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REVIEW ARTICLE

Aging, frailty and complex networks

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Abstract When people age their mortality rate increases exponentially, following Gompertz's law. Even so, individuals do not die from old age. Instead, they accumulate age-related illnesses and conditions and so become increasingly vulnerable to death from various external and internal stressors. As a measure of such vulnerability, frailty can be quantified using the frailty index (FI). Larger values of the FI are strongly associated with mortality and other adverse health outcomes. This association, and the insensitivity of the FI to the particular health variables that are included in its construction, makes it a powerful, convenient, and increasingly popular integrative health measure. Still, little is known about why the FI works so well. Our group has recently developed a theoretical network model of health deficits to better understand how changes in health are captured by the FI. In our model, health-related variables are represented by the nodes of a complex network. The network has a scale-free shape or "topology": a few nodes have many connections with other nodes, whereas most nodes have few connections. These nodes can be in two states, either damaged or undamaged. Transitions between damaged and non-damaged states are governed by the stochastic environment of individual nodes. Changes in the degree of damage of connected nodes change the local environment and make further damage more likely. Our model shows how age-dependent acceleration of the FI and of mortality emerges, even without specifying an age-damage relationship or any other time-dependent parameter. We have also used our model to assess how informative individual deficits are with respect to mortality. We find that the information is larger for nodes that are well connected than for nodes that are not. The model supports the idea that aging occurs as an emergent phenomenon, and not as a result of age-specific programming. Instead, aging reflects how damage propagates through a complex network of interconnected elements.

Keywords Aging · Frailty · Mortality · Frailty index · Complex networks · Mathematical modeling · Information theory · Frailty maximum

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Introduction

While it is not surprising that the mortality rate increases with age, it is striking that the increase is so simple—the Gompertz law for older humans shows that mortality increases exponentially with age

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(Gompertz 1825). This empirical law of aging was widely employed by actuaries and demographers, before it started to interest biogerontologists (Kirkwood 2015). It is intriguing that such a general relationship between age and mortality emerges, since the causes of death are typically quite varied. A mechanistic explanation of the Gompertz law can be made, e.g., using a reliability theory treatment of redundant systems (Gavrilov and Gavrilova 2001, 2006; Milne 2008). However, while this approach incorporates explicit time-dependent parameters it does not show how their time dependence arises. Explicit time-dependent parameters are also seen in many other models used to explain Gompertz's law (e.g., Strehler and Mildvan 1960; Arbeev et al. 2011; Avraam et al. 2013).

Even very old individuals do not just die from "old age". Instead, over the course of their life they accumulate multiple health problems that increase their vulnerability to possible causes of death. Such vulnerability accumulates differently for different individuals, and the more vulnerable typically die sooner than their coeval peers. To characterize this heterogeneity in vulnerability, Vaupel et al. introduced *frailty* (1979). As introduced, frailty was a fixed factor across an individual's life. They hypothesized that any population consists of individuals with different degrees of frailty, which was characterized by a greater mortality rate compared with others of the same age. This heterogeneity made it possible to explain demographic observations such as late life mortality plateaus (Yashin et al. 1985; Vaupel et al. 1998; Avraam et al. 2013).

We can alternatively consider heterogeneity in health (as opposed to in mortality) within a population of the same age (Mitnitski et al. 2016). This health heterogeneity can be quantified as the individual degree of health deficit accumulation, using health related data that are readily available in epidemiological and clinical databases (Mitnitski et al. 2001; Rockwood and Mitnitski 2007). The health deficits that are considered are defined broadly, as symptoms, illnesses, functional limitations, or laboratory abnormalities that generally increase with age. Usually, the deficits are dichotomized so that a deficit is scored as 1 and its absence as 0 (Mitnitski et al. 2001). For each individual, these scores are added and then divided by the number of deficits that were considered. The ratio of actual to potential health deficits is called a frailty index (FI). Databases with differing numbers and types of variables can be used: the FI is simply the fraction of actual deficits from the total possible number in that database. A systematic procedure for creating an FI has been validated (Searle et al. 2008; Peña et al. 2014) and is used in a wide variety of settings and across several databases (Clegg et al. 2013, 2016).

On average, across a large number of datasets the number of health problems increases with age (Mitnitski and Rockwood 2015). The FI increases characteristically with age with an upwards curvature, indicating an accelerating rate of the accumulation of deficits with age (Mitnitski et al. 2001; Kulminski et al. 2007) with a cross-sectional exponential rate of 0.03 ± 0.01 and longitudinal exponential rate of 0.045 ± 0.0075 (Mitnitski and Rockwood 2016).

Despite these reasonably consistent mean changes, there is great variability in how individuals accumulate deficits. In a large longitudinal health dataset, individual FI scores indicated both health worsening and health improvement (Mitnitski et al. 2012). Despite individual variability, regular patterns were deduced. The chance of moving from any one number of deficits to another number is strongly conditioned on the initial number of deficits. Change is typically slow, and "jumps" (recovering from or accumulating many deficits at once) are uncommon. A multistate transition model was introduced that allowed changes in all directions and that related the FI to mortality. It had excellent fit to the observed data, though again with age-dependent parameters (Mitnitski et al. 2006, 2013; Mitnitski and Rockwood 2015).

