Abstract

The gradual accumulation of damage and dysregulation during the aging of living organisms is readily quantified. Even so, the aging process is complex – with multiple interacting physiological scales. Computational models that simulate realistic individual trajectories of health during aging, and that include mortality, can significantly advance our understanding of aging. To do so, they must be systems-level models that incorporate interactions between measurable aspects of age-associated changes. To incorporate individual variability in the aging process, models must be stochastic. To be useful they should also be predictive, and so must be fit or parameterized by data from large populations of aging individuals. In this perspective, we outline where we have been, where we are, and where we hope to go in computational models of aging. Our focus is on systems-level models, and on their great potential in aging research.

Keywords

Computational Model · Stochastic Simulation · Machine Learning · Synthetic Populations

1 Introduction: Challenges of Studying Aging

Computational models are essential to make state-of-the-art predictions or to understand mechanisms within complex non-linear, stochastic, and interconnected systems such as the economy, the weather, or the climate. In this section we outline how aging organisms are also complex, interconnected systems. In particular, we highlight some challenges of understanding aging – and so also of modelling aging.

Aging populations exhibit increasing mortality rates. For humans, the risk of dying increases approximately exponentially for older ages – the famous Gompertz law of mortality (Kirkwood, 2015). Before death, individual health can be assessed in many ways. One such measure is provided by the Frailty Index (FI) which is the proportion of “things wrong” from a large selection of possible age-related deficits of health and function (Mitnitski et al., 2001). The FI is robust, flexible, and is strongly correlated with various outcome measures including mortality (Rockwood et al., 2006; Evans et al., 2014). Alternatively, Biological Age (BA) is an “effective age” defined in terms of an individual’s health, often using molecular aspects of health such as epigenetic methylation (Hannum et al., 2013; Horvath, 2013; Levine, 2020). Other summary measures of health have been developed, including allostatic load (McEwen and Stellar, 1993), and physiological disregulation (Milot et al., 2014). Different summary measures of health are not necessarily strongly correlated with each other at the individual level (Li et al., 2020), though we expect them all to be associated with future adverse health outcomes.

As assessed by the FI, the distribution of health measures broadens with age, corresponding to distinctive individual trajectories of health (Rockwood et al., 2004). Worsening health over an individual’s life is a random process, and is described as a stochastic accumulation of damage. It is thought that this damage underlies the increased mortality with age that is characterized by Gompertz’s law (Gavrilov and Gavrilova, 2001).

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Remarkably, even relatively simple empirical observations about aging and mortality are not well understood. Resolving the question of whether Gompertz’s law applies for extremely old populations or whether they exhibit a mortality deceleration or plateau remains challenging due to small data-sets (Gavrilov and Gavrilova 2019). The ‘mortality-morbidity paradox’ whereby female populations live longer than male populations, despite male populations apparently having better health, remains unexplained (Gordon et al. 2017; Kulminski et al. 2008). The mechanisms behind historically changing health and mortality within national populations (Crimmins 2015; Colchero et al. 2016), or behind differences between different socio-economic groups within a population (Andrew et al. 2012), are even more challenging to uncover. We have generally been limited to descriptive or correlative approaches to population-level questions about aging.

Four broad challenges of studying aging are clear: how can we affordably and effectively observe health and mortality across large populations, how can we better understand the mechanisms or causes underlying what we observe, how can we better predict outcomes at an individual or population level, and, finally, how can we better intervene to decrease mortality and to improve health during aging? These challenges are interconnected: better measurement leads to better understanding, which leads to better prediction, and ultimately to better treatment.

Success in aging research crucially depends on the broad availability of high-quality data. National studies, especially those that include longitudinal data on study participants, such as the CSHA (Canadian Study of Health and Aging Working Group, 1994), CLSA (Rain et al., 2009), NHANES (Centers for Disease Control and Prevention National Center for Health Statistics updated 2014), BLSA (Ferrucci 2008), ELSA (Stepoe et al., 2014), and the UK Biobank (Sidlow et al., 2015), are of increasing importance and utility. Emerging sources of data include electronic health records (EHR) (Clegg et al., 2016), molecular ‘omics data, and individual telemetry provided by health monitors or cellphones.

