Review

Artificial intelligence for aging and longevity research: Recent advances and perspectives

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ABSTRACT

The applications of modern artificial intelligence (AI) algorithms within the field of aging research offer tremendous opportunities. Aging is an almost universal unifying feature possessed by all living organisms, tissues, and cells. Modern deep learning techniques used to develop age predictors offer new possibilities for formerly incompatible dynamic and static data types. AI biomarkers of aging enable a holistic view of biological processes and allow for novel methods for building causal models—extracting the most important features and identifying biological targets and mechanisms. Recent developments in generative adversarial networks (GANs) and reinforcement learning (RL) permit the generation of diverse synthetic molecular and patient data, identification of novel biological targets, and generation of novel molecular compounds with desired properties and geroprotectors. These novel techniques can be combined into a unified, seamless end-to-end biomarker development, target identification, drug discovery and real world evidence pipeline that may help accelerate and improve pharmaceutical research and development practices. Modern AI is therefore expected to contribute to the credibility and prominence of longevity biotechnology in the healthcare and pharmaceutical industry, and to the convergence of countless areas of research.

1. Introduction

Aging can be defined as a gradual, multifactorial, time-dependent process leading to the loss of function, biological and physical damage, and the onset of multiple age-related diseases. Aging progressively affects most regulatory mechanisms due to the hierarchical organization of living systems. The human organism is a multi-level, complex system comprised of billions of independent cells that form different types of tissues. These tissues are the main blocks used to assemble organs, and these organs are organized in different systems including the lymphatic, respiratory, digestive, urinary, or reproductive systems to achieve specific tasks. Aging can be influenced by the complex interplay between environmental, mechanistic, biochemical and evolutionary constraints. Therefore, dysfunctions affecting only a few biological processes within the cells of one or several organs can propagate to all parts of the body. This explains why aging cannot be fully understood or

controlled when monitoring only a restricted number of physiological processes. Taken together, aging appears to be the long-term result of the disruption of different dynamical equilibriums established between antagonistic processes, rather than the result of a sudden appearance of isolated molecular processes or components with intrinsic negative effects. The systemic and multifactorial nature of aging explains why understanding its biology and mechanisms are so complex and why, as a consequence, aging research is continuously in need of multidisciplinary and global approaches. Novel experimental techniques have allowed the generation and accumulation of a huge amount of aging-related data, including genomic (Gleeson et al., 2017) (Yi et al., 2013) (Yi et al., 2013) (Bennett et al., 2016), transcriptomic (Artemov et al., 2015) (Bolotin et al., 2017), microRNA (Zabolotneva et al., 2013), proteomic (Di Meo et al., 2016), antigen (Ionov, 2010), methylation (Yin et al., 2017), imaging (Lee et al., 2017a,b) (Niklinski et al., 2017), metagenomic (Alexander et al., 2017), mitochondrial

(Sotgia and Lisanti, 2017), metabolic (Nielsen, 2017) and physiological (Pretorius and Bester, 2016). These data provide an unprecedented detailed overview of the aging process. However, the analysis and practical use of the information contained within this huge amount of data also requires adapted computational approaches such as machine learning (ML) and, more recently, the development of deep learning (DL) techniques which are the cornerstones of modern artificial intelligence (AI) technologies. From this point of view, recent AI advances have had a major impact within the field of aging research (Moskalev et al., 2017). The attractive feature of AI is its ability to identify relevant patterns within complex, nonlinear data, without the need for any *a priori* mechanistic understanding of the biological processes. AI unveils the mechanistic relationships taking place within the body. Today, DL and AI algorithms have been successfully developed and applied in many pharmaceutical areas (Mamoshina et al., 2016; Gawehn et al., 2015; Lenselink et al., 2017; Chen et al., 2018) with applications as wide-ranging as prediction of organic chemistry reactions (Wei et al., 2016), identification of aging biomarkers (Zhavoronkov et al., 2016), optimization of chemical synthesis (Segler et al., 2018), prediction of pharmacological properties of drugs (Aliper et al., 2016), analysis of relationships between certain lifestyle choices like smoking and accelerated aging (Mamoshina et al., 2018c), investigation of protein secondary structure (Spencer et al., 2015), modeling features of RNA-binding protein targets (Zhang et al., 2016), analysis of drug-induced hepatotoxicity (Xu et al., 2015), or the study of long non-coding RNAs (Fan and Zhang, 2015).

As emphasized by Deep Knowledge Analytics (www.dkv.global/analytics) in its recent industry analytical report entitled 'AI for Drug Discovery, Biomarker Development and Advanced R&D 2018,' AI is expected to make a major impact on healthcare. It can be used for the development of effective personalized medicine based on the interpretation of large medical databases gathered over the years by companies and healthcare providers. There are currently several companies applying AI technologies within the field of aging research. Bioage is a company using ML and genomic data for the development of biomarkers of aging and drug discovery for aging and age-related disease. Insilico Medicine is developing DL-based algorithms and deploying an integrated AI pipeline for aging research, biomarker development, and drug discovery in one end-to-end learning pipeline. The goal of the company is to find novel solutions for aging and age-related diseases using advances in genomics, AI, and big data analysis. Atomwise is using AI for aging research with a drug discovery pipeline targeting age-related diseases that still lack effective treatments, like Alzheimer's disease. These examples illustrate that AI technologies can be applied at different levels, with the goal of facilitating the development of new pharmaceuticals quicker, cheaper, and more effectively (Fleming, 2018). AI can be applied for accelerating the identification of biomarkers of age, for the identification of new targets and geroprotectors, for accelerating and optimizing the development of new compounds with specific desired properties, to improve patient prognosis by reducing error rate, for helping to select the most appropriate treatment by predicting treatment outcome (Trtica-Majnaric et al., 2010), and for predicting the chance of drug success during clinical trials or clinical trials outcomes. For a broad overview of the use of AI in biomedicine, we refer the reader to these current reviews (Rifaioglu et al., 2018; Ching et al., 2018; Tsigelny, 2018; Fabris et al., 2017).