The variability that is shown between individuals increases with age. Across databases, the statistical distribution of the FI typically shows a skewed histogram well represented by the Gamma density function (Mitnitski et al. 2001; Rockwood et al. 2004), similar to Vaupel's theoretical assumption for his frailty (Vaupel et al. 1979). The difference is that the FI is a *dynamic* measure, readily available from individual health data. The FI changes in time, reflecting age-related changes in individual health. In contrast, Vaupel's frailty was assumed to be a static factor over an individual's life course and it offered no guidance about how it might be assayed at the individual level.

Since its introduction in 2001, the FI has been calculated by many different groups, with estimates

including more than 1.5 million people. The results have been consistent across studies, even though they have used different numbers of deficits (from 20 to 130), different study designs (cross-sectional vs. longitudinal), and different data collection methods (e.g., clinical vs. self-reported data). The FI is a popular health assessment tool because it strongly associates with mortality and other adverse outcomes (Rockwood and Mitnitski 2007), and because it is robustly flexible. The FI stratifies people by their risk of death, and the FI's ability to stratify risk is relatively insensitive to which particular deficits are used (Rockwood et al. 2006). Much more important to risk stratification by the FI is the number of deficits that are included (Rockwood et al. 2006; Zeng et al. 2015). This helps us to understand why indicators of frailty with fewer deficits (e.g., the frailty phenotype with five characteristics; Fried et al. 2001) generally do not achieve the same degree of precision in predicting mortality. Other frailty measures can also be considered as special cases of the FI (Theou et al. 2013a) and often are specialized. For example, the frailty phenotype is based on characteristics associated with physical function. Other scales include neuro-physiological characteristics (Rolfson et al. 2006) or psychometric measurements (Gobbens et al. 2010). Even so, all of these frailty scales behave similarly, showing an increasing prevalence with age, an upward curvature on a frailty vs age plot, and a strong association with mortality risk (Theou et al. 2013a, 2014). The association between health-derived frailty (the FI) and mortality echoes Vaupel's original definition of frailty as an indicator of heterogeneity of individual's mortality risks. Nevertheless, health-derived frailty is useful since it can be applied to individuals, using a wide variety of health data.

For these reasons, the FI approach has been used in many settings. In a large-scale UK study, an electronic version (the eFI) was calculated from routine electronic health records for almost one million individuals aged 65+ years (Clegg et al. 2016). The FI is also a sensitive measure of health at younger ages (Rockwood et al. 2011). It has been used to assess the relationship between the health and wealth of nations. The average FI showed reciprocal relationships with national GDP per capita: in the highest-income countries of Europe, the prevalence of frailty was lower than in European countries with smaller income (Theou et al. 2013b). The FI can also characterize socioeconomic inequalities in health within countries (Hajizadeh et al. 2016). Other versions can be adapted to special patient populations, such as systemic sclerosis (Rockwood et al. 2014), intellectual disability (Schoufour et al. 2014), kidney disease (Hubbard et al. 2015), and HIV/AIDS (Guaraldi et al. 2015).

In most studies, the FI has been based on clinically relevant deficits. As such, it may not be surprising that it is linked to adverse outcomes and mortality. However, the FI has shown similar properties when calculated from routinely available laboratory tests (Howlett et al. 2014). Moreover, a biomarker based FI, compiled from 40 biomarkers of cellular aging, inflammation, haematology and immunosenescence also showed a strong association with mortality even when most of the individual biomarkers showed no or only weakly statistically significant associations with death (Mitnitski et al. 2015).

The FI has similar properties in animal models. A frailty index in mice was first calculated by Howlett and colleagues (Parks et al. 2012) using a range of health-related characteristics ($n = 31$) including the level of activity, hemodynamics measures, body composition and basic metabolic status. In a later iteration, a simplified noninvasive FI for mice was developed using clinical signs of age-related deficits (Whitehead et al. 2014). Striking similarities were found between the clinical frailty index in mice and in humans (Whitehead et al. 2014). In particular, after the age has been scaled by species norms the age-dependent FI trajectories virtually coincide between mice and humans. A recent paper showed that FI scores were associated with deficits from the molecular/cellular, to tissue, to organ level function (Moghtadaei et al. 2016).

The FI is a general and effective integrative health measure, but little is known about the basis of its consistency. The complexity of aging makes understanding this question daunting. However, the generalizability of the FI, its robustness to the number, choice, and the level (biochemical, cellular, organ, functional, or clinical) of deficits within the FI, and finally the similarity between human and murine models—all indicate that a generic systems biology approach could be used to approach the question of how the FI works as a systemic indicator of aging (Kulminski et al. 2007). Mathematical modeling lies at the core of this approach.

Objective

Our objective is to review in some detail a dynamical network model recently developed by our group (Taneja et al. 2016; Farrell et al. 2016). This is an extremely simplified approach that nevertheless helps us to understand mechanistically why and how deficits may accumulate, and the basis by which common characteristics of aging can arise from that accumulation. In particular, the model has no time-dependent parameters and so illustrates how Gompertz's law can arise holistically. This is useful in addressing the question of whether programmed aging (which, of course, implies time-dependent parameters) is necessary to explain the Gompertz law and other patterns of aging.

The model

General

Our model (Taneja et al. 2016; Farrell et al. 2016) links mortality with deficit accumulation through a complex network of interacting nodes, where the nodes, when damaged, represent individual deficits. This model is stochastic and, while simplified, cannot be solved by hand. Rather, our mathematical model allows us to computationally generate large stochastic sample populations that we can analyze in traditional ways. Alternatively, we can use these model populations to develop new analysis tools. For example, we do this to understand differences in the informativeness of individual deficits that make up the FI. We also use the model to explore the possible origin of the empirical maximum of the FI, which is no more than 0.7 for >99% of individuals (Rockwood and Mitnitski 2006; Bennett et al. 2013).

