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Review

Unifying aging and frailty through complex dynamical networks

Andrew D. Rutenberg[a], Arnold B. Mitnitski[b,*], Spencer G. Farrell[a], Kenneth Rockwood[b,c]

[a] Department of Physics and Atmospheric Science, Dalhousie University, Halifax, Nova Scotia B3H 4R2, Canada
[b] Department of Medicine, Dalhousie University, Halifax, Nova Scotia B3H 2Y9, Canada
[c] Division of Geriatric Medicine, Dalhousie University, Halifax, Nova Scotia B3H 2E1, Canada

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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.

* Corresponding author.
E-mail address: Arnold.Mitnitski@dal.ca (A.B. Mitnitski).

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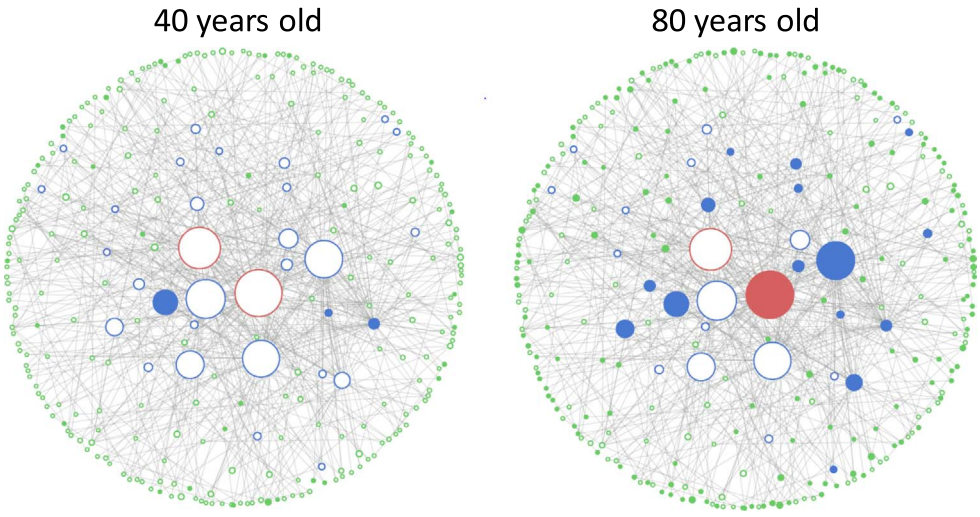

Fig. 1. Connectivity networks of a model individual at age 40 years (left) and then at age 80 (right). The circle size of each node is proportional to its connectivity. Damaged nodes are filled, undamaged nodes are empty. Individuals die when both mortality nodes (red circles, being the two most connected 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

