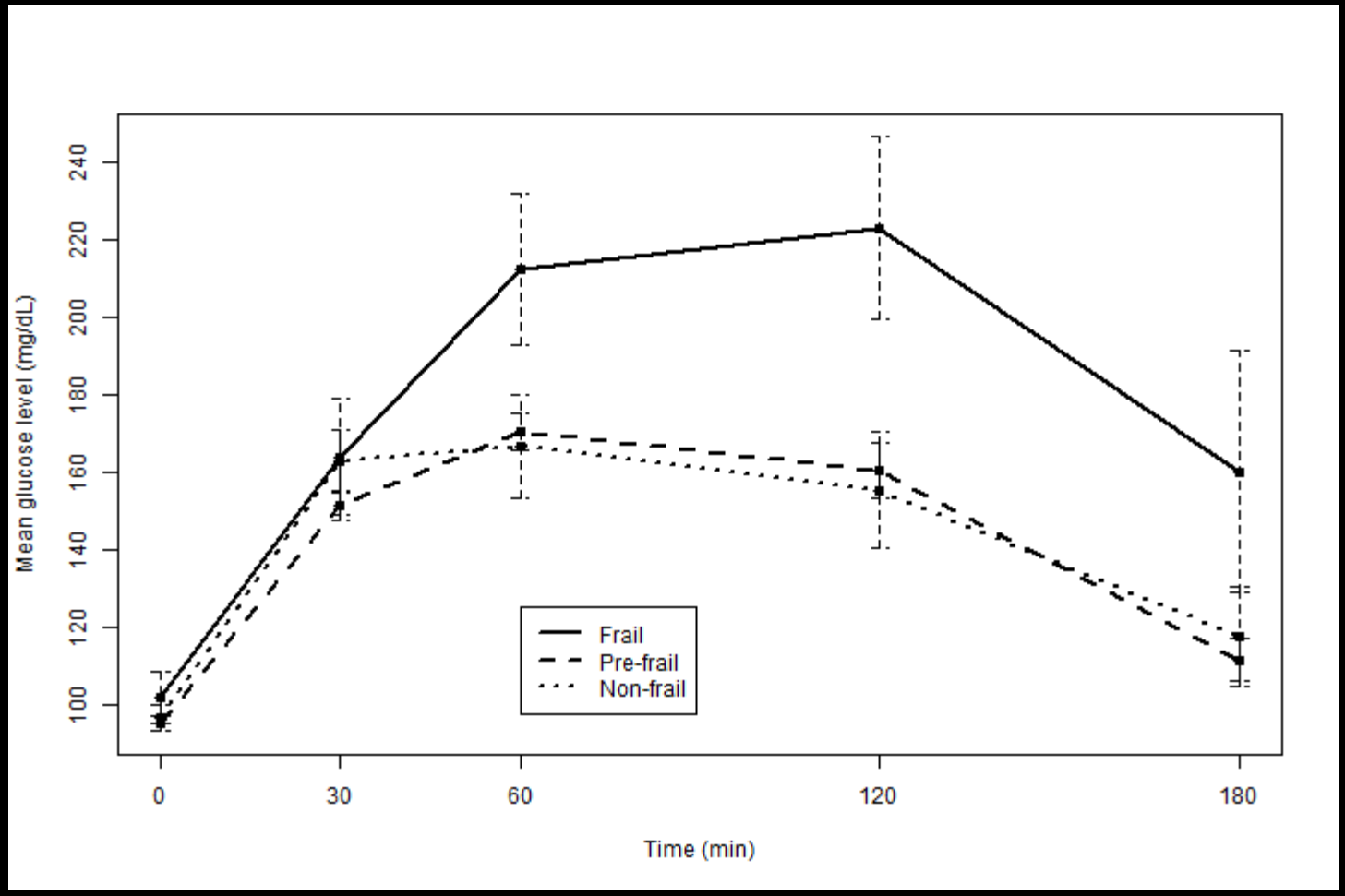
Stimulus-Response Studies in WHAS

- WHAS is a cohort study of community-dwelling women since 1994 (age 70-79 years, N=436)
- Stimulus-response studies in 2008-09 on a subset of survivors (age 84-95 years)
  - Glucose tolerance test
  - ACTH stimulation test
  - Magnetic resonance spectroscopy of PCR kinetics in skeletal muscle
  - Influenza vaccination
  - Low-level activity

