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Mapping the road to resilience: novel math for the study of frailty

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Abstract

Frailty stands at the nexus of geriatrics and gerontology, and requires both basic biology and clinical knowledge for its analysis. Understanding frailty difficulties much more than simply adding another outcome measure in epidemiological studies. The major challenge is the identification of multiple feed-forward and feed-back signaling pathways involved in the maintenance of biological homeostasis in complex organisms that may fail with aging. The cause of frailty and loss of resilience is probably a progressive loss of redundancy in these response patterns and connections.

Advances toward the development of a theoretical model that can potentially embrace the complexity of frailty should be highly encouraged, especially models designed to explain the biology of aging which can promote a better integration and communication between scientists who study this problem from different perspectives.

We welcome another valuable contribution from the Hopkins group on the ongoing discussion of frailty in the geriatric literature (1). After an initial period of enthusiasm when the entire aging research community was talking about it, the discussion of frailty tend to fade to a more moderate tone and has been restricted to a smaller circle of interested scientists. Understanding frailty turned out to be more difficult than simply including another outcome measure in epidemiological studies (2). Frailty, in fact, stands at the nexus of geriatrics and gerontology, and requires both basic biology and clinical knowledge for its analysis (3). It is refreshing to see that Varadhan and colleagues (1) were not intimidated by the arduous task and, on the contrary, present an advance toward the development of a theoretical model that can potentially embrace the complexity of frailty.

There are many positive aspects about this article. The most important is the recognition of the existence of multiple feed-forward and feed-back signaling pathways involved in the maintenance of biological homeostasis in complex organisms. We completely agree that the principal secret of frailty and resilience should be found in the progressive loss of redundancy in these response patterns and connections. Also of note is the suggestion that efficiency in recreating some sort of stable equilibrium after a standardized challenge --rather than by assessing simple background measures -- should be used to derive measures of frailty, with special attention to the time dimension. Indeed, there is a considerable discrepancy in the current literature between the theoretical definition of frailty as a derangement in the signaling network that maintains and regains homeostatic equilibrium and many manuscripts that define and study frailty using static measures and constructs (3,4).

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For us, as geriatricians and epidemiologists, the manuscript is somewhat too theoretical and at some points even cryptic. To be honest, this problem is mostly due to our limited background knowledge of mathematical modeling, especially concerning structural equations. However, progress in the field can only be achieved by better communication between scientists coming from different disciplines and therefore, considerable effort to translated these ideas into language more accessible to non-mathematicians could greatly advance science in this field. The strongly theoretical cast of this article also raises questions about the extent to which these models can be applied in the practical interpretation of specific experiments. There is long lasting experience in science that transposing theoretical models to clinical experiments is often made problematic by some unexpected problem or complication (5).

Of course we would therefore have preferred that Varadhan and his group (1) present a full example of how their modeling strategy can improve the interpretation of a real experiment. *In primis*, complex modeling, especially in biological fields, requires either very precise measures or huge sample size. This has become evident in modern genetic studies, for example, where it is not uncommon for genome-wide association studies to report data on 10's thousands of individuals (6). Unfortunately, our measures of biomarkers and hormones are further constrained not only by assay limitations but also by the fact that we are usually measuring concentrations at a secondary level quite far from where the action takes place. For example, energy generation and production of reactive oxygen species occur for the most part within the mitochondria; and how much these events are reflected by changes in the circulating levels of inflammatory biomarkers is questionable. New techniques of magnetic resonance spectroscopy are attempting to address this issue, but are still in developmental stage that may require years before they can be implemented (7,8).

A second, perhaps more important issue is the possibility of oversimplification. The model presented here is meant to capture one critical homeostatic strategy, which can evolve in a continuum of states but using the same basic repertoire of gambits. However, this approach violates one of the most important principles of biology: redundancy (9). It is likely that a number of alternative strategies are utilized in different individuals, which are selected based on available resources, genetic makeup, and the presence of previous impairments. An alternative approach, which has been previously proposed (10), is that homeostatic efforts can lead to multiple discrete "states of equilibrium", analogous to quantum mechanics states (Figure 1). At the top of the hierarchy of health is an ideal state that one can call "perfect health", characterized by robustness, low energy consumption and a wide array of homeostatic "weapons" available to counteract challenges to stability. Inevitably, at some point, a stressful event challenges this ideal stability beyond its ability to compensate fully. Instead of drifting on a trajectory toward progressive decompensation, the system may tend to evolve to a lower state of relative stability, which is less energetically efficient and less redundant in terms of homeostatic responses but still stable until challenged above a critical threshold. The organism would thus progressively adopt a "best possible homeostatic state" that it can afford in successive responses to critical challenges (10). A fascinating hypothesis is that this adaptation is required because of loss or dysfunction of specific stem cells.

Now, it is reasonable to hypothesize that acquiring this new state of equilibrium may require substantially changing rules and priorities. As a very simple example. Ventilatory rate (minute volume) is tightly controlled and determined primarily by blood levels of carbon dioxide, as determined by metabolic rate. However, if the blood level of oxygen falls below a certain level (60 mmHg), the level of oxygen becomes the essential regulatory parameter and completely overrides carbon dioxide-based regulation. The rules have changed, and along with them the essential homeostatic parameters. As mentioned above, there may be already coded in our biological program several possible alternative strategies to maintain homeostasis, and several possible less optimal states of equilibrium. Because genetics and the environment are both

finite, we can expect progressive substantial advances in the definition of the range of possibilities. The bottom line is that a model that aims to capture resiliency and frailty must be able to incorporate and handle this complexity.

Finally, it is important to remember that mathematical models drain their power from empirical knowledge. They should be considered tools and not solutions. We are discovering every day new signaling molecules and pathways that plays a critical role in homeostatic mechanism. No mathematical modeling can cope with the lack of essential information. Thus, models are as good as our knowledge of the biology of aging, and can only be useful if they promote a better integration and communication between scientists that approach the same problem from different perspectives. The study of frailty is no exception.

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Figure 1.

The ideal, optimal health is characterized by robust homeostasis, energetic efficiency and redundancy. Challenge above the threshold of compensation cause a transition to one of possible alternative homeostatic states that are less stable, less energetically efficient and less redundant (complexity reduction). It is likely that each state function according to different mechanisms, and can evolve in any other possible state, thus the map to resiliency may be quite different in different individuals (Note that only part of the possible arrows are shown, just to improve readability). Level A through C represents discrete levels of equilibrium, organized hierarchically, similar to what happen in quantum mechanics.