The aim of this review is to provide a technical overview of the advances and opportunities offered by AI for aging biomarkers development and anti-aging drugs discovery. This work emphasizes that despite their specific technical requirements, the computational methods used for these tasks can be integrated within a single workflow to optimize several steps of aging research—from the identification of aging signatures to target identification and ad hoc molecule generation. Currently, biomarker development is an intensive area of research in geroscience, as it lays the foundation for efficient preclinical and clinical evaluation of potential health span-extending interventions. We

describe how deep learned aging clocks are used to identify aging biomarkers and other targets of interest. The emergence of AI-based methods for small molecule drug discovery is a major change in the standard drug discovery pipeline. For decades, computational methods have been used for accelerating the identification of potential leads during the early stages of the drug discovery process. However, with its ability to generate molecules with specific properties, AI based molecular generators provide new, promising opportunities. At this time, the main algorithms designed to that end are described, and the advantages and current challenges of these approaches are summarized. One of the major challenges for the use of AI technology is to obtain more reliable predictions. This relies strongly on the ability to extract the most relevant features. This paper examines the current strategies used in aging research to extract more biologically relevant features and make AI-based models more easily interpretable. To conclude, a short discussion addresses a challenge specific to the development of increasing use of AI within healthcare—privacy protection regulatory issues, which became a major concern with the increasing amount of personal data being stored, used, or even shared by AI-powered healthcare applications.

2. Advances in artificial intelligence

2.1. Machine learning

Machine learning (ML) refers to algorithms that can learn from and make predictions on data by building a model from sample inputs. ML is commonly employed for computing tasks where designing and programming explicit algorithms with good performance is difficult or infeasible. Today, most commonly used traditional ML methods include k-nearest neighbors (kNN) (Altman, 1992; Kramer, 2013), logistic regression (LR) (Walker and Duncan, 1967), support vector machines (SVM), also called support vector networks (Cortes and Vapnik, 1995), gradient boosting machines (GBM) (Mason et al., 1999; Friedman, 2001; Ayyadevara and Kishore Ayyadevara, 2018), and random forest (RF) (Ho, 1995; Breiman, 2001; Fratello and Tagliaferri, 2018). The performance of these methods can vary depending on the type of task (regression or classification), types, and amount of data to handle.

2.2. Deep learning

Deep structured learning, also called deep learning (DL) or hierarchical learning, refers to a class of ML techniques that exploit many layers of non-linear computational units to model complex relationships among data. These architectures, composed of multiple layers, are commonly called deep neural networks (DNNs), or sometimes stacked neural networks. The difference between the initial single-hidden-layer artificial neural networks (ANNs) and DNNs is the depth; that is, the number of layers of nodes through which data is processed. Usually, more than three layers (including input and output) qualify as "deep" learning. Thus, "deep" is a technical term that means more than one hidden layer. As other standard neural network architectures, DNNs are efficient universal approximators. But they have additional characteristics as they are based on the learning of multiple levels of features or representations of the data. They use a cascade of many layers of nonlinear processing units for feature extraction. Each successive layer uses the output from the previous layer as input. Higher level features are derived from lower level features to form a hierarchical representation. This hierarchy of features is called a deep architecture. These methods are capable of learning multiple levels of representations that correspond to different levels of abstraction. These levels form a hierarchy of concepts. Among the different architectures proposed so far, recurrent neural networks, generative adversarial networks, and transfer learning techniques are gaining popularity within aging research and are often considered for various applications in healthcare. As a consequence of the rise of DL, traditional ML methods

are now commonly used as baseline models to assess the performance of more recent DNN-based models.

2.3. Reinforcement learning

Reinforcement learning (RL) refers to goal-oriented algorithms, which learn how to attain a complex objective or maximize along a particular dimension over many steps (Arulkumaran et al., 2017; Kulkarni, 2017). The key feature of RL algorithms is that they operate in a delayed return environment, where it is not obvious to understand which action leads to which outcome over many time steps. Thus, RL aims at correlating immediate actions with the delayed returns they produce. The reinforcement takes place in the sense that RL algorithms are penalized when making the wrong decisions, and they get rewarded when making the right one. RL algorithms are expected to increase performance in more ambiguous, real-life environments (Nguyen et al., 2017a,b).

2.4. Generative adversarial networks

Generative Adversarial Networks (GANs) are structured, probabilistic models for generating data. Being an unsupervised technique, GANs can be used to generate data similar to the dataset that the GAN was trained on (Goodfellow et al., 2014; Goodfellow, 2017). Although relatively new, GANs have already been applied in various fields, including making predictions of compound properties or for molecular structure generation (Kadurin et al., 2017b; Kadurin et al., 2017a; Polykovskiy et al., 2018; Zhavoronkov et al., 2018a,b). A GAN consists of two DNNs called Discriminator and Generator, both differentiable functions. The discriminator estimates the probability that a given sample is coming from the real dataset. It works as a critic and is optimized to distinguish the fake samples from the real ones. The generator outputs synthetic samples using a noise variable as input following a distribution. It is trained to capture the real data distribution so that it can generate samples with distribution which are as real as possible. The generator should improve its output until the discriminator is unable to distinguish the generated output from the real ones.

The two models compete against each other during the training process. The goal of the generator is to try to trick the discriminator, while the discriminator attempts to not be cheated. This process is called a zero-sum game. It happens between the two models and motivates them to improve their functionalities in order to obtain generated samples indistinguishable from the real data.

From a conceptual point of view, GANs share similarities with RL. GANs appear more advantageous in the sense that it is possible to "backpropagate" the gradient information from the discriminator back to the generator network. Consequently, the generator knows how to adapt its parameters in order to produce output data that can fool the discriminator.

2.5. Transfer learning

Transfer learning (TL) is a ML method where the set of learned features of a model for a specific task is reused, or repurposed, as the starting point for a model on a second task. In practice, TL can be applied in DL only when the model features learned from the first task remain general. It means that the features learned on the task must also be suitable for the second task (Torrey and Shavlik, 2010). In practice, TL is used as an optimization technique that allows saving time or getting better performance. This can be of great interest given the vast computational and time resources needed to develop and train DNN models on problems such as computer vision and natural language processing tasks, for instance.

2.6. Meta learning

Meta learning aims at applying ML algorithms on metadata obtained from ML experiments to improve the performance of the learning algorithms themselves. The hypothesis behind meta learning is that by using different kinds of metadata such as properties of the learning problem, algorithm properties (performance measures), or patterns obtained from the data, one can learn, select, or combine different learning algorithms to more effectively solve a given learning problem (Zhou and Wu, 2018; Gupta et al., 2018). This approach could be especially useful in the context of aging research because the most effective way to train learning algorithms depends on the type of data used as well as on the nature of the questions to be answered.