A network of interacting nodes

We have developed a simplified model of the human organism as a network of interacting nodes (Fig. 1) (Taneja et al. 2016; Farrell et al. 2016). Each individual is represented by a distinct network with N nodes, where N is generally much larger than the number of nodes n that make up the frailty index. Each node $i \in \{1, 2, \ldots, N\}$ represents a possible deficit and

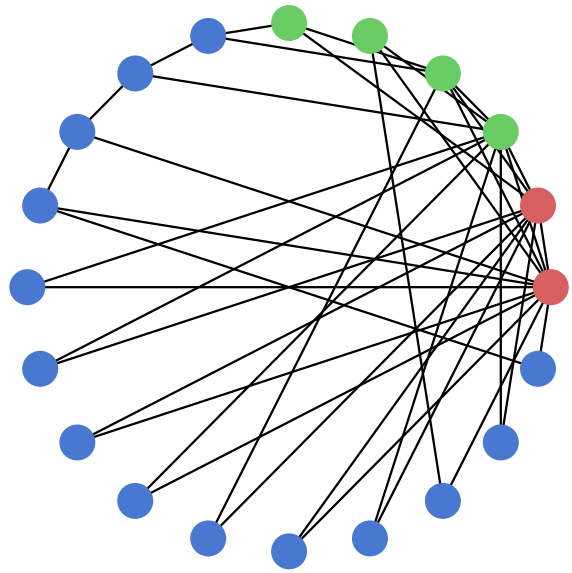

Fig. 1 Schematic representation of an individual's health as a network of N = 20 nodes (*circles*), that are connected to each other (*black lines*). Two mortality nodes (*red circles*) are the most highly connected, four frailty nodes (*green*) are next most highly connected. (Color figure online)

can be in one of two states for every individual: either healthy and undamaged (with $d_i = 0$, where the deficit is absent), or present and damaged (with $d_i = 1$, where the deficit is present). The nodes are not evenly interconnected—some have more connections than others. We characterize the connectivity of the network by a degree distribution $P(k) \sim k^{-\alpha}$, where $P(k)$ is the probability of a node having a degree k. The degree of a node is simply the number of connections the node has with other nodes, so we must have $k \in \{1, 2, \ldots, N-1\}$ since every node is connected to the rest of the network. For simplicity we use a commonly observed scale-free distribution, with a characteristic exponent α (Barabasi and Albert 1999). Such a distribution approximates the situation in which a relatively small number of nodes ("hubs") are well connected, whereas most nodes have relatively few connections.

To be clear, not all nodes are or need be deficits—deficits arise when nodes are in a damaged state. Each node has a local environment defined by the damage state of its connected nodes. In analogy to the FI, we define the *local frailty* f_i of the ith node as the fraction of damaged to the possible deficits on connected nodes:

$$f_i = \sum_{j}^{\text{connected}} d_j/k_i, \quad (1)$$

where k_i is the number of connected nodes. The local frailty (1) enhances the damage rate and reduces the repair rate of the ith node with an exponential dependence (Farrell et al. 2016):

$$\Gamma_+ = \Gamma_0 \exp(\gamma_+ f_i), \quad (2a)$$

$$\Gamma_- = \frac{\Gamma_0}{R} \exp(-\gamma_- f_i). \quad (2b)$$

Exponential functions are used in many applications in statistical physics and chemistry to represent the kinetics of complex changes (see also the classic work on aging and mortality by Strehler and Mildvan (1960)). Parameters of the model, such as Γ_0, R, γ_+, and γ_-, are found from fitting population mortality rates, the average FI trajectory, and the FI distribution at different ages (Taneja et al. 2016; Farrell et al. 2016). We find that repair (R and γ_-) is not significant (Farrell et al. 2016), while the overall damage rate (Γ_0) is tightly constrained by the increase of the FI at early ages. The γ_+ parameter, which characterizes how strongly a node interacts with its neighbors through its local frailty, is important. This parameter leads to exponentially increasing damage rates that are dependent on the state of the network.

Individual mortality results from the damage of the two most connected nodes, reflecting our intuition that mortality is impacted by many factors (Farrell et al. 2016). While we have investigated other numbers of mortality nodes (Taneja et al. 2016) we found that two mortality nodes provide the best fit with the data (Farrell et al. 2016). We note that while using network nodes for a mortality condition works and is convenient, we should not think of mortality as arising simply from one or two deficits. We can simply say that our mortality condition is sufficient to recover existing phenomenology.

We assess the "health" of an individual network with n frailty nodes, which are the most highly connected nodes that are not also mortality nodes (Fig. 1). By insisting that frailty and mortality nodes are distinct, any connections we find between frailty and mortality must come from the network interactions. Because frailty nodes are highly connected, they should provide an assessment of the overall health of the network even though we use very few frailty nodes n compared to the number of nodes in the network N. This is analogous to how the observational FI provides a good measure of human health (Clegg et al. 2013), while including relatively few possible deficits compared to e.g., the size of the human genome or transcriptome (Pan et al. 2008; Mercer et al. 2011).

The frailty index (FI) is the fraction of damaged frailty nodes and has a value F, where

$$F = \sum_i d_i/n. \quad (3)$$

Initially, at age t = 0, all nodes are undamaged ($d_i = 0$) and all f_i and $F = 0$. Transitions between undamaged and damaged states of each node occur randomly under the influence of the external environment. With the passage of time, as more nodes became randomly damaged the local frailties increase and so the chance of further damage increases (through Eq. 2a) while the chance of recovery diminishes (through Eq. 2b).