There are also many scales of health measures to consider: from molecular and cellular, to tissue, to organismal. For example, at the molecular scale methylation clocks have emerged as convenient epigenetic hallmarks of health and aging (Hannum et al., 2013; Horvath, 2013). Other high-throughput technologies such as genomics, transcriptomics, proteomics, metabolomics, and microbiomics provide affordable ways of conducting aging studies over populations (Livshits et al., 2018; Lehallier et al., 2019; Ahadi et al., 2020). Conversely, clinically relevant aspects of health such as activities of daily living (ADL) and other measures of functional disability are particularly important to the aging of individual older adults. Such ‘higher’ levels of function are dependent on many aspects of ‘lower-level’ biological and molecular function in a variety of tissues. Understanding how different scales of organismal function interact with each other should help us to effectively translate advances from one scale to another, and identify interventions that target the lower-level biological function before it manifests as functional disability (Ferrucci et al., 2018).

Continuing the historical advances in either life expectancy or healthy-aging will be increasingly challenging but, naturally, is of great interest to the geroscience community. Targeted interventions for aging individuals will often be in the context of significant comorbidities or polypharmacy. Systemic treatments such as exercise (Fried, 2016; Partridge et al., 2018), caloric restriction (Most et al., 2017; Mattson et al., 2017), or senolytics (Xu et al., 2018), act at cellular or molecular scales but the desired effects are often at the organismal scale. Understanding interventions includes understanding how the effects of interventions propagate between organismal scales. This will likely depend on the health-state and age of the individual – as well as the intervention under consideration. Nevertheless, greater understanding could help us select, guide, apply, and improve interventions for individualized treatment.

Animal models of aging have instructive similarities and differences with respect to human aging (Cohen, 2018). Simple animal models are particularly amenable to studying the effects of controlled interventions in the aging process. Efficient automated image analysis is also starting to lead to high-quality longitudinal studies of model organisms (see e.g. worms (Swierczek et al., 2011) Zhang et al., 2016), or flies (Seroude et al., 2002). Developing insights from frequently-measured high-dimensional organismal health states within large model populations will require new suites of analysis and modelling tools.

Given the complexity of the aging process, how can theoretical models make use of available and emerging sources of data in order to improve our understanding of aging within and between populations or species, to better predict individual aging outcomes, and to both understand existing interventions and to develop better individualized interventions in the aging process?

2 Theoretical approaches to Aging

Conceptual models such as the hallmarks of aging (López-Otín et al., 2013), seven pillars of aging (Kennedy et al.,...
Dynamical models explicitly simulate individual health trajectories vs age, i.e. longitudinal data. Because they generate synthetic individual data, they can serve much the same role as model organisms – whereby differences with respect to human aging can be significant but hopefully are also informative.

Dynamical models can include explicit interpretable mechanisms. Whereas statistical regression models can quantify the relationship between aspects of aging, they do not determine how the relationship arises. With dynamical models one can build mechanisms into the model. Any success of a dynamical model in reproducing real-world phenomena then suggests the viability of the underlying mechanisms, and allows the modeller to explore other phenomena that arise from the same mechanisms – which allows them to test the model.

A summary of early modelling work is provided in the review by Yashin et al. (2000). Yashin and colleagues also developed the quadratic hazards model (or stochastic process model, SPM) of aging (Yashin et al., 2012; Arbeev et al., 2016). It postulates that individual deviations from age-dependent norms of physiological measures interact with and exacerbate each other.

The concept of interactions between health measures can be embodied in a network of interactions, where nodes (or “vertices”) are the health measures while the interactions are connections between nodes (links, or “edges”). Such explicit networks were used to model mortality, such as the reliability theory of Gavrilov and Gavrilova (2001), or the network model of Vural et al. (2014). We developed what we now call a generic network model (GNM) to also model health measures such as the FI, and found that we could describe both population-level aging and mortality with a simple network of interactions that could be implemented on a computer to generate large synthetic populations (Taneja et al., 2016; Farrell et al., 2016, 2018).

Nevertheless, the health attributes (nodes) of our GNM did not directly correspond to specific observed health attributes. The reason for that approach was simplicity: all connected nodes have the same interactions, with simple undirected connections of equal weight, as illustrated in Figure 1. This enabled us to capture population-level health and mortality. To be able to predict detailed individual health states, we would need to empirically capture many interactions between observed individual health attributes within a population.