3. Databases for DL for aging research

Various initiatives have been launched to organize and disseminate the large amount of biological data generated in aging research. CellAge (http://genomics.senescence.info/cells/) is a manually curated database of genes associated with cell senescence. The data come from gene manipulation experiments in different human cell types. This database is hosted within the Human Ageing Genomic Resources, a collection of databases and tools designed to help researchers study the genetics of human ageing (Tacutu et al., 2018). It includes various resources such as the LongevityMap (http://genomics.senescence.info/longevity/)—a repository of genetic association studies of longevity which aims at aggregating the current knowledge of the genetics of human longevity (Budovsky et al., 2013). GenAge (http://genomics.senescence.info/genes/) is a benchmark database of age-related genes. Geroprotectors (http://geroprotectors.org/) is a curated database of geroprotectors. It contains more than 250 life-extension experiments in 11 wild-type model organisms, and data about more than 200 chemicals promoting longevity, including compounds approved for human use that are available. The different features of this database are described in (Moskalev et al., 2015). The online crowd sourced pathway annotation database, AgingChart (http://agingchart.org) provides a list of pathways implicated in aging and longevity (Moskalev et al., 2016). Another source of information regarding aging research is the International Aging Research Portfolio (IARP) (https://agingportfolio.org/). IARP provides users with access to information about current trends in aging research, major centers of research, key investigators, and associated research programs (Zhavoronkov and Cantor, 2011) (Kolesov et al., 2014). IARP aims at helping to fund organizations to collaborate, make decisions, and set future directions for research efforts in aging.

4. Applications of AI in aging research

4.1. Aging biomarker discovery and personalized medicine

Precision medicine is dependent on robust quantitative biomarkers. Biomarkers of aging are tools able to provide a quantitative foundation upon which to evaluate the therapeutic efficacy of clinical, health-span-extending interventions. However, one of the current major impediments in human aging research is the absence of biomarkers that may be targeted and measured to track the effectiveness of anti-aging therapeutic interventions. This might be explained by the fact that standard biomarkers are usually developed with the purpose of measuring a strictly defined physiological process, and specific clinical procedures based on the use of predefined biomarkers. As a result, they are not necessarily adapted for measuring the effects of a systemic process such as aging. Currently, many biomarkers of aging monitor not only one, but a restricted set of physiological functionalities whose disruptions are known to trigger the onset of specific diseases and malfunctions correlated with aging. Although this strategy provides accurate results and useful information about aging itself, the considered biomarkers are not always able to represent the health state
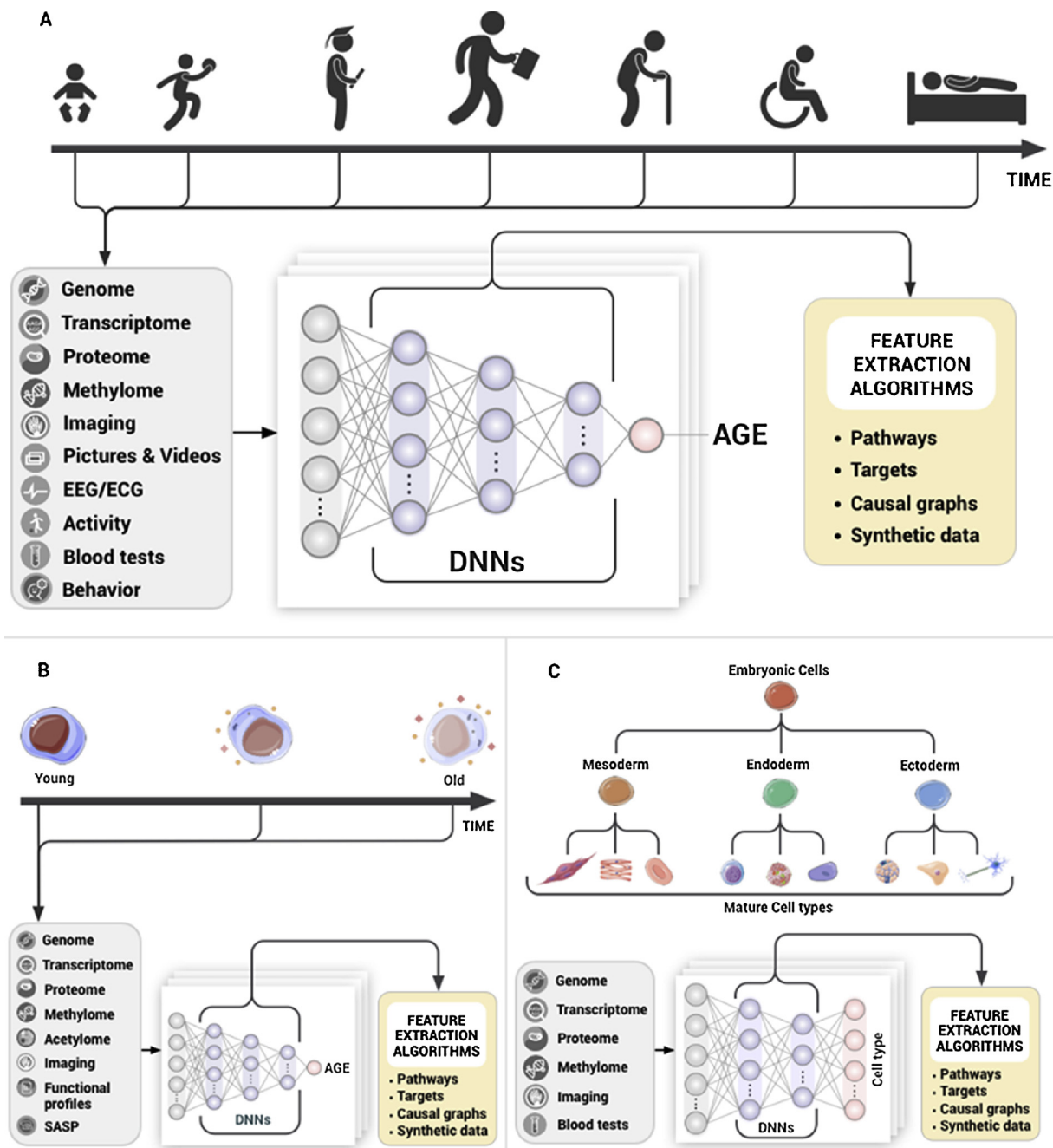
Fig. 1. Applications of artificial intelligence to aging research for biomarker development and target identification. 1 A. Machine-learned predictors of biological age at the organismal level and population level. 1B. Machine-learned age predictors at the cell and tissue-level. 1C. Machine-learned predictors of cell type and differentiation state.