We generated a population of a large number (up to 10^7) of "individuals" each of which had N = 10,000 nodes. An exact computational implementation of fixed rate stochastic processes was used [variously called SSA, or the Gillespie algorithm, or kinetic Monte Carlo, see (Farrell et al. 2016) for details]. The results below are presented with the following parameters: $\alpha = 2.27$, $\gamma_+ = 10.27$, $\gamma_- = 6.5$, $R = 1.5$, $\langle k \rangle = 4$, and $\Gamma_0 = 0.00113$/year (Farrell et al. 2016).

Figure 2a shows the mortality rate as a function of age (Farrell et al. 2016), overlaid with data obtained from US statistics (Arias 2014). After age about 40 the calculated mortality rate corresponds well with the observational data. Figure 2b shows the age-specific trajectory of the average FI (Farrell et al. 2016), also in a good agreement with observations (Mitnitski et al. 2013). The observational changes in the distribution of the FI with age are shown in Fig. 3a, following (Gu et al. 2009). The model shows similar patterns (Fig. 3b) although in order to obtain the frailty limit observed in panel a, we had to introduce a false-negative rate q with value $q = 0.3$ (Farrell et al. 2016). This false negative rate reflects the finite sensitivity with respect to mortality of individual deficits. The choice of this parameter does not affect the ability of the model to fit the age-specific FI trajectory and the Gompertz law (Taneja et al. 2016; Farrell et al. 2016).

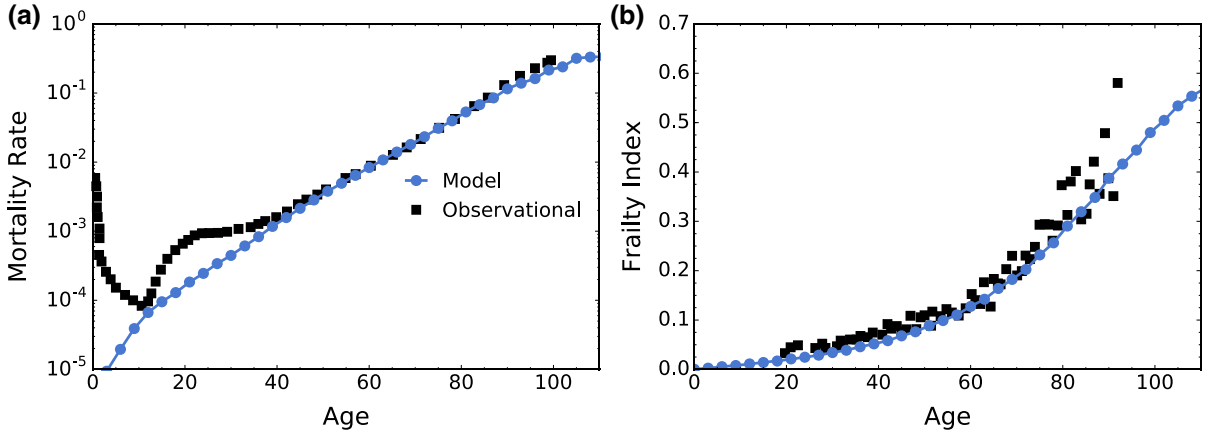

Fig. 2 **a** Mortality rate versus age. Observational data (*black squares*) is from U.S. population mortality statistics (Arias 2014) and model data is shown by the solid blue line (with *blue circles*). **b** Average FI versus age. Observational FI data (*black squares*) is from the CSHA (Mitnitski et al. 2013). Model data is shown by the solid blue line (with *blue circles*). Default parameters were used for the model in both panels, including q = 0.3. Figure is adapted from (Farrell et al. 2016). (Color figure online)

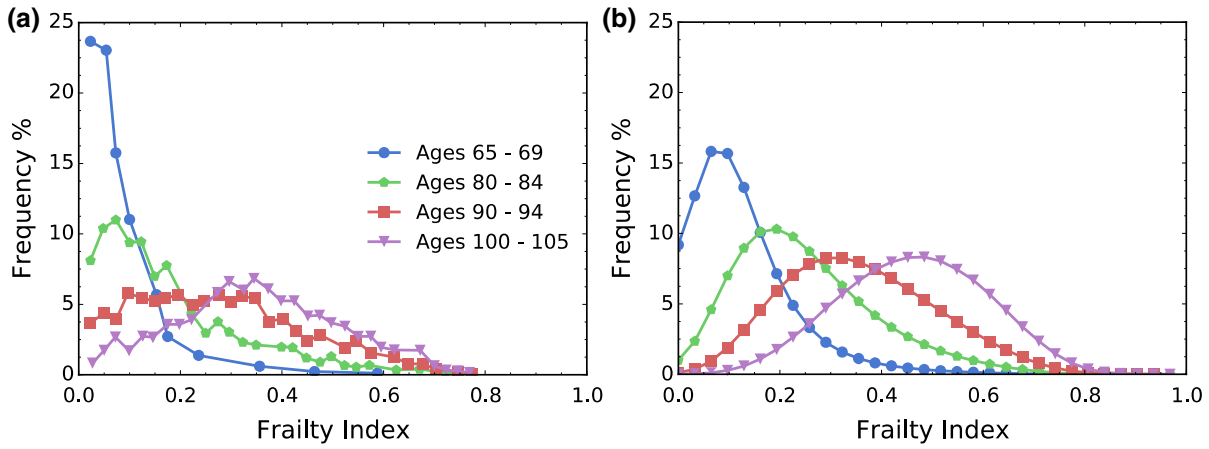

Fig. 3 Distributions of the FI for different ages. Age ranges are indicated by the legend, and are the same in both panels. **a** Observational distributions from Chinese population data (Gu et al. 2009). Note the FI limit around 0.8. **b** Model distributions with a false negative rate, i.e., q = 0.3. The 99th percentile of the population of 100–105 years has max FI = 0.78. Figure is adapted from (Farrell et al. 2016). (Color figure online)

