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New Light on an Age-Old Issue

Heather E. Whitson^{1,3}, Carl F. Pieper^{1,4}, and Harvey J. Cohen^{1,2}

¹ Center for the Study of Aging and Human Development, Duke University Medical Center, Durham, NC

² Department of Medicine, Duke University Medical Center, Durham, NC

³ Geriatrics Research Education and Clinical Center (GRECC), Durham VA Medical Center, Durham, NC

⁴ Department of Biostatistics and Bioinformatics, Duke University, Durham, NC

Abstract

In this issue, Varadhan and colleagues propose a methodologic framework that seeks to quantify impaired resiliency in dynamic systems underlying the frailty syndrome. We view this work, which is based on modeling stimulus-response data, as an exciting expansion of longstanding theories of age-related decline in physiologic reserve across systems. We outline ways in which this methodology might make substantial contributions in frailty research and clinical practice, and we discuss potential obstacles in its operationalization.

Varadhan and colleagues present a compelling framework for understanding and quantifying the loss of physiologic resilience that many researchers postulate to be the key factor underlying frailty (Varadhan et al., in press, this issue). The model is an extension of the longstanding notion that organic systems undergo a progressive constriction of homeostatic reserve with age (homeostenosis) and that this lost reserve is manifest by the organism's increased vulnerability to perturbations. The concept that the organism's lack of resiliency reflects maladaptive responses, dysregulation, and diminished complexity in dynamical systems at the molecular, cellular, and physiologic level is not new. The fundamental concept was espoused by Selve in the 1930s¹ and Fries in the 1980s² and subsequently applied to general clinical situations³ as well as specific disease-related stressors⁴. What *is* novel about the proposed framework is its potential to quantify the nature of these age-related changes in model systems.

If the mathematical models presented here can be operationalized to produce accurate dynamic response curves for important physiologic systems, the framework has exciting clinical applications. For example, stimulus-response testing could identify patients who have abnormal responses to physiologic challenges, yet appear robust in the absence of perturbation. These patients are important to identify because they may be poor candidates for elective surgery or aggressive therapy and excellent candidates for interventions to reverse frailty or prevent functional decline. Indeed, we have previously noted that the research definition of frailty (physiologic vulnerability which may or may not be associated with overt disability) does not equate perfectly with the conventional clinical image of frailty (a feeble-appearing elder)⁵. We have proposed that frailty should be viewed as a spectrum that encompasses pure physiologic vulnerability as well as the obviously decrepit state, and we have noted that one short-coming of most frailty indices is that they may under-detect the important subclinical portion of the spectrum⁵.

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The stimulus-response framework presented here has the potential to refine the current understanding of frailty in other important ways. First, there is a lack of consensus about the best theoretical conceptualization of frailty. Varadhan et al. are proponents of the notion that frailty is a syndrome with a rather specific phenotype⁶, while other groups have operationalized frailty based on deficit accumulation, demonstrating that a much less specific ‘count of what’s wrong with a person’ is similarly associated with risk of adverse outcomes^{7, 8}. It would be informative to compare the dynamic response curves of individuals characterized as frail by the two strategies. Perhaps the biologic underpinnings of these distinct conceptualizations of frailty are more similar than different.

On the other hand, dynamic response curves may refine our understanding of frailty by identifying sub-categories of frailty based on different degrees of impairment in various physiologic systems. Although systems biology assumes mutual interactions among diverse systems, it is possible that a person could lack resiliency to certain stressors, but be robust in the face of others. We imagine one patient whose hemodynamic response system is impaired such that he is unable to regain equilibrium after even a modest amount of blood loss, and we imagine a second patient whose immune system is impaired such that her inflammatory response to antigen is dysregulated. Both patients are at high risk of adverse surgical outcomes, but the danger for Patient #1 is hemodynamic collapse from blood loss whereas the danger for Patient #2 is sepsis. The ability to evaluate which systems contribute most to a patient’s innate vulnerability has practical implications for management and theoretical implications for advancing frailty research.

Despite exciting advances that could result from the proposed framework, there are issues that may hinder its implementation. A major challenge is identifying appropriate physiologic systems for study, especially since multiple mechanisms have been implicated in the development of frailty^{9–12}. An ideal system would play a critical role in maintenance of equilibrium, yet be simple enough to be characterized and modeled mathematically. This requires 1) a full understanding of how the system operates (including feedback and redundant signaling), 2) the ability to measure important parameter markers accurately and relatively non-invasively, so that experimental measurement itself does not introduce perturbation and 3) a large number of datapoints, measured almost instantaneously to capture the magnitude and directionality of changes.

Because controversy exists regarding the theoretical construct of frailty, we strongly agree with the authors that the preferred method for determining normal versus abnormal dynamic response curves is based on physiologic understanding and statistical interpretation of data, rather than pre-designation of frail and non-frail subjects. However, the preferred approach requires a system in which all key model parameters can be understood and analyzed. While the authors provide an elegant estimation strategy for use in a simple system, the estimates obtained by recursive models are highly influenced by proper specification of the model¹³. Here, proper specification includes the time lag between stimulus and the various responses. While multiple measures assist in identifying such parameters, the issue highlights the need for simple systems where the stability and generalizability of the equations across stimuli, subjects, and populations can be assessed. Other estimation models may provide important clues as to the time lags and magnitude of the effects in the specification of the recursive model¹⁴. Finally, to estimate and assess the model, external stimulation is required to bring the organism out of homeostasis. The results from this artificial stimulation may differ from those obtained from a ‘true’ stressor.

There are additional ethical considerations in human perturbation research: after all, the intent of the experiment is to knock a potentially vulnerable subject off his equilibrium to determine how well - or whether - he recovers. If the experimental perturbations are minor enough to be

acceptably safe, it remains to be determined whether abnormal recovery patterns will correspond to clinically important frailty by predicting major outcomes. Due to these and other issues, laboratory and animal models may be a necessary step in further developing the framework described here. Nonetheless, the proposed framework constitutes a valuable contribution which shines a beam of light across what could be a new frontier in frailty research.

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