Reconstructing interactions from observed data is a daunting prospect. If hundreds of individual health attributes are measured, then there are tens of thousands of interactions to determine between all possible pairs of attributes. Nevertheless, initial progress is being made on smaller-sized problems. Using only cross-sectional binarized health data, we have developed a network model that includes specific observed health attributes (Farrell et al., 2020). To accomplish this,
Fig. 1 Links (grey lines) between nodes (circles) in a generic network model (GNM) of aging. Shown are a selection of 112 nodes, out of $10^4$ used in the model. Nodes do not represent particular observed health variables, but larger circles indicate nodes with more links. The most connected nodes are coloured orange, and are used in the aggregate health measure (frailty index, or FI) of the GNM. Note that the links do not change with age, while the binary health-state of the nodes does change with age between healthy and unhealthy. This model, with stochastic damage rates that can be implemented computationally (Taneja et al., 2016; Farrell et al., 2016, 2018), can generate large synthetic populations that reflect observed age-dependent health and mortality rates.

Fig. 2 Weighted and directed links (arrows) between nodes (circles) in a weighted network model (WNM) of aging. Shown are 10 nodes, each of which represents specific observed binary health variables from cross-sectional studies. Only the more significant links are shown, with weights represented by the line thickness and arrow size. This model, with stochastic damage rates that can be implemented computationally (Farrell et al., 2020), can generate large synthetic populations that reflect observed population-average age-dependent health and mortality rates.

Fig. 3 Simulated joint distributions of FI at death and death age from the network model described in Farrell et al. (2020), and illustrated in Fig. 2, given four individuals with the indicated initial baseline deficits (filled red points indicate their baseline age and FI). This demonstrates the capability of simulating populations of synthetic individuals, starting from different baseline conditions. The two columns show baseline ages of 65 (A and C) and 85 (B and D), the rows show different baseline FIs of 0.1 (A and B) and 0.3 (C and D), for a FI with 10 deficits. Note that the maximal observed FI is 1, reflecting the small number of deficits used in its construction.

The model parameters are distinct for each node and the network connections between nodes are distinctly weighted. An illustration of such a “weighted” network model (WNM) is shown in Figure 2. The new model can be used to generate individual health trajectories and mortality from any starting point, as illustrated in Figures 3 and 4, or to generate large synthetic populations with observable health states.

While these synthetic populations resemble observed aging populations, we are not yet able to robustly infer specific interactions between the observed health attributes, and we find that many different networks are consistent with the observed data. We are currently developing a more generalized approach, using continuous-valued longitudinal datasets, to make individual predictions of aging trajectories and infer a robust network of interactions on the level of blood biomarkers and functional disabilities.

3 Computational models

All but the simplest dynamical models need to be implemented computationally. Computational models allow us to simulate and explore the quantitative consequences of various hypotheses. That is, since computational models require well-defined algorithms, they force us to make our assumptions explicitly. By varying those assumptions we can explore their consequences.
This can clarify and illuminate possible mechanisms of aging.

Computational dynamical models can generate large synthetic populations of individuals with complete health trajectories and mortality. Such “perfect” data facilitates the systematic development of data analysis tools, including determining their statistical power for finite populations with missing data. More fundamentally, computational models also allow for a close examination of mechanisms at the population level: how does changing an assumption or a model parameter change the resulting health and mortality statistics of the population? The mechanisms behind the observed statistics of aging populations is a fundamental question of aging. This constructive flavour of modelling lends it to self to inter-organismal comparisons, since we can ask whether parameter tuning alone can explain differences between organisms or whether the structure of the aging model needs also to be changed. Similar comparisons can be made between any distinct subpopulations of any one organism, including medically treated vs untreated populations or genetically distinct populations.

Structural changes should not be needed to accommodate small differences between populations. Conversely, structural differences between models will lead to distinctive effects that can be observed and therefore tested in observations of natural populations. However, testability will be challenging for mechanisms that are not already well characterized. For example, we expect that the effects of genetically heterogeneous human populations that will eventually be important to characterize and include in models, but it will be hard to separate those effects from the intrinsic variability of the aging process. Nevertheless, a successful modelling framework should allow us to identify the statistical signatures of proposed mechanisms – which will facilitate subsequent testing.

To paraphrase Box [1976], all models are at least partially wrong but some can nevertheless be useful. However, rather than just trying to be mostly right or fairly useful, models should be improvable. This requires cycles of testing, development, and application to continually confront models with observable data. The benefit of this approach is that we can continually adjust our implicit or explicit assumptions to better and more usefully reflect emerging datasets.