Glucose Tolerance Test

- Response to 75-g oral glucose (measure blood glucose, insulin, ghrelin and leptin levels at 0, 30, 60, 120 min)
- To detect whether impaired glucose metabolism is implicated in frailty
- Frail = 9; prefrail = 17; nonfrail = 47 (N=73)

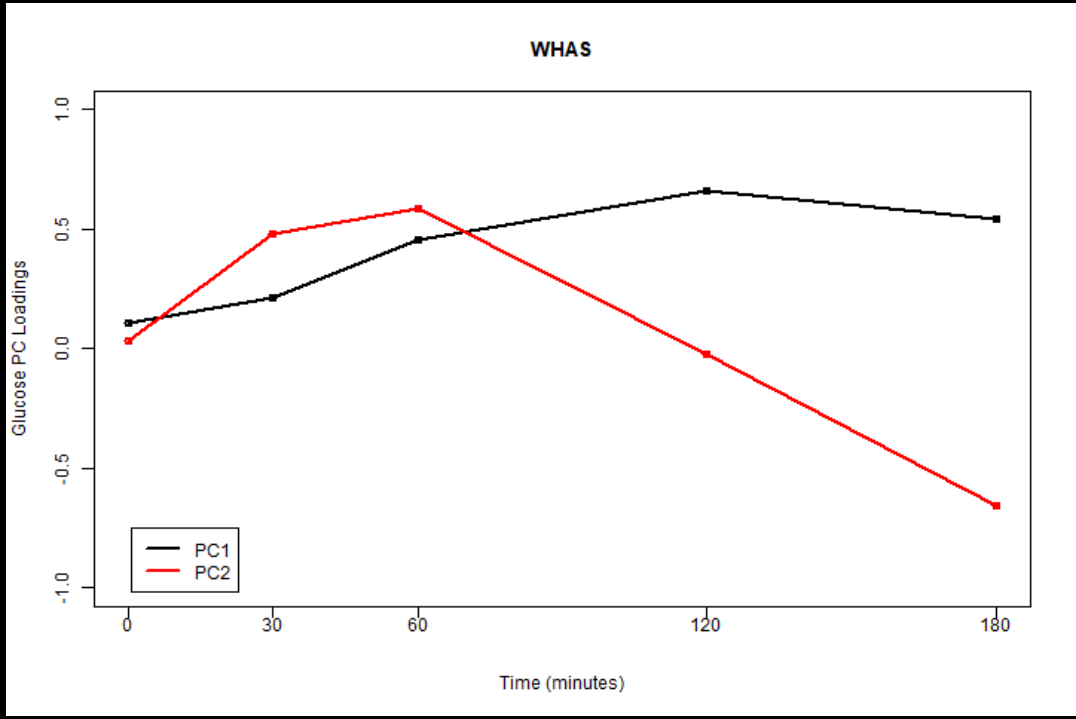
Glucose Levels by Frailty Status



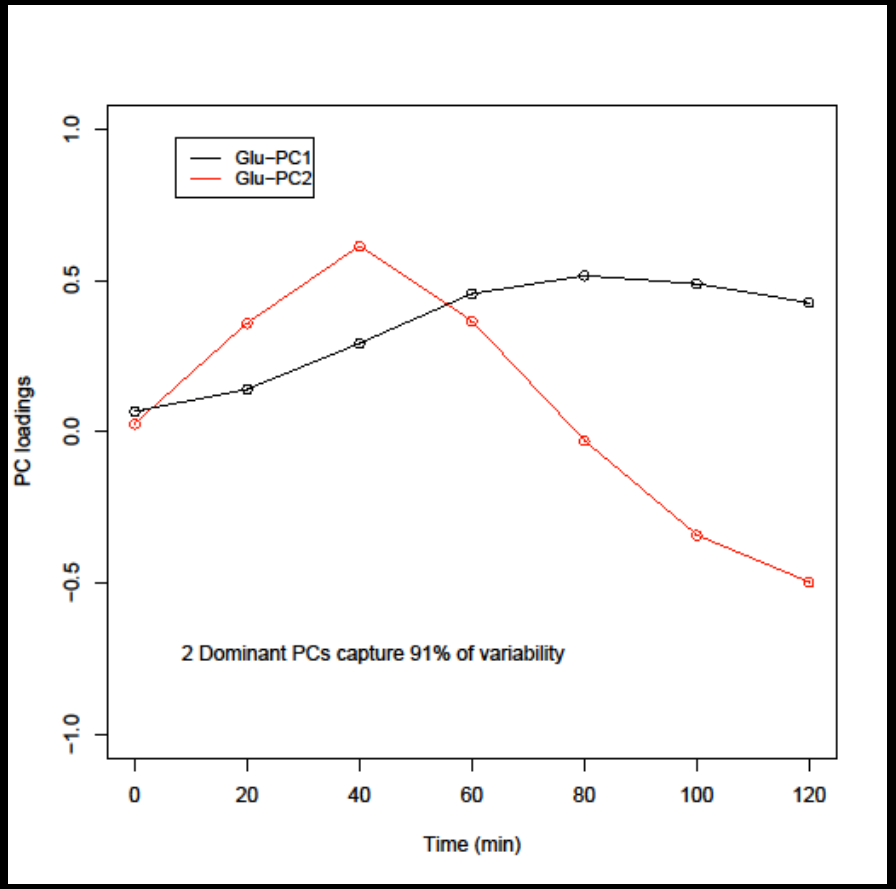
Functional Principal Components

- To parsimoniously capture the temporal variability in dynamic response
- $Y_i(t_j) = f_i(t_j) + \epsilon_i(t_j)$
  - $\epsilon_i(t_j)$ = measurement error + high-frequency oscillations > K
- $f_i(t_j) = \sum_{k=1}^{K} U_{ki}\, \varphi_k(t_j)$
  - where $\varphi_{k(t)}$ are basis functions (PC loadings); U_{ki} are random coefficients (PC scores)
- K = 2 is often sufficient