Mutual information of FI and mortality

The FI and age are both informative to the human health (Mitnitski et al. 2016). How the knowledge of these variables helps to predict death can be quantified using information theory (Steinsaltz et al. 2012; Blokh and Stambler 2016). The relationships between age, the FI and mortality can be characterized using Shannon entropy, which is a quantitative measure of uncertainty in a random variable (Shannon 1948). Let *p(a)* be the probability distribution of the individual age-at-death *a*. The Shannon entropy *S(A)* is given by

$$S(A) = -\sum_{a} p(a) \log p(a), \tag{4}$$

where the capital *A* on the left-side of the equation indicates that the age-at-death has been averaged over by the sum. The entropy is larger for broader distributions, which correspond to larger uncertainty. For those who survived to specific age *t*, the entropy of the conditional age-at-death distribution *S*(*A*|*t*) makes it possible to quantify the information added to the unconditional distribution by the age t (Eq. 4). Information increases as the entropy (uncertainty) decreases. Since the age t constrains the distribution

of death ages, the conditional entropy $S(A|t)$ will have a lower value than the unconditioned entropy. The reduction in uncertainty by knowing age t can be found by the difference between unconditional and conditional entropies, which is a measure of how the uncertainty in the death age is reduced by knowing the age t. This difference is called the *mutual information* between the age-at-death A and age t:

$$I(A;t) = S(A) - S(A|t). \quad (5)$$

The mutual information of two variables quantifies how knowing one variable reduces the uncertainty in the other variable. This can also be interpreted as a correlation between the two variables. Using mutual information, we can characterize how much information knowing a person's age adds to estimating their risk of dying. Likewise, we can see how much information the FI adds to assessing the risk of death, and most importantly, we can calculate how much information one adds when the other is known.

To provide a measure of the predictive value of the FI in respect to individual mortality, we calculated the mutual information between the age-at-death and specific values of the FI, between age-at-death and all values of the FI, and between age-at death and all deficit values of individual nodes. For example, the mutual information between the age-at-death and all values of FI at a given age t is the information gained by knowing the FI at a given age t:

$$I(A;F|t) = S(A|t) - S(A|F,t), \quad (6)$$

where the capital F indicates that we have averaged over all values of F at age t (Farrell et al. 2016).

The information gained by including a specific range of FI values at a given age can be compared to knowing age alone is shown in Fig. 4. Intriguingly, larger F are most informative for younger individuals—and can exceed the information gained from knowing age alone (Farrell et al. 2016). This is because larger FI values indicate much earlier age-at-death than the young ages would indicate. Also, the information can become negative for very old individuals who have a very low FI. This is because they will live longer than most people of the same age (in virtue of having a low FI) though they are at an age when average mortality is high and life expectancy is

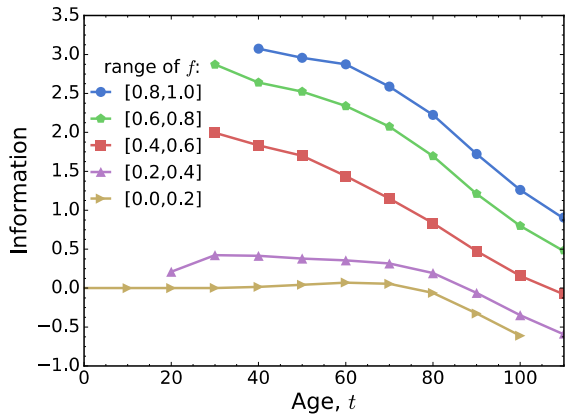

Fig. 4 Specific mutual information I(A;flt) = S(Alt) − - S(Alf,t) for distributions conditional on both age and the FI. This is the information gained by knowing a specific range of the FI, as indicated in the legend, versus just knowing their age. The negative values of I(A;flt) for older individuals with low frailties indicates that they have wider (normalized) death-age distributions compared to the population average at that age. Figure is adapted from (Farrell et al. 2016). The data is from our network model

short. In consequence, their low FI indicates more uncertainty in their age-at-death than their age alone would indicate.

If we average the information gained over the different values of the FI, then we obtain the mutual information of FI with the age-at-death distribution—conditioned on the current age (Fig. 5a). This average mutual information is always positive, indicating that uncertainty is always decreased on average by knowing the FI. The peak around age 80 indicates the age at which the FI is most predictive on average. The FI is less predictive at younger ages because most of the population has low values of FI. It is less predictive at older ages because there is less uncertainty in the age-at-death to begin with. Significantly, the mutual information provided by the FI increases with the number of possible deficits n included in the FI. The more nodes that are used, the higher is the information. By plotting the maximum mutual information (observed close to age 80 years in Fig. 5a) versus n, we see that the information increases approximately logarithmically with n (note the logarithmic scale in Fig. 5b). This means that by doubling the number of possible deficits we increase the maximum information by a fixed amount (Farrell et al. 2016). The implication of this increase is that the same