3.1 Generalizability

Given the complexity of any organism, together with the complexity of the aging process, we can anticipate an enormous number of parameters required to tune complex models to fit a population. This tuning (also variously called fitting, learning, parameterization, or regression – depending on the context) is necessary if we want to do more than explore the qualitative consequences of a small set of model assumptions. Fitting the model to the data is necessary to make predictions for individuals, to compare populations, and to generate realistic synthetic populations.

We can distinguish between effective and fundamental parameters. Fundamental parameters would be model independent, can be measured or derived with a variety of techniques, and are unchanged in different contexts. Effective parameters (of effective theories [Transtrum et al., 2015]), on the other hand, cannot be precisely replicated in different contexts and cannot be derived from any fundamental assumptions. We expect that almost all parameters of models of aging will be effec-

Fig. 4 Distribution of sampled FI trajectories vs age from the network model described in Farrell et al. (2020) and illustrated in Fig. 2, given four individuals with the indicated initial baseline deficits. Trajectories are shown for samples with the median predicted death age, for the same individuals shown in Fig. 3. The purple shading indicates the percent of trajectories passing through each local region. The red circles indicates the baseline age and FI from which the simulation is started. The two columns show baseline ages of 65 (A and C) and 85 (B and D), the rows show different baseline FIs of 0.1 (A and B) and 0.3 (C and D), for a FI with 10 deficits.
tive parameters, i.e. they will be at least somewhat dependent on the choice of model. Nevertheless, effective parameters should not be treated as arbitrary tuning-knobs of a model. More useful parameters will change less between studies, will be more interpretable, and will lead to better model predictions. Determining good model structure that facilitates useful parameterizations is an iterative process that is one goal of successful modelling.

The technical details of fitting a model are well understood. Simple models can be hand-tuned to agree with population-level measures; however such simple models will not provide the best individual-level predictions. More sophisticated models can be fit with maximum likelihood, or other objective or “loss” functions, to obtain a model that best fits the available data. Bayesian approaches are also possible, where posterior distributions of parameters are obtained, rather than single point estimates.

An ideal data set would have a large homogeneous population, with complete, detailed health information that is longitudinally sampled frequently over individual lifetimes with uncensored mortality data. A computational model should be able to capture the important behavior exhibited in such data, so that it can then be used for individual predictions. Better computational models would provide better predictions. Are there other ways of distinguishing between such models? After all, even the best human data sets have small heterogeneous populations compared to national or global scales, with significant amounts of missing and censored data, and with irregular and infrequent longitudinal sampling with respect to the daily or weekly variability of our individual health status.

The answer hinges on how generalizable the model is to different data sets. If the model fit to one dataset poorly generalizes to other datasets — then the model has “failed”. It has failed in a useful way \cite{Box1976}, if we can expand the model in an interpretable way to accommodate both datasets. It has failed in a disappointing way if we cannot, and if we cannot understand why not.

It will be exciting to ask whether we can also generalize models to different applications. For example, consider interventions in the health of individual organisms due to drugs, surgery, treatment, lifestyle, accidents, illness, or (in the case of model organisms) experimental manipulation. Can a model predict the outcomes of such interventions? Better predictions could be used to both improve individual treatment plans and manage the health-care of increasingly greying populations \cite{Harper2014}. Nevertheless, we might expect that any predictive model that is optimally tuned to predicting specific mortality or health outcomes will not be easily generalized to predict other outcomes. While part of this limitation naturally arises from the data used to train the model, some of this limitation will also come from the model structure itself, since computational models will not be able to capture effects that are not allowed for in the model structure. Since the model structure itself may limit generalizability, some model structures (‘types of models’) will be better than others for this purpose.

3.2 Sloppiness, overfitting, and bias

Any computational model of aging will also be at risk of underdetermined parameters, overfitting, and bias from the data sets used in training.

