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Review

Unifying aging and frailty through complex dynamical networks

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ABSTRACT

To explore the mechanistic relationships between aging, frailty and mortality, we developed a computational model in which possible health attributes are represented by the nodes of a complex network, with the connections showing a scale-free distribution. Each node can be either damaged (i.e. a deficit) or undamaged. Damage of connected nodes facilitates local damage and makes local recovery more difficult. Our model demonstrates the known patterns of frailty and mortality without any assumption of programmed aging. It helps us to understand how the observed maximum of the frailty index (FI) might arise. The model facilitates an initial understanding of how local damage caused by random perturbations propagates through a dynamic network of interconnected nodes. Very large model populations (here, 10 million individuals followed continuously) allow us to exploit new analytic tools, including information theory, showing, for example that highly connected nodes are more informative than less connected nodes. This model permits a better understanding of factors that influence the health trajectories of individuals.

1. Introduction

Aging is the cumulative effect of degradation occurring at every level of the organism. One consequence of human aging is an exponentially accelerating mortality with age, according to the Gompertz law (Kirkwood, 2015; Gavrilov and Gavrilova, 2006). This law considers age, but not health status: the potency of age as the only risk factor for mortality reflects undefined changes in health. This unmeasured heterogeneity in health (and thus in the risk of death of people of the same age) is termed "frailty" (Vaupel et al., 1979). Clinically, frailty is recognized as a multiply-determined state of increased vulnerability; it increases with age (Rockwood, 2005; Rockwood et al., 2017; Clegg et al., 2013; Xue et al., 2016). Reflecting these many determinants, a broad range of health deficits can characterize individual frailty through a frailty index (FI), which is the proportion (from 0 to 1) of possible health deficits that are present in an individual (Mitnitski et al., 2001). The FI resolves much of the otherwise unmeasured heterogeneity in health of people of the same age, and is correlated with individual mortality (A. Mitnitski et al., 2017; Kulminski et al., 2008; Rockwood et al., 2017; Clegg et al., 2013).

Progress in understanding frailty in humans in relation to aging requires models. Animal models of health offer convenience, economy, and qualitatively similar behavior to human aging and mortality (Howlett, 2015). Mathematical models of aging can play a similar but complementary role, and have a long history (Yashin et al., 2000). Computational ("in silico") models can capture individual variability of health and mortality with stochastic transitions in health states. These computational models allow us to inexpensively generate large populations, examine hypotheses of cause and effect, develop new analytical tools, and explore sample size effects. Computational models of organismal aging nevertheless entail significant simplification; they are not intended to directly address particular details of individual health. However, they can explore the mechanisms that underlie the simplicity and success of the FI (Mitnitski and Rockwood, 2015; A. Mitnitski et al., 2017). How aging gives rise to frailty remains poorly understood and requires new approaches. Complex networks provide natural models of inter-relationships in biology, physics, and social interactions (Barabasi, 2016) and can be used to explore the relationships between aging, frailty and mortality.

In this mini-review, we summarize our recent work—providing a mechanistic understanding of why and how deficits accumulation, summarized by the frailty index, is related to aging and mortality at the systems (whole organism) level.

2. Results and discussion

We have used a complex network to model human aging and relate it to frailty (Fig. 1) (Taneja et al., 2016; Farrell et al., 2016; A.B.

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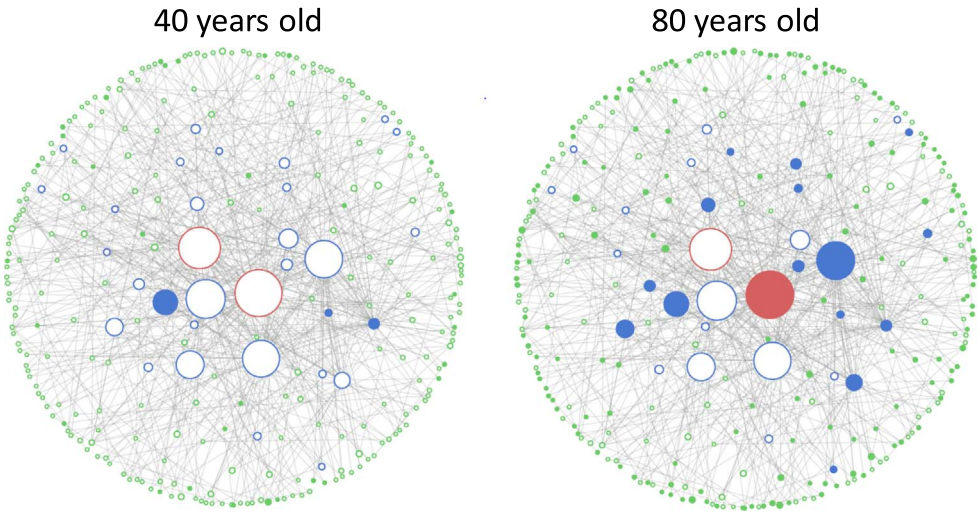

Fig. 1. Connectivity networks of a model individual at age 40 years (left) and then at age 80 (right). The circle size of each node is proportional to its connectivity. Damaged nodes are filled, undamaged nodes are empty. Individuals die when both mortality nodes (red circles, being the two most connected nodes) are damaged. Also shown are 30 frailty nodes (blue circles), and 268 others (green circles). At age 40 neither mortality node is damaged, whereas 3 of 30 FI nodes are (FI = 3/30 = 0.10) as are 34 other nodes; at age 80, one mortality node, 15 FI nodes (FI = 15/30 = 0.50), and 173 other nodes are damaged. This individual died at age 82. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Mitnitski et al., 2017). Nodes of the network can each be either undamaged or damaged (thereby representing *deficits*). Damaged nodes can be repaired, reflecting an important source of the observed dynamics of frailty (A. Mitnitski et al., 2017). Nodes correspond to generic health attributes, and are not explicitly identified. The connections between nodes represent significant correlative connections, which can be causal. A relatively small number of nodes ("hubs") are well connected whereas most peripheral nodes are not, as is captured with a scale-free distribution of the number of connections for each node (Barabasi, 2016; Taneja et al., 2016). The two most connected nodes are *mortality nodes*; the next most connected nodes which are not mortality nodes are *frailty nodes*. Frailty nodes broadly correspond to clinically or biologically significant health characteristics. Most nodes have few connections.