with enough accuracy. Therefore, there is still a need to develop biomarkers which are objectively quantifiable and easily measurable characteristics of biological aging. The design of such biomarkers, from an experimental point of view, is a time-consuming and tedious multistep process that includes proof of concept, experimental validation and analytical performance validation. AI technologies offer effective alternatives for the development of aging biomarkers (Fig. 1A and B) and DL-based aging clocks have already been used to identify quantitative biomarkers. Different configurations and architectures have been studied. Data types include medical big data obtained through genetics, genomics (McCue and McCoy, 2017; Leung et al., 2016), biochemistry (Tetko et al., 2016), proteomics (Issa et al., 2014) and clinical imaging (Lee et al., 2017a,b). DL-based aging clocks may also differ through training and validation protocols.

The use and development of such aging clocks must be done with caution. Indeed, it is important to distinguish the chronological age—the number of years an individual has been alive—from the biological age. The biological age, commonly referred to as the physiological age or the metabolic age, is the measure of how well the different organs, physiological processes, and regulatory systems of the body perform and to what extent are being maintained. In theory, monitoring biological age provides an estimate of the health status of an individual. Aging clocks estimate biological age from biological data and perform linear or non-linear regressions for estimating the chronological age of the individual. Thus, the training protocol of aging clocks aims at minimizing the difference, called aging acceleration, between the physiological age—estimated by the model—and the actual chronological age of the individual. However, it was shown that improving

tchronological age estimation accuracy through error minimization can also undermine the biological age acceleration significance and reduce the ability to differentiate among disease states or mortality risks (Mamoshina et al., 2018b; Pyrkov et al., 2018). When using ML tools, such as DL architectures to unravel complex and nonlinear relations between the features in the data and produce even more accurate models, it is important to consider that the search for improved accuracy does not induce a significant loss of biological information. Nevertheless, more accurate chronological age estimations from biological samples can find applications as described below.

4.1.1. Imaging biomarkers

Magnetic resonance imaging (MRI) is an advanced imaging technique used for the observation of different diseases and parts of the body. Different computational methods can be used for analyzing the results of MRI. The analysis can be done either for classification—assigning a label to an MRI series (normal/abnormal, level of severity, etc.) or for segmentation—to identify the boundaries of various tissues. In both cases, the analysis necessitates an extraction of information from images. The most recent advancements in this field were obtained using convolutional neural networks (CNNs), a type of neural network specialized for processing image data (Akkus et al., 2017; Badrinarayanan et al., 2017; Pereira et al., 2016; Liu et al., 2018). Although MRI images can be used as exclusive inputs for DL models, other studies have shown the potential to combine them with additional features. For example, in (van der Burgh et al., 2017), a deep learned survival predictor for patients suffering from amyotrophic lateral sclerosis—a progressive neuromuscular disease—was assembled using MRI structural connectivity and brain morphology data in addition to commonly used clinical characteristics. The model demonstrated 84.4% accuracy for classifying patients as short, medium, or long-potential survivor.

Structural MRI data has also been used for age estimation. It serves as a biomarker for aging in adults, and for patients with conditions such as Alzheimer's disease (Cole et al., 2016). Recently, a DNN-based approach using structural, volumetric features derived from T1-weighted MRI was shown to outperform RF or ANN for age prediction (Bermudez et al., 2017). The technique was used on a sample of 3348 subjects aged from 4 to 26 years. A biomarker called Brain Age Gap (BAG) was created. DNNs elicited a BAG of 2.87 years compared to 2.77 years with ANN, and 2.94 years using RF. Performance of the DNN was improved by using ensemble methods, with a mean absolute error (MAE) of 2.38 years with a DNN ensemble. These results demonstrate that age can be accurately predicted with unimodal imaging in a young population using engineered features instead of raw images. The algorithm developed in this study could also be used as a biomarker for neurodevelopment and disease detection that can be easily translatable to the bedside.

Other types of biomarkers of aging using images as inputs have been suggested. For instance, in (Bobrov et al., 2018), the authors propose a novel, non-invasive class of visual photographic biomarkers of aging using the photographic images of eye corner areas for aging prediction. The eye corner area of the human face is believed to be the most prone to aging (Flament et al., 2013). To train and validate the model, a dataset of around 8000 high-resolution left and right eye corner photos with labeled with true, chronological age. The model is based on a modified version of Xception (Chollet, 2017), a DNN-based model where all layers, except the last fully-connected layer are initialized with pre-trained weights from the ImageNet database. Experiments showed that the model is able to achieve a mean absolute error of 2.3 years within the age range of 20 to 80 years old. Those results suggest that high-resolution images of eye corner wrinkles can be utilized to obtain accurate chronological age estimation. Interestingly, age predictions for individuals of 70 years old and older were less accurate. A hypothesis suggested by the authors is that the divergence in human phenotypes becomes larger as they age. On the other hand, younger people have relatively the same amount of wrinkles and pigmentation. This characteristic has also affected the accuracy of age prediction among very young individuals.

4.1.2. "Omics" biomarkers

A transcriptomic-based age predictor was presented in (Mamoshina et al., 2018b). To train this model, 545 transcriptomic samples from 12 datasets of human skeletal muscle labeled according to the chronological age, were collected. For this study, several regression models were built including Elastic Net, SVM, kNN, RF, and Deep Feature Selection (DFS) Model. A linear regression was used as a baseline and its performance compared to other ML approaches. Although all models achieved a strong correlation of predicted and chronological age, SVM and DFS models clearly outperformed the other methods in age prediction, achieving R2 values of 0.83 and 0.83 and mean absolute error (MAE) values of 7.20 and 6.24 years, respectively. The performance of models was also evaluated on gene expression samples of the skeletal muscles from the Gene expression Genotype-Tissue Expression (GTEx) project.