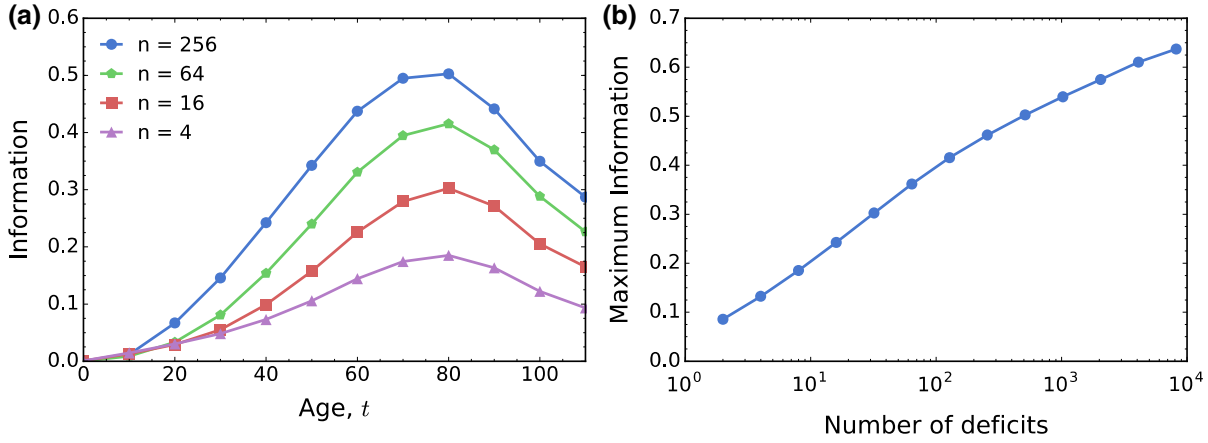

Fig. 5 **a** Mutual information conditioned on age I(A;Flt) versus age. This is the specific mutual information averaged over the frailties f. As indicated by the legend, the information increases with increasing number of possible deficits n included in the FI. Figure is adapted from (Farrell et al. 2016). **b** The maximum information from (**a**) versus number of possible deficits (nodes) used to calculate the FI. Note the logarithmic scale for the number of possible deficits, n. The data is from our network model

information at age 80 with $n = 4$ deficits can be obtained much earlier (at age 40) with $n = 64$ deficits.

Discussion

General

Our computational network model rests upon a few key qualitative assumptions: (1) Individual health can be approximated by a network of interconnected nodes (representing possible deficits) each of which can be in one of the two states (damaged or undamaged); (2) The evolution of the state of the network is governed by continuously acting stochastic perturbations (representing the environment) that can switch the state of each node between undamaged to damaged; (3) The transitions of individual nodes are also affected by the states of the "neighboring" (connected) nodes, such that damaged neighbours hasten damage of a node; (4) The network architecture, or how nodes are connected with other nodes, varies greatly between nodes and is approximated by a scale-free power-law degree distribution. This asymmetry of the degree distribution reflects our intuition that some biological or clinical characteristics (e.g., basic or instrumental activities of daily living, or gait speed) are related to many other variables whereas most variables have only a small number of such connections (e.g., a swollen knee or a mole); (5) The two nodes with the highest number of connections are considered to be mortality nodes: death is caused by their damage. Since they are well connected, this leads to the overall state of the network determining mortality rates rather than any small subset of the nodes.

Our model is very simple and reflects very general properties of the organism: its network structure, the asymmetry of this network, the role of the environment, and the cumulative effect of damage. Local damage, i.e., the damage of individual nodes, accelerates through the network because damage of a one node facilitates the damage of all other nodes linked with that one. The results of the computational simulation of our model are in a good agreement with the observational data (Taneja et al. 2016; Farrell et al. 2016). For example, the model recovers the Gompertz law of mortality, the accelerated accumulation of deficits with age, and the broadening of the FI's distribution with age. Even so, we needed an additional assumption in order to satisfy the observation that $FI_{max} < 1$ (Farrell et al. 2016); (6) a false negative rate (of about 0.3) allowed us to fit the observed frailty limit (Fig. 3).

Why do old people tend to die sooner than young people with the same FI?

While our network model allows us to represent observed patterns in mortality and the accumulation of deficits, it also helps us to address other important but poorly understood questions. For example, why does

age remain a significant contributor to mortality risk in models that include the FI? One way of answering this question is to consider the mutual information between age-of-death and the FI, which is maximal around 80 years of age. This allows us to turn the question around and ask, instead, when is the FI a useful addition to knowing a person's age? The answer is that very young individuals typically are healthy, with low FI, so the FI provides little additional information on average. Very old individuals will die soon, and so while the FI helps to stratify their ages-at-death, it does this within a narrow range. For adults' age 70–90 years old, the FI provides the most information on age-at-death on average. The FI also provides more information for younger individuals with a high FI.

For individuals with the lowest FI scores ($FI = 0$, often referred to as the "zero state"), we can ask why older adults are more likely to die than are younger ones (Mitnitski et al. 2006; Mitnitski and Rockwood 2015)? The network model also shows that death typically occurs much later in younger individuals with lower FIs than in those who are older who have the same FI (Farrell et al. 2016). In both cases, we see that the set of variables used to construct the FI must be incomplete, i.e., that the persisting value of age in predictive models reflects some *unknown factors* that are not captured by the FI. In the model, mortality occurs only due to the accumulation of damaged nodes (Farrell et al. 2016). This implies that the FI does not encapsulate the full extent of damage in individuals. Mortality can occur spontaneously in the network model, much like the sudden death of a young athlete due to an inherited ventricular arrhythmia or a subarachnoid hemorrhage. We also note that since frailty and mortality nodes do not have identical connections with other nodes in the network, damage in the rest of the network can affect them differently. Age is a convenient individual variable that gives us information about the network damage that is not included in the FI. Since knowing an individual's age is "free" while the FI requires assessment, we can simply say that the FI complements rather than replaces age.

