Published in final edited form as:
Mech Ageing Dev. 2008 November ; 129(11): 675–676. doi:10.1016/j.mad.2008.09.012.

Opinion Letter in Response to "Stimulus-response paradigm for the study of homeostatic impairments associated with frailty", by Varadan, et. al

Lewis A. Lipsitz, MD
Hebrew SeniorLife Institute for Aging Research, Beth Israel Deaconess Medical Center Gerontology Division, Harvard Medical School, Boston MA

Over the past decade, clinicians and investigators have begun to recognize "frailty" as a common geriatric syndrome associated with a high rate of morbidity and mortality, and therefore deserving of rigorous investigation. Previous work in the area of frailty has examined components of this syndrome, including muscle loss (sarcopenia) [1], elevations in inflammatory cytokines or coagulation factors [2], and cardiovascular abnormalities [3]. While these and other abnormalities may play important pathophysiologic roles, it is also possible that they are markers of underlying regulatory abnormalities that impair the integrated function of multiple physiologic systems. Since frail individuals often have multiple age- and disease-related impairments that limit their ability to meet the demands of everyday life, I view frailty as a manifestation of the degradation of multiple interacting physiologic systems that are normally responsible for healthy adaptation to daily stresses. Mathematical models that can quantify alterations in the dynamics of physiologic systems and their interactions may help characterize the syndrome of frailty and enable investigators to test interventions to prevent its onset.

In their opinion paper, Varadan and colleagues also define frailty as an increased vulnerability to stressors due to dysregulation of multiple physiological regulatory systems. They also recognize that the study of frailty requires a dynamic approach that characterizes the complex interplay between physiologic systems and how they change with age and disease. They have developed a theoretical mathematical model that represents one type of regulatory process that may become altered in frail individuals – the stimulus-response mechanism. While this model is an excellent beginning, it remains untested with real data and fails to account for other physiologic mechanisms that may degrade in frail individuals. For example, the model focuses on the timing of recovery from a single stimulus, rather than the full array of responses that might be altered in a complex dynamical system. Impaired adaptation to a physiologic stimulus may manifest not only as prolonged recovery, but also as 1) an exaggerated or blunted amplitude of response (e.g., hyperglycemia or bradycardia, respectively), 2) the emergence of periodicities (e.g., tremor, ventricular tachycardia, or seizures), or 3) the occurrence of random events (e.g., a fall, stroke, or myocardial infarction). These responses may occur within the same system that was stimulated (e.g., hyperglycemia following a glucose load) or in a different system altogether (e.g., myocardial infarction following a sympathetic stimulus).

Another limitation of the model proposed by Varadan, et. al. is that it is based on a single stimulus at one point in time, while most dynamic systems in the human body respond to

multiple stimuli repeatedly over time and on different time scales. The interactions of multiple control processes that constitute these systems result in highly complex outputs such as the time series produced by beat-to-beat heart rate fluctuations during daily activities, the moment-by-moment changes in center of pressure during standing, or the second-by-second variations in respiratory intervals during breathing. In nonlinear dynamical systems such as these, a variety of complex behaviors may emerge with properties that resemble chaos and fractals. These behaviors include self-similar fluctuations with long-range correlations across multiple time scales (e.g., normal sinus rhythm, and electroencephalographic waves) and sudden bifurcations with the emergence of new states (e.g., REM sleep or anaerobic metabolism). My colleagues and I have previously demonstrated that the complex behaviors of nonlinear physiologic systems that control heart rate, blood pressure, respiration, balance, and blood hormone levels degrade with aging and disease [4,5]. We have proposed that frailty results from the loss of complexity in the outputs of physiologic systems and that this loss of complexity leads to an impaired ability to adapt to stress. Accordingly, alternative models are needed to describe the wide variety of behaviors of physiologic systems over time and how they change with the onset of frailty.

One such model described by our group is based on a simple signaling network composed of a lattice of nodes and the bi-directional connections between them (a Boolean network) [6]. These nodes are analogous to the brain and endocrine organs, as in the model by Varadan et. al., or they could represent a series of neurons in a neural network, or substrates and products of a biochemical pathway. Each node receives input from its nearest neighbors and has a finite probability of receiving additional input from distant nodes. As is frequently observed in physiologic systems, the short- and long-range connections between nodes are “noisy”, such that communication is occasionally blocked by random noise. To process the input it receives, each node must operate according to a specific physiologic “rule” that defines its output. For example, the negative feedback rule in the Varadan et. al. model could be used to define the output of a node. Another example is the “majority rule,” which specifies that the output of each node is the same as the majority of its inputs. In our model we tested a variety of rules that represent physiologic processes and allowed each network to evolve over time. At the start, each node is randomly assigned a value of zero (inactive) or one (active), and the output of each node is added up to give the state of the network at that point in time. With each subsequent iteration, the rule determines the next output of each node and the summed state of the network. As the network model evolves over time, a time series is created. With a finite number of distant connections and a certain level of noise, we found that a simple majority rule produces complex fractal-like behavior that resembles that seen in complex time series from healthy physiological systems. Using such a model, one can demonstrate how the degradation of signaling pathways within a physiologic system can result in the loss of complexity that characterizes frailty.

To better understand the concept of frailty as a loss of adaptive capacity (or resiliency) that results from the degradation of *multiple* physiologic systems, we need nonlinear dynamical models that can reproduce the complex, fractal-like nature of healthy physiological processes and their loss of complexity in frailty. While Varadan and colleagues have contributed a sensible model of one of these systems, more work is needed to capture the complex interactions between systems that enable healthy individuals to adapt to the daily demands of life.

References

1. Lauretani F, et al. Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. J Appl Physiol 2003;95(5):1851–60. [PubMed: 14555665]

2. Walston J, et al. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities. Arch Intern Med 2002;162:2333–2341. [PubMed: 12418947]

3. Newman A, et al. Associations of subclinical cardiovascular disease with frailty. J Gerontol Med Sci 2001;56A:M158–M166.

4. Lipsitz LA, Goldberger AL. Loss of 'complexity' and aging. Potential applications of fractals and chaos theory to senescence. JAMA 1992;267(13):1806–1809. [PubMed: 1482430]

5. Lipsitz LA. The dynamics of stability: the physiologic basis of functional health and frailty. J Gerontol Biol Sciences 2002;57A(3):B115–B125.

6. Amaral L, Diaz-Guilera A, Moreira A, Goldberger A, Lipsitz L. Emergence of complex dynamics in a simple model of signaling networks. Proc Natl Acad Sci 2004;101(44):15551–15555. [PubMed: 15505227]