4.1.3. Multi-modal biomarkers

One of the first methods for identifying biomarkers of aging through population age estimates using DNNs was proposed in (Zhavoronkov et al., 2016). In this study, an ensemble of 21 DNNs of varying depth structure was used to predict human chronological age. The features, a set of 41 biomarkers for each sample, were extracted from tens of thousands of blood biochemistry samples from patients undergoing routine physical examinations. Although being highly variable in nature, the blood biochemistry tests are easy to perform. Furthermore, they are in clinical use and commonly used by physicians. The best performing DNN in the ensemble demonstrated a R2 of 0.80 with a MAE of 6.07 years, while the entire ensemble achieved a R2 of 0.82 and a MAE of 5.55 years. In order to analyze the importance of the different features used, the permutation feature importance (PFI) method was utilized. The five most important biomarkers identified were; albumin whose low level is associated with increased risk for heart failure in the elderly, glucose which is linked to metabolic health; alkaline phosphatase whose level in blood increases with age; erythrocytes which are known to be damaged by oxidative stress; and urea which is known for increasing oxidative stress. These five biomarkers monitor the physiological status of renal, liver and metabolic systems, and respiratory function. The associated features can be used for tracking physiological processes related to aging.

As explained above, aging acceleration is a biologically relevant variable associated with the prevalence of major diseases and mortality. Consequently, aging acceleration can also be connected to overall health using a scale based on deviation from the patient's predicted chronological age. This concept is applied in (Wang et al., 2017) where a DNN-based predictive model of physiological age was developed with the Mount Sinai Health System (MSHS) EMR data. Physiological measurements, including vital signs and lab tests from the EMR, were used as features to train the model. To identify the most relevant features regarding age predictions, correlation analysis was performed. Among all the vital signs, pulse pressure and systolic blood pressure show the strongest positive correlation with chronological age for both genders. Lab tests positively correlated with age included urea nitrogen, glucose, hemoglobin A1C, PROTIME/INR; whereas lab tests that most negatively correlated with age are glomerular filtration rate estimate, albumin, total protein, red blood cell count, and hematocrit. Furthermore, correlations between physiological measurements and chronological age were also investigated using unsupervised hierarchical clustering on the LOWESS smoothed trends of the most common physiological measurements across all patients. This approach allows clustering of different physiological measurements with similar trends. Finally, regression analysis was performed to evaluate how these variables combine together to predict physiological age. The

performances of three methods—RF, Elastic Nets, and DNN—were compared and the DNN showed the best performance. The DL model was then used for the prediction task. The results show that a combination of vital signs and lab tests is more predictive of chronological age than each data type used alone. Patients for which physiological age was higher than the chronological ones elicit increased prevalence of hypertension and cardiovascular disorders, increased chronic inflammation, possibility of chronic anemia, poor nutritional status, decreased kidney function and potential liver damage. On the other hand, patients predicted younger have, in general, opposite physiological patterns for many of the physiological measurements, with some exceptions. The specific physiological patterns identified include low risk for hypertension and hyperlipidemia, healthy kidney and liver functions, healthier nutritional status, and higher risk for venereal diseases.

Taking into account ethnic differences in health, diet, lifestyle, behavior, environmental exposures, and average rate of biological aging, it was assumed that deep learned biomarkers of aging are population dependent (Cohen et al., 2016; Zhavoronkov et al., 2016). Using the results obtained for predicting patient biological age using blood biochemistry, a set of population specific DL-based predictors of biological age trained upon blood biochemistry and hematological cell count datasets was presented (Mamoshina et al., 2018a). Samples from patients belonging to three distinct populations—Canada, South Korea, and Eastern Europe— were selected. Compared to the first study, the models used less features (21 compared to 41 features) to train three separate deep networks on three specific ethnic populations. Models were trained on 19 blood test features, 15 biochemistry markers, including Albumin, Glucose, Hemoglobin, Cholesterol, Sodium, Urea, LDL Cholesterol, Triglycerides, Hematocrit, HDL Cholesterol, Total Protein, Calcium, Creatinine, Potassium, and Total Bilirubin, and four are cell count markers, including Erythrocytes, and Platelet count. Patient sex and population type were also incorporated in the feature set. As in the previous work, the age prediction was treated as a regression task. The model takes a vector of blood test values and returns a single value of patient age. To evaluate the association of the predicted age acceleration or age slowdown with all-cause mortality, hazard ratios were also computed. The results showed that the best-performing predictor achieved an MAE of 5.94 years, having greater predictive accuracy than the best-performing predictor of the previously reported aging clock (which achieved an MAE of 6.07 years). Furthermore, as for the previous studies, deep learned predictors outperformed conventional ML models. Interestingly, population type appeared as one of the most important markers for age quantification. These results confirm the hypothesis that ethnically diverse aging clocks are capable of predicting chronological age, and quantify biological age with greater accuracy than generic aging clocks.

4.1.4. Epigenetic biomarkers

Epigenetics refers to the mitotically heritable modifications in gene expression which do not involve changes within the genetic code. Epigenetic mechanisms are rather complex, including a combination of molecular, chemical and environmental factors (constituting the epigenome) together with the genome, in establishing the unique functionality of each cell type. DNA methylation is the most studied epigenetic mark. DNA methylation is characterized by the addition of a methyl group to the cytosine in a cytosine-phosphate-guanine dinucleotides or a CpG site. It was demonstrated that DNA methylation marks elicit an age-associated pattern which has been used earlier to design several epigenetic clocks of biological age (Hannum et al., 2013; Horvath, 2013). The assessment of epigenetic DNA methylation age is based on the association of the methylation level in selected CpG sites with chronological age, in a population. The methylation level of those sites can be used to evaluate the chronological age of individuals (Mitnitski, 2018). Whereas DL techniques were recently applied to identify epigenetic marks (Kim et al., 2016; Liu et al., 2016), ML methods are also applied to develop tools using DNA methylation

patterns as a biomarker of aging. For example, in (Torabi Moghadam et al., 2016) a pipeline of Monte Carlo Feature Selection and rule-base modeling was developed in order to identify combinations of CpG sites that classify samples in different age intervals based on the DNA methylation levels. In (Levine et al., 2018), an epigenetic biomarker of aging was developed using data from whole blood. This biomarker was found to correlate with age in every tissue and cell tested. Furthermore, it is able to predict a variety of aging outcomes, including all-cause mortality, cancers, health span, physical functioning, and Alzheimer's disease. The combination of large amounts of epigenomics data produced and stored in the digital space, along with the development of AI technologies, will lead to the design of more accurate epigenetic clocks in the near future (Schumacher, 2018).