Damage accumulation versus genetic programming

Our network model illuminates a long-standing debate about the causes of aging: damage accumulation versus age-specific genetic programming (Gavrilov and Gavrilova 2002; Kowald and Kirkwood 2016; Young et al. 2016). A deliberate and important feature of our model is the *absence of any time-dependent parameters*. The only extrinsic factor in the model is the environment, through the random switching of the states of the nodes from undamaged to damaged and back. The absence of age-related variables supports the idea that aging can be explained simply as the accumulation of damage, and does not need to be programmed. In this context, we take programmed to mean age-specific failure or damage of e.g., genetic origin. While we cannot assert that age-specific damage is impossible in principle, our simple network model shows that deficit accumulation alone, through the propagation of damage in a network of interconnected elements, can explain the major patterns observed in human aging. We believe that aging emerges as the propagation of damage through a complex network of interconnected elements.

Relationship between model deficits and observational human health deficits

One might straight-forwardly think of our model nodes as physiological or functional variables that have specific thresholds. For functional variables like walking speed these thresholds may be one sided, where damage corresponds to a range of limitations. Alternately, nodes might be the risk factors of Manton and Yashin (Yashin et al. 2012; Manton et al. 1994), so that damage corresponds to deviations on either side of an optimal trajectory that might be time-dependent (Yashin et al. 2012). In our model, only some of our deficits directly affect mortality nodes, whereas all of them also affect the state of other nodes. This is in contrast to Yashin's quadratic hazards model, where all deficits directly affect mortality rates but not each other (Yashin et al. 2012).

We need not identify nodes of our model with specific physiological or functional variables. We might think of high-level nodes as representing combinations of variables, much as functional variables such as balance, mental function, or gait speed represent many physiological aspects of the body. Conversely, we might think of multiple low-level nodes representing a single physiological variable. In this way, we could have a graded response to damage—with higher damage levels of a given

physiological variable corresponding to more low-level damaged nodes. While we thus have flexibility in how we think of the model nodes, we note that previous studies of non-binarized deficits did not find significant improvements in predicting mortality (Peña et al. 2014)

This flexibility of representation of our network model begs the question of how we could use observational data to test the assumed scale-free interconnections of our network? We believe that information theory, and in particular the spectrum of information of individual deficits, provides a simple but powerful tool that is sensitive to the details of the network. This remains an important challenge for future work. It also presents an opportunity, since greater understanding of the interactions between observational nodes is likely to improve our fundamental understanding of the aging process.

Informativeness of deficits depend on their connectivity degree

The model confirms our intuition that possible deficits with more connections are more informative. Interestingly, the relationship between the information per deficit and the average deficit degree, the "information spectrum", is approximately linear for our best-fit network exponent α (describing the distribution of connections between nodes) (Fig. 6). This is intuitively appealing, since linearity indicates that every connection provides approximately the same amount of information. Nevertheless, for other values of α the relationship is more like a power-law (Farrell et al. 2016). Directly determining the network exponent α from observational data would allow us to examine the information spectrum and compare it to the α obtained from a fit to the mortality and FI phenomenology.

Implications of the frailty limit

With our network model, we were only able to recover the observational frailty limit (FI < 1) with a finite false-negative rate ($q = 0.3$) (Farrell et al. 2016). We justified this by similar magnitude finite sensitivities reported in clinical diagnosis, which contrasts with the otherwise perfect association of model deficits with increasing mortality. We can also think of the false-negative rate as representing the contribution of sub-clinical damage to both mortality and further network damage. Since such a false-negative rate will depend on the particular deficit, we would expect that the resulting frailty limit will depend upon the collection of particular deficits—i.e., it will vary from study to study. Indeed, this variation of the frailty limit between studies is observed (Farrell et al. 2016).

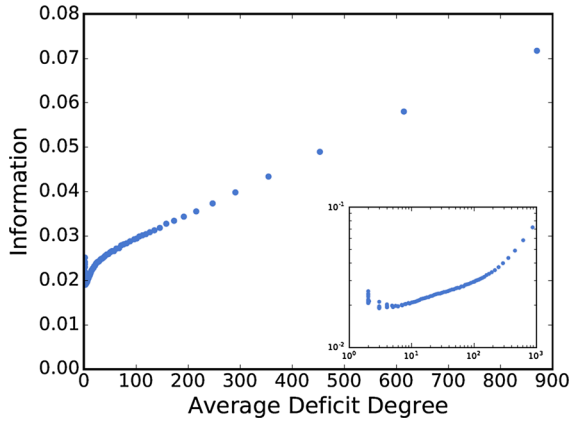

Fig. 6 The "information spectrum" of the network. The mutual information per node (possible deficit) for individuals at age 80 (when the mutual information of the FI is maximal) versus the average degree of connection of the node. Different values of the network scale-free exponent α are indicated by the legend. $\alpha = 2.27$ (*blue points*) correspond to the best fit with the observational data. In all cases the information increases with deficit degree. For $\alpha = 2.27$ the increase is approximately linear with degree. The inset shows the same data on log–log scale, showing the approximately power-law behavior at smaller degrees. (Color figure online)

Nevertheless, an alternative picture of the observed frailty limit is that it represents the limiting burden of the organism to a cumulative degree of insult. If we posit that different deficits provide differing amounts of burden, then we could also explain the "non-universal" character of the frailty limit between studies. It may be possible that modifications to the network model, perhaps through a different mortality rule, could avoid the false-negative rate we imposed to recover the frailty limit (Farrell et al. 2016) while still retaining the other aging phenomenology.