Nodes are damaged randomly reflecting environmental influences, intrinsic features, and their interaction – such as through inflammation (Fulop et al., 2015; Jazwinski and Kim, 2017). Through interaction, the rate of damage of an individual node increases as more of its connected neighbors are damaged. Let the local frailty f_i be the fraction of damaged nodes connected with the i-th node (where $0 < f_i < 1$). The damage Γ_+ and repair Γ_- rates for the i-th node can be approximated using an exponential function of the local frailty: $\Gamma_+ = \Gamma_0 \exp(\gamma_+ f_i)$; $\Gamma_- = \Gamma_0 / R_0 \exp(-\gamma_- f_i)$ and the constant parameters Γ_0, R_0, γ_+,γ_- (Taneja et al., 2016; Farrell et al., 2016; A.B. Mitnitski et al., 2017). The overall proportion of damaged frailty nodes corresponds to the FI. There are three additional parameters of the model: the scale-free exponent α, the average degree of connectivity (i.e. the number of connected nodes) to a given node, $\langle k \rangle$, and the number of frailty nodes. The values of these parameters can be found in Farrell et al., 2016. The best fitting of mortality was obtained using 2 mortality nodes. Although the information values increased with a larger number of nodes, the number of frailty nodes did not influence the shapes of the mortality and average frailty curves (Farrell et al., 2016). The behavior of our complex network quantitatively captures Gompertz's law (Fig. 2), the accelerated growth of the FI with age, the broadening of the distribution of the FI with age, and its observed submaximal values (at FI < 1) (Farrell et al., 2016; A.B. Mitnitski et al., 2017).

Three examples illustrate both the power and the limitations of quantitative modeling. First, a quantitative model requires every assumption to be explicit, and this allows hypotheses of causal relationships to be explored. Even though hypotheses are difficult to falsify with only a specific model together with a finite parameter range, the plausibility and consistency of hypotheses can be validated. For example, programmed aging implies an explicit age-dependence of cellular or organismal function (A.B. Mitnitski et al., 2017). Contrasting

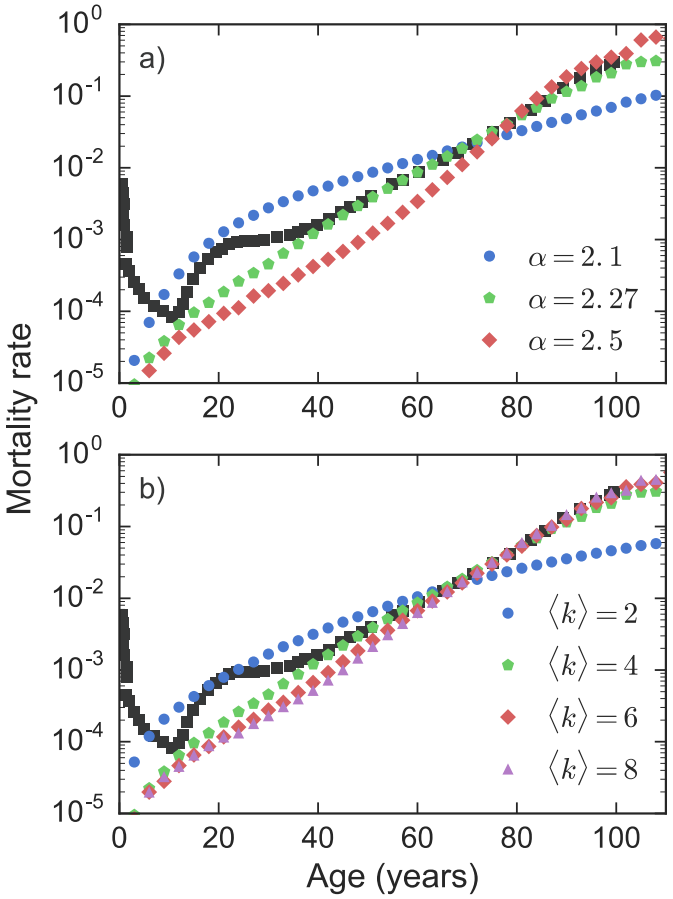

Fig. 2. Variation of the mortality rate with age with network parameters. The default model parameters are used for different average connectivities $\langle k \rangle$ (b), or for different scale-free exponents α (a). Black squares indicate observational statistics (Arias, 2014). Parameter values are as indicated by the laegends; otherwise default parameters are used with $\Gamma_0 = 0.00113$ (per year), $R_0 = 1.5$, $\gamma_+ = 10.27$, $\gamma_- = 6.5$, $\langle k \rangle = 4$, and $\alpha = 2.27$. $N = 10^4$ network nodes were used. After (Farrell et al., 2016). Our model does not address development and so does not exhibit increased early-childhood mortality.

this is the hypothesis that aging results implicitly from the accumulation of damage (Kowald and Kirkwood, 2016). Our model supports this latter hypothesis, by showed that aging phenomenology could be recovered with no explicit age-dependent rates of damage or mortality.

Models allow us to explore quantitative hypotheses and so generate testable predictions. For our second example (Farrell et al., 2016),