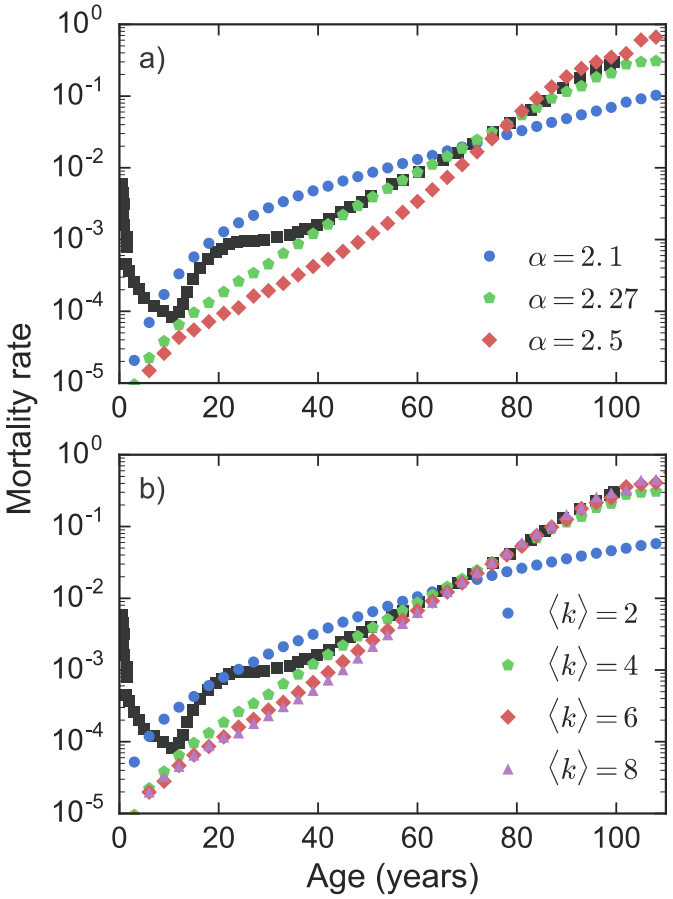

Fig. 2. Variation of the mortality rate with age with network parameters. The default model parameters are used for different average connectivities $\langle k \rangle$ (b), or for different scale-free exponents α (a). Black squares indicate observational statistics (Arias, 2014). Parameter values are 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),

various observational studies have exhibited an upper frailty limit. Although many studies have a limit of about 0.7, in some it is much lower – down to 0.3 for example (Clegg et al., 2013; Drubbel et al., 2013; Harttgen et al., 2013). We were only able to recover a frailty limit below 1.0 in our model by adding a finite diagnostic sensitivity for individual deficits (Farrell et al., 2016). Since a finite sensitivity would apply to the FI in general, and not just the FI limit, we predict that studies with significantly lower limits would also have significantly lower average FI at a given age. Indeed, this is observed (Clegg et al., 2016; Drubbel et al., 2013; Harttgen et al., 2013).

In a third example of the power and limitations of modeling, consider the impact of choices about network structure. To construct our network model, we had to make assumptions about how connections were made between nodes. We assumed that as with most biological networks (Barabasi, 2016; A.B. Mitnitski et al., 2017), relatively few nodes were connected with many other nodes, whereas most nodes were only connected with a few other nodes. This echoes the intuition of “geriatric giants”, that high order health impairments of, e.g., walking speed, balance, cognition, or daily function integrate information about many aspects of health; in consequence, they are highly connected. In contrast, although in biological systems no two attributes are entirely independent of each other, many physiological aspects of health are only indirectly related. We were also driven to this assumption (Fig. 1), because our model did not exhibit observed aging phenomena otherwise. This implies that the network structure is important in human aging.

Highlighting the importance of the network structure, both network parameters of the model significantly influence the shape of the mortality rate vs age plot: the scale-free exponent α that inhibits network hubs, and the average number of connections of each node $\langle k \rangle$. Increasing either network parameter increases the Gompertz slope of the mortality curve at older ages (Fig. 2A and B). Interestingly, the rate of mortality at younger ages changes in the opposite direction as α or $\langle k \rangle$ is increased. This corresponds to the well-known phenomenon of the so-called Strehler-Mildvan correlation – an inverse relationship between the slope and the intercept in the Gompertz law (Strehler and Mildvan, 1960; Gavrilov and Gavrilova, 2006).

We can use computational approaches to rapidly model the stochastic health trajectories and mortality of > 10 million individuals. Since the model data set is clean, large, and perfectly characterized, we can use it to explore new ways of analyzing observational data, since we can directly assess how well the analysis works. For example, information theory provides a non-parametric way of quantifying how much knowing the FI reduces our uncertainty in the mortality of an individual (Farrell et al., 2016). We can also use information measures to assess how much we learn about mortality by knowing an individual's age, or how much additional information is obtained by knowing an individual's FI given that the age is already known.

We find that larger FIs (i.e. with a larger number of actual health deficits) are most informative for younger individuals and can even exceed the information gained from knowing age alone (Farrell et al., 2016). Larger FIs indicate much earlier age-at-death than the young ages would typically indicate. On average, we also find that the information gain provided by the FI increases monotonically with the number of possible deficits included in the FI. This gives theoretical support to the recommendation to include all available health deficits in the FI. It further supports an inclusive, rather than a parsimonious, approach to evaluating the large number of potential biomarkers available through ‘omics’ inquiries.

We can also investigate the informativeness of individual deficits. Our model demonstrates that information value of individual deficits depends on how connected they are to other nodes in the network. Deficits with more connections are more informative about mortality (Farrell et al., 2016; A.B. Mitnitski et al., 2017). As our model network has relatively few well-connected nodes and many more less connected ones, we have a broad range of connectivities. This allows us to assess the information that individual health nodes provide about mortality, which is the focus of current inquiries.