4.2. Target identification

Identifying targets of interest is another critical aspect in the development of effective anti-aging treatment. Different computational approaches have been developed, including screening differences in pathway activation patterns using pathway perturbation analysis. Those methods characterize pathways as transcriptomic maps and can be used to identify pathways eliciting high changes between young and old individuals. The results of such analysis provide information about pathways involved in aging (Fig. 2A). Another approach relies on screening libraries of already known compounds using DNNs for identifying compounds with potential pro-longevity properties (Fig. 2B) (Aliper et al., 2016). Features used by aging clocks can also be analyzed to identify new targets. This approach was followed in (Mamoshina et al., 2018b) where the list of genes used to predict age based on transcriptomic profiles of skeletal muscles was further analyzed to identify the genes most important for age prediction. Several methods were used to evaluate the importance of features (genes) on age prediction. Methods include ranking genes by absolute values of their regression coefficients for an ElasticNet model, applying the RF feature importance algorithm to extract the Gini importance value of each gene, and analyzing the relative importance values assigned to genes by the DFS model. The Borda count algorithm was used to summarize ranks provided by these different methods and obtain final importance values. In addition, the wrapper method, which was applied to identify the most important blood markers for age prediction (Zhavoronkov et al., 2016) was also used.

Interestingly, the list of the most important genes selected by the Borda algorithm contains several genes already known as therapeutic targets. To provide a more comprehensive overview of how those genes are related to the aging of skeletal muscles, pathway perturbation analysis was performed using the iPANDA algorithm (Ozerov et al., 2016) to compare signatures of young and old muscle tissue. iPANDA belongs to the fourth generation of data driven pathway analysis methods (Vanhaelen et al., 2017). Using a simplified description of the pathways, these statistical-based methods can handle high dimensionality data to analyze changes between two conditions in the expression of genes belonging to common pathways. As these methods work in terms of pathway activity levels and not in terms of individual genes, they reduce the genomic complexity from tens of thousands of features to measurements on dozens of pathways (Khatri et al., 2012; Li et al., 2015). The two conditions were defined as follows. The samples from individuals 16–30 years old were classified into the "young" group while individuals over 60 years old were used to assemble the "old" group. The list of differentially expressed genes were computed and their expression profiles and a pathway database of 1856 annotated and manually curated signaling pathway maps were used as an input for the iPANDA algorithm. The results confirmed the established mechanisms of human skeletal muscle aging, including dysregulation of cytosolic $Ca2+$ homeostasis, PPAR signaling and neurotransmitter recycling along with IGFR and PI3K-Akt-mTOR signaling.

Drug repurposing is a commonly used alternative approach for
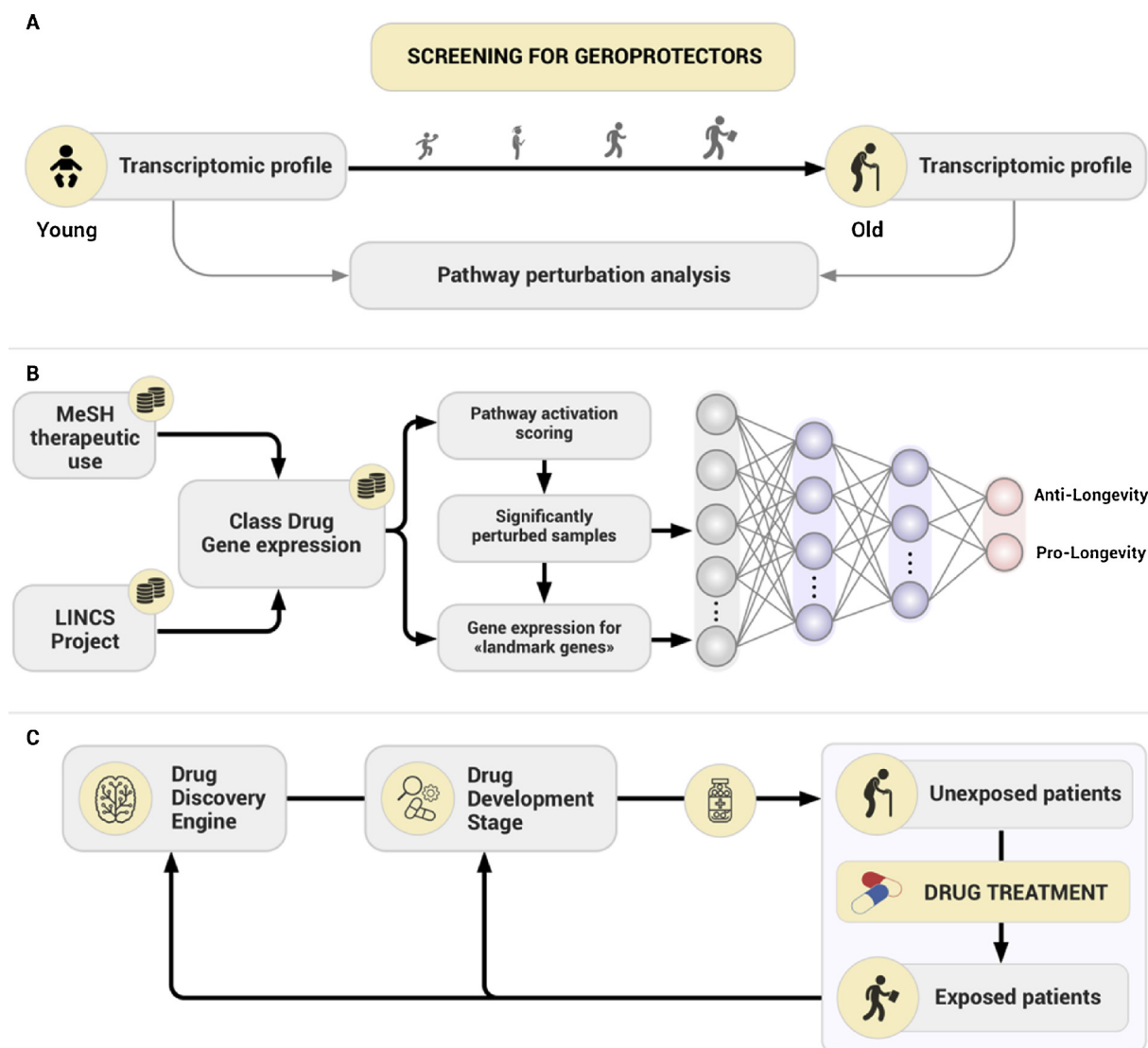
Fig. 2. Computational screening for geroprotectors and anti-aging drugs is a multiple process. (A) Pathway and transcriptomic signatures extracted when comparing young and old individuals help to identify potential candidates and targets. (B) Already existing drugs and compounds can be screened using DNN-based approaches to identify key properties associated with anti-aging drugs and identify drugs with the desired set of characteristics. (C) Once designed, approved drugs and compounds reach the market. Feedback from users and patients provide useful information about the reliability of the drug discovery pipeline. Computational pipelines are flexible and can thus be easily adapted to meet patient expectations.