Underdetermined parameters are parameters of the model that are not well constrained by the available data, but are nevertheless important for model functioning. A loose analogy may be handedness of ambidextrous people: while a hand might be used for handwriting, which hand is much less constrained. Sloppiness results in strong correlations between parameters that each range widely in magnitude. As a result, when considered individually these poorly constrained or “sloppy” parameters have large uncertainties \cite{Gutenkunst2007, Transtrum2015} — even when the model can still make robust predictions. This may not be a problem for models with effective parameters that aren’t directly interpreted, since the robustness of model prediction is not necessarily affected by sloppy parameters. However, if direct interpretation of parameters is desired, sharpening sloppy parameters involves either acquiring new data that allows more precise parameter determination or adding assumptions to the model. Large clean datasets generated by computational models can be used to determine the types of observational data that would be needed to sharpen parameters.

Overfitting is another generic problem with complex models with many parameters. Here, parameter values are fine-tuned to extract small improvements in fitting to the training data at the expense of good performance with new data. Overfitting is assessed by using dedicated training data and separate but comparable test data to assess model performance. Since fitting typically occurs through an iterative computational algorithm, overfitting can be minimized by model selection or stopping the fitting process when model performance on a held-out portion of the training data (the validation or development data) begins to decline.
When test data is not comparable to training data then poor model performance can reflect poor generalizability due to limitations of the training data rather than overfitting. Some problem of generalizability arises in most training datasets, because they have biases in demographics (age distribution, sex, race), health-state of enrolled participants, medical treatment during the course of the study, or in any other possible category within the dataset.

While there are many biases possible in data analysis, modelling bias can also arise due to the structure of model not being able to account for all aspects of the data. For example, survivor bias (Murphy et al., 2011) can be troublesome for models that do not capture mortality properly. When measured covariates have associations with mortality, the drop-out of individuals during the study due to mortality can bias the results. Models must account for survival effects with joint longitudinal-survival models (Hickey et al., 2016) that model health and survival together – otherwise modelling efforts can erroneously try to accommodate survival effects within the disease progression itself.

4 Machine Learning

Machine Learning (ML) is a loosely-defined term for a collection of data-based models that are typically fit or “trained” with large high-dimensional data sets. Typical goals of ML approaches are classification (the most common application (Domingos, 2012), though not our focus here), regression, and generating synthetic samples with the same properties as the observed data.

Neural networks are often used in more sophisticated ML models (Goodfellow et al., 2016), as in deep learning (LeCun et al., 2015). Neural networks consist of layers of artificial neurons that each have many linearly combined input connections from previous layers, and many output connections to subsequent layers. All connection parameters for every neuron are trainable. Non-linear transformations in each neuron allow multiple layers (i.e. “deep” networks) to represent functions of arbitrary complexity (Leskno et al., 1993; Raghunath et al., 2017).

Powerful neural networks have enormous numbers of parameters that must be trained for the network to represent the desired function. Neural networks are designed so that this training is computationally efficient and parallelizable. However, overfitting is a concern with so many parameters, and it is managed by careful use of regularization, which imposes restrictions on the parameters learned by the model. Test data, not used in training, is an important part of evaluating model performance and behavior.

Any unknown component of a model of aging can therefore be learned with a neural network, given sufficient training data. However, the researcher still needs to develop the overall structure of the model (i.e. how all the pieces “glue” together), choose appropriate neural network architectures, and manage the algorithms (and their “hyper”-parameters) that train the model while avoiding overfitting.

While initial exposure to ML is not for the faint of heart, new ML tools are easily learned and used after some expertise is gained. It is more challenging to achieve the goals of generalizability, where models perform well on data that is unlike the training set, and interpretability, where the mechanisms of the model can be understood and related to mechanisms in other model systems. Both of these goals are difficult because the flexibility of deep neural networks together with the efficient training algorithms requires huge numbers of parameters (limiting interpretability) and leads to strong bias outside the regime of training data (limiting generalizability). While large natural data sets can help with generalizability, interpretability has been more difficult to achieve (Rudin, 2019).

4.1 ML approaches in ageing research

Several ML models have been developed specifically for aging. Pierson et al. (Pierson et al., 2019) developed a model that infers “rates of aging” for individuals that correlate with risk factors of aging, and that can be used to forecast future health. Avchaciov et al. (2020) developed a model that infers “rates of aging” for individuals that correlate with risk factors of aging, and that can be understood and related to mechanisms in other model systems. Both of these goals are difficult because the flexibility of deep neural networks together with the efficient training algorithms requires huge numbers of parameters (limiting interpretability) and leads to strong bias outside the regime of training data (limiting generalizability). While large natural data sets can help with generalizability, interpretability has been more difficult to achieve (Rudin, 2019).
larly promising direction for machine learning in aging research.