Age remains a convenient individual variable that provides significant information about mortality, even when the FI is known. The risk of death for older individuals is greater than for younger people with the same FI. This implies that the FI alone does not yet encapsulate the full extent of age-related damage, so that more informative FIs may be possible. Whether further improvements can provide more information in addition to age remains to be seen. Since age is easy to assess, the FI complements rather than replaces age for health and mortality prediction.

Electronic health records now make possible routine FI capture in large populations using the deficits at hand (Clegg et al., 2016). Since every individual will have longitudinal records over their lifespan, it will become possible to include individual frailty “trajectories” into health assessment. The corresponding challenge is that opportunistic evaluation of health is likely to be biased - occurring more at times of health change or crisis than at regular intervals or annual checkups. Our computational model can precisely track when every deficit occurs for each individual, providing insights for the best use of longitudinal health data. In particular, we can quantify how sparse sampling degrades the information provided, or the effects of biased sampling that only occurs during health-changes.

Longitudinal FI analysis might be most useful when clinical intervention is being considered. Computational models allow us to characterize the effects of global or local damage to individual networks. Given that highly connected nodes are the major contributor to the risk of death, our model allows us to study how local damage to these hub nodes changes the rates of deficit accumulation and patterns of mortality. This affords investigation of how interventions to repair individual nodes might postpone damage propagation. By comparing the longitudinal behavior of the model with clinical data, our goal will be to assess the signatures of successful clinical intervention in people with complex needs.

Network medicine (Barabasi et al., 2011) endeavors to use the underlying networked connections observed in the human organism (e.g., genetic, intracellular, metabolic, regulatory) to better treat disease. A key message of a networked approach is that different aspects of health at any level of organization of the organism cannot be considered in isolation from the other elements. The connections themselves, as between diseases, can be phenomenological (Barabasi et al., 2011). Within this framework, our network model allows us to explore how connections at all levels contribute to loss of function and to mortality. While the composition of our nodes remains unspecified, they can be thought of as, e.g., genetic/molecular and subcellular/cellular deficits, or damage at the level of tissue or organs, or clinically detectable functional or disease deficits. These can be detectable as biomarkers (Mitnitski et al., 2015; Lorenzi et al., 2016; Kim et al., 2017), then laboratory abnormalities (Howlett et al., 2014; Blodgett et al., 2016), then clinical deficits (Rockwood et al., 2017; Jazwinski and Kim, 2017). In our model, the network approach makes it possible to understand how the local and potentially reversible damage in the network ultimately leads to the irreversible event of mortality.

Important challenges remain. Although there appear to be systematic differences in frailty by sex (Gordon et al., 2017), this is not yet captured by our model. We have also not yet found a satisfactory way to address resilience (Ukraintseva et al., 2016), although recent advances are suggestive (Gijzel et al., 2017). Nevertheless, our network approach provides a successful foundation on which to address these and other aspects of aging phenomena with an explicitly quantitative approach.

3. Conclusion

Our network model of interconnected nodes reflects the interdependence of health attributes. These attributes can be summarized in the frailty index. Our recent work, reviewed here, offers theoretical

support for how variability in deficit accumulation gives rise to variability in the risk of death for people of the same age, which is the basis of frailty in both its statistical and clinical senses. The network model shows how the local damage caused by the random perturbations propagates through the complex dynamics network of interconnected nodes. The model explains not only the known patterns of mortality (the celebrated Gompertz law) but also how health status (indicated by the frailty index) gives rise to increasing vulnerability of people when they age. Even with no age-dependent terms the model generates characteristic mortality patterns, suggesting that aging is not programmed. There remain a large number of questions still to address. With our model, we are able to both ask and answer them with explicit quantitative approaches.

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Declaration of interest

KR is Chief Scientific Officer of DGI Clinical, which has contracts with pharma on individualized outcome measurement. In July 2015 he gave a lecture at the Alzheimer Association International Conference in a symposium sponsored by Otsuka and Lundbeck. At that time he presented at an Advisory Board meeting for Nutricia. He is a member of the Research Executive Committee of the Canadian Consortium on Neurodegeneration in Aging, which is funded by the Canadian Institutes of Health Research, with additional funding from the Alzheimer Society of Canada and several other charities, and from Eli Lily, Pfizer Canada and Sanofi Canada.

AM is employed part-time by DGI Clinical. ADR and SF have no conflicts.

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