finding new targets or indications for already approved drugs. Computational drug repurposing is a highly active field of research within pharmacology, and many computational approaches are being developed using various kinds of techniques (Hodos et al., 2016; Vanhaelen et al., 2016; Alaimo et al., 2016; Vanhaelen, 2019). The capabilities of DL and AI technologies are also being investigated in this context. In (Aliper et al., 2016), the authors proposed to use DNN-based system to classify drugs into therapeutic categories based solely on their transcriptomic data. Datasets used as inputs include samples exposed to various drugs selected across A549, MCF-7, and PC-3 cell lines. These samples were gathered from the LINCS Project and linked to 12 therapeutic use categories derived from the MeSH therapeutic use section. However, it appeared that training the DNN using the entire dataset of 12,797 genes generated very poor results. In order to address this issue, feature selection methods were used at the genomic and pathways levels. At the genomic levels, the features were obtained with gene expression level data for "landmark genes,"—genes that capture approximately 80% of the information and possess great inferential value. These features were used to train the DNN classifier. At the pathway level, the activation scores of 271 signaling pathways were computed

resulting in a final dataset containing 308, 454, and 433 drugs for A549, MCF7, and PC3 cell lines, respectively. Using this dataset, another DNN classifier based only on pathway activation scores for drug perturbation profiles of three cell lines was assembled. Interestingly, it appeared that this second classifier performed much better, suggesting that pathway level data is more complementary for DNN and better suitable for classifying drugs into therapeutic use categories. Interpreting their results from a repurposing perspective, the authors argued that the "misclassified" samples for a certain drug could be an indication of its potential for novel use in these exact "incorrectly" assigned conditions. Misclassification, therefore, may lead to unexpected new discoveries.

Once treatments and drugs have been developed and marketed, it is important to assess to what extent they can lead to a significant improvement of health status. Although feedback received from patients over time can provide meaningful information to improve the drug development stages or optimize the drug discovery engine (Fig. 2C), it should be emphasized that the effects of aging take years or decades to unfold and the experimental observation of the effects of anti-aging treatments is not necessarily straightforward. For instance, these
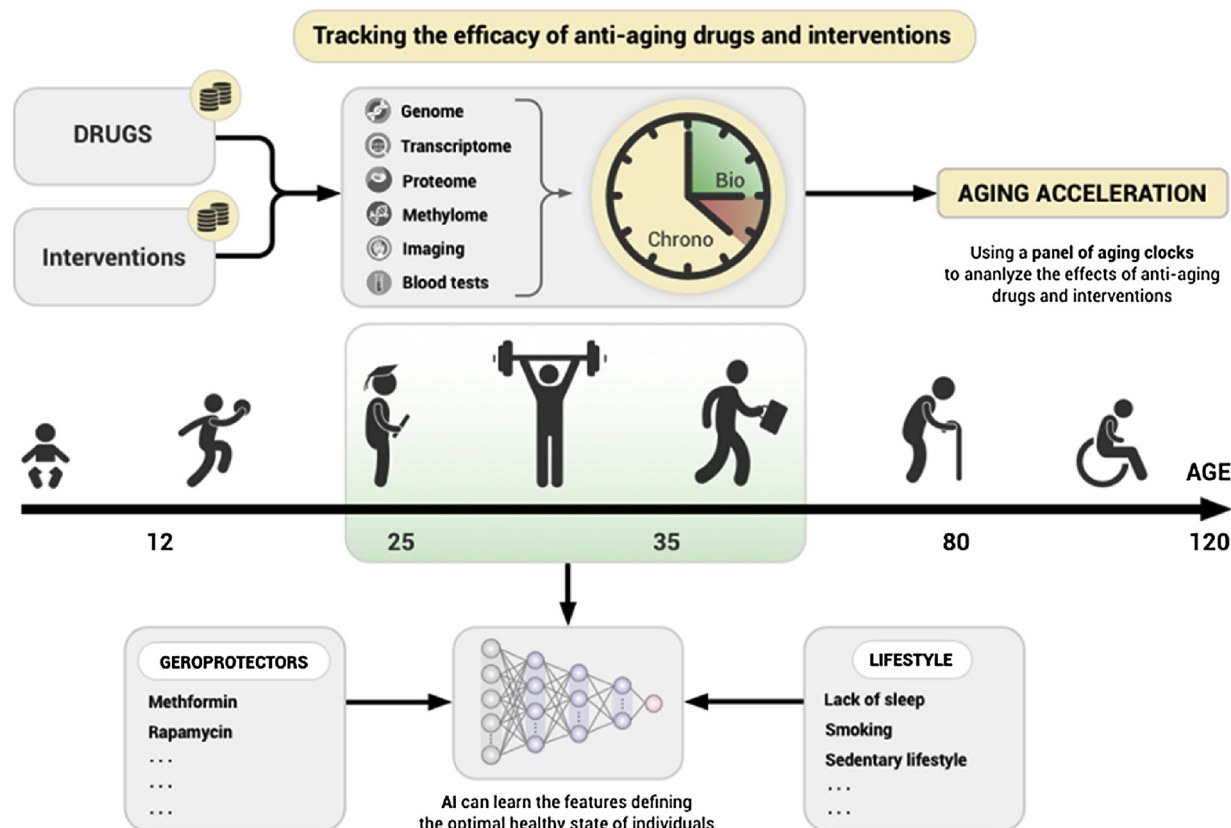
Fig. 3. Assessing the efficacy of anti-aging drugs and proposed treatments is critical for advances in aging research. Samples exposed to such treatments or drugs can be used as inputs for aging clocks. Estimation of age acceleration can be obtained. Comparison with non-exposed samples gives a first estimation of the in vivo effects of these treatments. Another approach relies on the use of AI to extract features characterizing the optimal healthy state reached by most individuals from 25 to 35 years old. Computational analysis can track how these features are affected by various treatments such as the use of geroprotectors. On the other hand, the effects of various common daily behaviors and lifestyles can also be integrated within these studies.