To forecast multi-dimensional health trajectories, existing machine learning approaches for modelling disease progression could be adapted to model aging progression. While many of these do not model mortality (Schulam and Suchi, 2015; Alaa and van der Schaar, 2018; Fisher et al., 2019; Walsh et al., 2020), joint longitudinal-survival models could be adapted (Lim and van der Schaar, 2018). A stochastic process model of aging has already been developed that models both health trajectories and mortality (Yashin et al., 2007; Arbeev et al., 2011; Yashin et al., 2012; Arbeev et al., 2014), but it has not yet been applied to high-dimensional datasets.

Given efficient algorithms for parameter determination (learning) together with arbitrary functional dependence (deep learning), we see great promise for ML approaches in the study of aging. Natural applications are filling in missing data, identifying natural subpopulations or categories of aging organisms, incorporating multiple heterogeneous data sources, and modelling the aging process itself as a stochastic dynamical process.

5 Challenges for aging models

In the introduction, we listed four challenges of studying aging: how to better observe health in aging populations, how better understand the mechanisms behind what we observe, how to better predict individual health, and how to better intervene in the aging process. In this section we revisit those challenges in the context of computational models of the aging process.

5.1 E-health and self-reported data

Focused population surveys are expensive. Large scale studies such as CSHA (Canadian Study of Health and Aging Working Group, 1994) or NHANES (Centers for Disease Control and Prevention National Center for Health Statistics, Updated 2014) are limited to populations on the order of 10,000 individuals. Even the impressive UK Biobank has less than one million individuals (Sudlow et al., 2015). In contrast, the use of electronic health records (EHR) (Clegg et al., 2016) or self-reported data from self-reporting apps, could also reach large fractions of national populations. These developments will provide natural datasets with large populations that have lifetime longitudinal information, perhaps quite finely-grained in time.

However, significant biases are found in EHR data (Vassy et al., 2018) and also in self-reported health data (Zajacova and Dowd, 2011; Gunasekara et al., 2012). While it would be difficult to explicitly account for these biases in order to reconcile EHR and self-reported data with corresponding national prospective studies from similar populations, an easier challenge will be to directly exploit this data for individual-level health models and predictions (Jylhä, 2009).

5.2 Defining and comparing populations

Some über-model of aging might explicitly capture each aspect of individual variability, including a life-history of diet, lifestyle, injury, medication, and health-care. More realistically, most variability will first need to be captured implicitly within aging models through parameterization or model structure – tuned for different natural subpopulations. Race (Williams, 2005), sex (Gordon et al., 2017), socioeconomic position (Kiesebeck et al., 2007), social vulnerability (Wallace et al., 2015), access to health-care (Santana, 2000) or pensions (Aguila et al., 2018), rural/urban (Yu et al., 2012), and nationality, are all categories that have been studied by aging researchers. Chronic disease, genetic disorders, and certain patterns of multimorbidity or polypharmacy could also serve as natural categories. A challenge will then be to reduce the significance of these natural categories for individuals by making the more of the implicit differences between the populations explicit – allowing for better individualized study of aging and treatment. To be able to achieve this requires good data coverage across many subpopulations, but also good models that can characterize and model the differences.

We would expect that different species, i.e. animal models of aging, would require some structural differences to model accurately. Part of this is that different data is available for them. For example, cognitive data is less available in animal models, and health-care is often irrelevant. Nevertheless, modelling animal aging and determining what those differences are will help us understand how aging naturally progresses, and how health-care changes the aging process for humans. Modelling could help us to determine how much human interventions mitigate and/or exacerbate the intrinsic variability of human populations to produce the observed variability of individual aging.
5.3 Multiple scales

Different physiological scales present exciting opportunities in aging research. For example, molecular data is appealing because it can be high throughput and low-bias. Nevertheless, outcomes at higher (functional) scales are typically of greater individual interest. One challenge is to identify interactions between scales, from molecular to behavioral, and to incorporate them in aging models (Ferrucci et al., 2018; Mitnitski and Rockwood, 2019; Kuo et al., 2020). Reliably bridging the scales, particular in light of patchwork individual data (over scale, over time, and over individual measures), is an important challenge. Understanding how different scales work is the essence of understanding the aging process. How does damage propagate from the molecular to activities of daily living? Conversely, how do interventions of lifestyle or injuries propagate towards the molecular?