Frailty instrument based on more deficits predict mortality better than those with fewer deficits

The FI predicts mortality better than other frailty assessment instruments (Theou et al. 2013a, 2014). The difference between them lies in the number of possible deficits used. A typical FI has an order of

magnitude more items than many other frailty measures (e.g., 40–50 in the FI vs. 5 in the Fried phenotype). As shown in Fig. 5b, the predictive value of the model FI increases monotonically with the number of possible deficits included in the FI. This gives theoretical support to the empirical evidence, and also supports our intuition to include all available relevant health deficits in the FI (Searle et al. 2008). It is increasingly important to realize the flexibility of the FI. The advent of electronic health records (EHRs), such as the electronic FI (eFI) being employed in the National Health Service in England and Wales, will make it possible to routinely calculate FIs with the deficits at hand (Clegg et al. 2016).

Our naive expectation had been that including many deficits would eventually dilute or diminish the value of the FI. However even with as many as 8000 deficits in the FI, which is essentially the entire model network, our model shows no evidence of dilution (Farrell et al. 2016). No dilution has been seen in observational studies either (Song et al. 2014; Rockwood et al. 2007). Why not? The answer appears to be that the FI probes the entire network of individual health, and that any additional deficits provides better coverage of that network. There does not appear to be any advantage to avoid using readily available health-assessment items in a frailty measure (Velanovich et al. 2013; Louwers et al. 2016).

Complex networks in biomedical applications and gerontology

The FI has been a useful *empirical* health assessment tool. Now, our model provides strong theoretical support for the FI. The network model is useful in representing health of individuals, in stratifying people by the risk of mortality and other adverse outcomes, but also in understanding why including more rather than fewer items in the FI gives a better prediction of mortality. Health deficits are *interdependent*; each of them is linked with many others, and each of them contains information about many others (Mitnitski et al. 2016). This led us to suggest a network approach, which allowed us to employ powerful mathematical methods that had been used for investigating complex network dynamics in physics, biology, social media, and communication (Watts and Strogatz 1998).

While there have been many applications of networks to biological systems (e.g., Promislow 2004; Budovsky et al. 2007; Wolfson et al. 2009; Hidalgo et al. 2009; Tacutu et al. 2010; Vural et al. 2015; Wang et al. 2015; Ghiassian et al. 2016; Yanai et al. 2016), we are aware of only one other network model of aging (Vural et al. 2014). Their network model fitted observed mortality patterns in six different non-human organisms. The important difference with our model is that Vural et al. (2014) imposed mortality when a threshold on the fraction of damaged nodes was passed. While they did not explore FI phenomenology, we have shown that such a threshold mortality does not recover the observed distributions of FI (Farrell et al. 2016).

Perspectives

Our model allows researchers to conduct computer experiments (in silico). These can be invaluable to develop new analysis tools such as information measures, when experiments using human data are impossible or where there is a lack of frequently observed longitudinal data. Our model allows the generation of large amounts of high-quality comprehensive data on millions of "individuals", each of which is represented by up to 10,000 nodes. The timing of every deficit change is recorded for every individual in our model population. This data can be used to investigate individual longitudinal trajectories which can then be compared with sparse longitudinal observations. This presents us with the ability to explore how sparse sampling affects the analysis of frailty trajectories. For example, our model shows little sensitivity to the deficit repair rate, which implies that deficit repair may not affect longevity statistics or the overall FI (Farrell et al. 2016). Due to the possibility of rapid re-damage after deficit repair, the investigation of deficit repair is likely to be confounded by sparse frailty trajectories. Such effects can be characterized with our network model, so that we can more reliably estimate repair rates from sparse observational data.

Computational models could also take into account changes in relationships between health deficits. These might result from, for example, changes associated with stress-response or with resilience paradigms (Rattan 2013; Ukraintseva et al. 2016). In this way, a network model could let us explore how such changes might influence individual trajectories of the FI and mortality (Yashin et al. 1985, 2012). This could

provide a way of understanding how the same allele can have beneficial or harmful effects in varying circumstances (Kulminski et al. 2016). Similarly, our network model will also allow us to study how local damage of various magnitudes would change the rates of deficit accumulation and patterns of mortality. While understanding local damage is important, it is not experimentally accessible for human populations. Computational models allow in silico experimentation to allow us to characterize damage phenotypes and complement and extend our analysis of empirical (clinical) data.

Conclusion

Aging and frailty are closely intertwined. Frail older adults are at a greater risk of accelerated decline in many aspects of function. The many characteristics associated with frailty can characterize or define the aging process, even without "consensus concerning the physiological/biological pathways associated with…frailty" (Fulop et al. 2010). Our goal has not been to build such a consensus. Rather we have embraced aging and frailty within the dynamical properties of a complex network, like that of the human organism.

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Authors' contributions ABM, ADR and KR conceived the study. SF carried out the coding, calculations, and figure preparation; this was done in close consultation with ADR. All authors contributed to, read, and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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