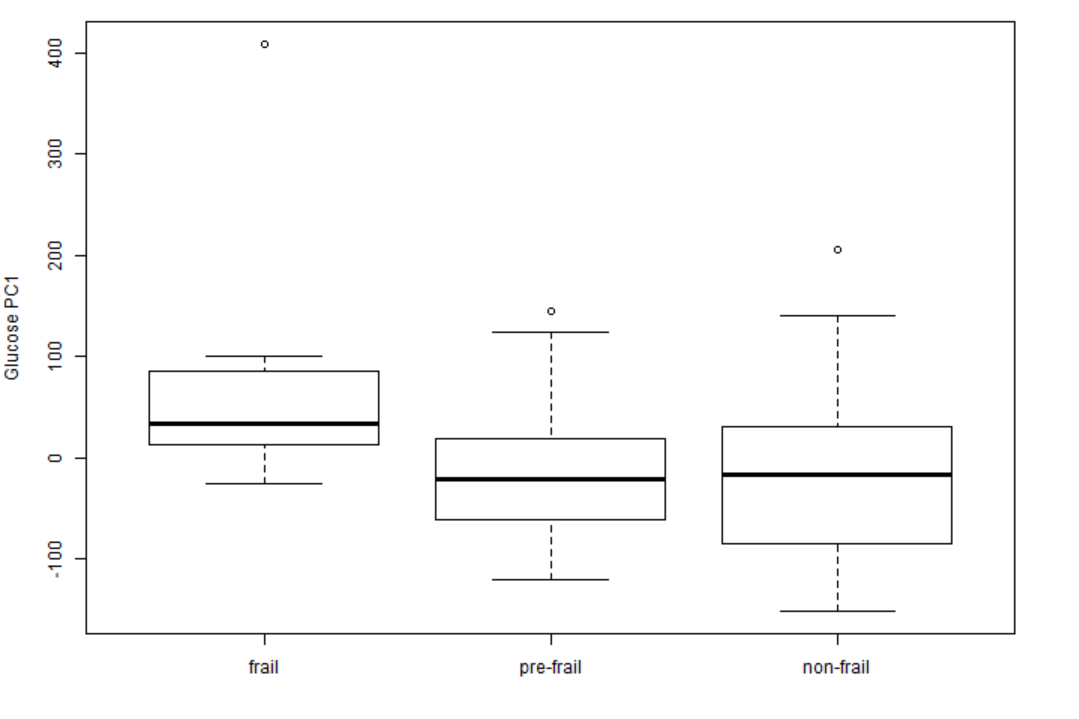
PC Loadings for Glucose in WHAS



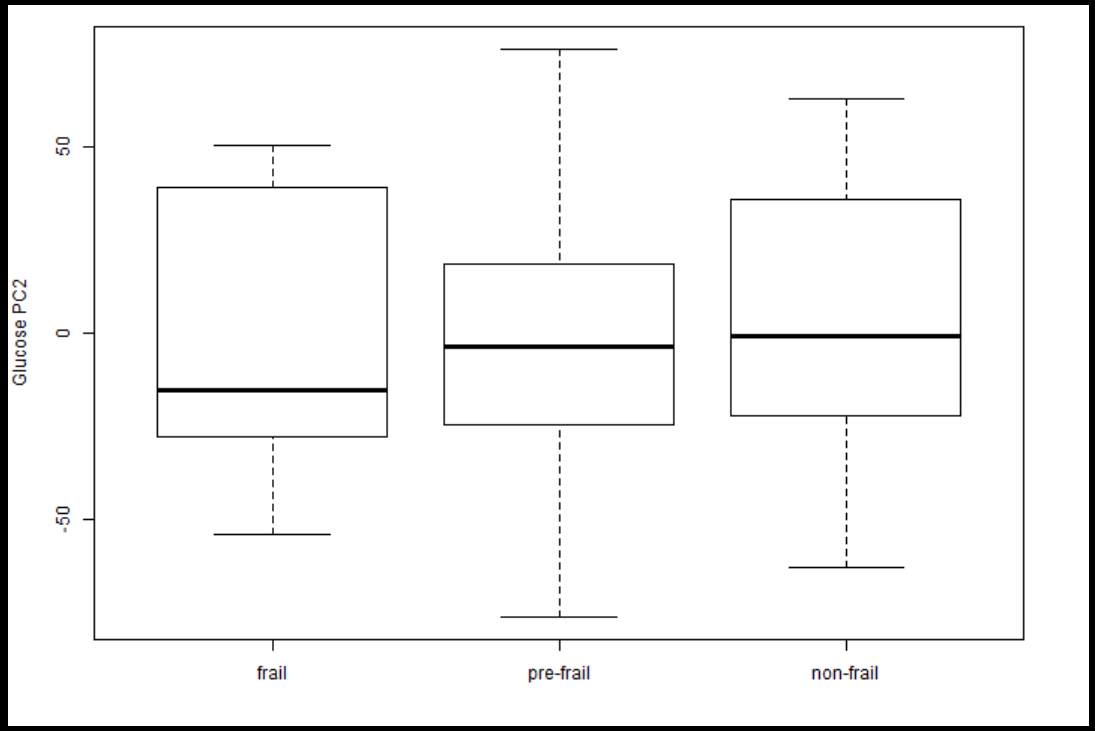
PC Loadings for Glucose in BLSA



First PC by Frailty Status



Second PC by Frailty Status



Variability

- Two types of variability: intra-person and inter-person variability
- Within person variability: low-frequency versus high-frequency variations
- Often, high-frequency variations are indicative of reactive tuning (e.g., heart-rate variability, gait pattern variability)
- 1/f spectral pattern indicates robustness
- Variability versus complexity

Variability

- Inter-person variability is an essential aspect of aging: the Anna Karenina principle!
  - "Happy families are all alike; every unhappy family is unhappy in its own way"
- Between-person variability may be partly due to increased within-person variation (dysregulation of homeostatic controls or loss of complexity)
- "Gerentropy"

Characterizing Variability

- Spectral analysis for within-person variability
- Nonlinear random effects (hierarchical) models for both types of variability
- Model parameters vary across groups of individuals
- Different parameter distributions for non-resilient and resilient

Some Important Considerations

- What is the goal of studying resilience?
- Which physiological system to study?
- Which stimulus to apply or study (controlled versus natural)?
- Which responses to measure?
- Should we consider multi-system interactions?

Some Important Considerations

- Design of experiment
  - selection of subjects
  - strength and duration of stimulus
  - sample collection frequency
- Modeling: parametric versus non-parametric
- How to distinguish normal vs. dysregulated response?

Challenges Ahead

- We need to think critically about the utility of stimulus-response paradigm
- Will it yield novel and useful insights?
- A coherent biological framework is essential to obtain useful insights
- NIA has funded animal-model studies to develop “assays” (stimulus-response experiments) for measuring resilience

Challenges Ahead

- Experiments are intensive and involve significant burden for older adults
- Decreased participation of frail + increased variability of responses → low SNR
- Is it feasible to do these experiments on a large scale?
- Animal models can yield useful insights but transportability is an issue

Thank You

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Integration of Short- and Long-Term Dynamics