5.4 Longitudinal studies

Large-scale longitudinal data collection provides an opportunity for aging models to employ these data to better capture the aging process of individuals, including individual variability. Natural questions include how much is gained by more frequent measurements, how to best handle variables observed at irregular time intervals and with varying degrees of missing observations, how to model mixtures of qualitative and quantitative measurements or of self-reported and molecular measures, and how to include individual health histories in individual health predictions. Computational models of aging are well placed to use longitudinal data. The challenge is to do so; and to do so with a computationally efficient approach given the vast amount of data potentially available.

5.5 Predictions

Although individual predictions of health trajectories and mortality are natural goals for computational models of aging, a challenge is how to evaluate and judge the quality of the predictions. Evaluation is straightforward retrospectively, by using separate training and test populations with either cross-sectional or longitudinal data with linked mortality. The determination of what quality of predictions are possible with what sort of data for individuals of a given age and health status are important questions to answer.

5.6 Medicine, illness, and interventions

Being able to predict the individual results of medical interventions (including medication), of illness or injury, or of life-style interventions such as exercise is crucially important. Most individuals experience many such interventions over their lifetime, so these are implicitly and approximately included in models of national aging populations. Indeed, we assume that such interventions are the origin of many national differences or differences within a national population over history.

A grand challenge will be to make these interventions explicit, particularly within models of individual health during aging. If successful, such explicit models will allow better individual prediction, better identification of intrinsic variability, and the ability to tailor or individualize interventions to better reflect individual priorities. To do this well we may need to include earlier data across individual life courses for large populations, including electronic health records and longitudinal data.

6 Looking ahead

Early modeling has been restricted to simple theoretical or statistical explorations of the aging process, through damage accumulation or regression models. Though this approach has limited ability to predict individual health, it has advanced our conceptual understanding of how aging could work.

More recently, various models have started to address observational data that includes the detailed health and mortality of large numbers of individuals, which we call “networked” models since they capture interactions between different aspects of individual health. Our work in this area has included explicit complex networks (Taneja et al., 2016; Farrell et al., 2016, 2018), but the networks can also be theoretical (Yashin et al., 2012; Arbeev et al., 2016), correlational (Hidalgo et al., 2009; Roque et al., 2011; García-Peña et al., 2019), or implicit in the approach. Few models have addressed both individual health and mortality, though these are now starting to emerge (Farrell et al., 2020).

Once multiple stochastic models with both health and mortality are developed, then the natural scientific selection of “better” models can proceed by confronting their simulated results with observed data. Natural measures of goodness of models include predictive quality, generalizability across different population demographics (including age and health, but also sex and chronic conditions), interpretability, and the ability to effectively and efficiently train with big heterogeneous data
sets. The ability to efficiently and effectively predict future individual health trajectories will be revolutionary, particularly if models include the effects of injury and disease, or the benefit of various medical and pharmacological interventions.

While observational data sets will only increase both in the number of individuals, in the number of physiological aspects of health that are reported, and in the frequency of longitudinal measurements, the amount of easy-available data available to train, test, and compare modelling approaches is still limited. Public “challenge” datasets could provide realistically imperfect but extensive longitudinal health data together with mortality statistics to allow for comparison between and improvement of modelling approaches. Providing raw data together with cleaned data is important, since improvements in data-cleaning (Van den Broeck et al., 2005) can also lead to model improvement – and computational pipelines of data-cleaning will be increasingly necessary for large population studies.

We will never achieve a “death-clock” where we can precisely predict an individual’s death, nor a health-calendar of precisely how their health will change as they age. Nevertheless, we may be able to classify and identify useful aging phenotypes, to obtain good predictions of individual health-trajectories and mortality, and to identify the most useful health interventions for a given individual. Because computational models can capture the effects of many interacting aspects of human physiology, they are promising tools to use to help address these questions.

How computational models can and will be used will depend on how successful they become. We believe that they will lead to a deeper understanding of how aging works, both for human aging and for model organisms. They could also help to control for the effects of different populations, to improve national or regional comparisons of the determinants of health. We also expect that models will be able to capture the effects of various health interventions at the individual level. If models become sufficiently good, they would be able to help individuals to develop and adapt their personal health plans. We are hopeful.

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