difficulties are observed when analyzing the effect of the calorie restriction (CR) diet. This diet is characterized by a reduction in caloric intake below usual levels. Observations indicate that CR contributes to health benefits and extends lifespan. This observation was initially made in species eliciting a short average lifespan when CR was initiated early or in mid-life and was sustained for a substantial portion of the lifespan while maintaining adequate intake of essential nutrients. However, as emphasized in a recent study where the effects of CR were analyzed over a period of 2 years (Redman et al., 2018), obtaining similar conclusive results for humans requires performing these experiments over a longer period of time. In addition, other parameters, which vary over time, such as environmental, economic and social factors or lifestyle, must be taken into account. One can expect that the accumulation of health data will allow a more systematic use of computational methods to assess *a posteriori* the effects of anti-aging drugs and treatments. For instance, aging clocks can be used to measure how the aging acceleration in treated patients varies upon treatment (Fig. 3). Information gathered from individuals can also be used to identify the main features that characterize the optimal healthy status of an individual. This information can be applied to understand how anti-aging drugs counteract lifestyle deleterious effects.

4.3. Small molecules drug discovery

Computational techniques are also developed for the design of drug compounds and for generating large, virtual chemical libraries which can be more efficiently screened for *in silico* drug discovery. Drug discovery and development timelines can be further optimized by using DL and AI technologies to characterize drug candidates according to likely efficacy and safety, prior to preclinical and clinical trials. The

disruption of the standard discovery pipeline through AI technologies will be beneficial for the identification of new candidates for developing anti-aging therapies.

In this context, generative models, based on the GAN paradigm for instance, have great potentials due to their ability to generate virtual molecules with desired chemical and biological properties. Several of such models have been proposed for molecular de novo design and molecular feature extraction. In what follows, we examine the main models recently released and shortly describe the challenges faced.

Kadurin et al. (2017a) proposed the first DL-based generator of molecules. The core of the architecture is based on an adversarial autoencoder (AAE) and aims at generating novel molecular fingerprints with a defined set of parameters. A molecular fingerprint is a numerical method to encode the structure of a molecule. The most common type of fingerprint, called binary fingerprint, is a series of binary digits that represent the presence or absence of particular substructures in the molecule. The system takes a vector of binary fingerprints and log concentration of the molecule as inputs, and outputs a concentration and a vector consisting of probabilities assigned to each bit of the fingerprint. For training on fingerprint, the log concentration of 6252 compounds profiled on the MCF-7 cell line and the corresponding growth inhibition percentage (GI) data, which indicates the reduction in the number of tumor cells after drug treatment, were used. To assess the validity of the predictions, the generated fingerprints were used to screen several millions of compounds from the PubChem database and identify the compounds for which anticancer activities are observed. Other relevant biomedical properties of interest have also been either tested or demonstrated.

This work was improved in (Kadurin et al., 2017b) where an advanced AAE model for molecular feature extraction was presented.

Compared to the previous work (Kadurin et al., 2017a), this model, called druGAN (drug Generative Adversarial Network), also uses fingerprints as a representation of the molecules. In order to measure the similarity between the generated molecules and the original data, the authors used the Tanimoto similarity, which is a synonym of Jaccard similarity in this context. Experiments showed that druGAN elicits higher adjustability in generating molecular fingerprints, has a better capacity of processing very large data sets of molecules, and is more efficient in unsupervised pretraining for regression model. The study includes a comparison between the druGAN and a variational autoencoder (VAE) model. VAE models are another type of commonly used generative models based on DNN architectures. Interestingly, different tests demonstrated that both AAE and VAE models can perform very well depending on the kind of task to be solved. Consequently, both VAE and AAE can be considered as valuable tools that can be used in drug discovery pipelines on fingerprints and on other representations of the molecular structure. However, the authors pointed out different limitations of present AAE architectures. For instance, the study used MACCS molecular fingerprints, which are not ideal representations of molecular structure. The molecular fingerprint has two disadvantages. First, one fingerprint can match several molecules, so there is no one-to-one mapping from a molecule to the fingerprint, and second, the fingerprint representation contains less information about the molecule topology than the string representation. Those disadvantages are not shared by other more chemically and biologically relevant representations of the molecular structures such as the string representation of the molecule (SMILES), InChI, or molecular graphs. This suggests that using alternative representations could lead to better performances of generative adversarial models (Fig. 4A).

Following this conclusion, a VAE model for learning continuous representation of molecules represented in SMILES format was introduced by Gomez-Bombarelli et al. (Gómez-Bombarelli et al., 2018). Models based on Recurrent Neural Networks (RNNs), a type of architecture more adapted for data of sequential nature such as SMILES, have also been investigated. For example, in (Bjerrum and Threlfall, 2017), the performances were further improved by using long short-term memory (LSTM) cells and gated recurrent units (GRU). Architectures based on the GAN paradigm were also developed. For example, sequence generation via deep reinforcement learning (DRL) was proposed in (Yu et al., 2017). The architecture, called Sequence Generative Adversarial Network (SeqGAN), combines GAN with a RL-based generator. Another extension of SeqGAN called ORGAN (Objective-Reinforced Generative Adversarial Network) was proposed in (Guimaraes et al., 2017). This model adds an "objective-reinforced" reward function for particular sequences into the SeqGAN reward loss. Further works based on objective functions for molecular design within the ORGAN paradigm was done in (Sanchez-Lengeling et al., 2017). The proposed architecture, ORGANIC (Objective-Reinforced Generative Adversarial Network for Inverse-design Chemistry), used various criteria as objective filters to train the ORGAN model. The results showed the use of different objective reward functions makes it possible to bias the generation process and generates molecules with desired user-specified properties.

Following these works, the RANC model for the design of small-molecules was later presented (Zhavoronkov et al., 2018a). RANC is based on the GAN and RL paradigms. Moreover, RANC uses a differentiable neural computer (DNC) as a generator. DNC is a category of neural networks, with increased generation capabilities due to the addition of an explicit memory bank. This additional module can help to mitigate common problems found in adversarial settings. RANC was trained on the SMILES string representation of the molecules and results showed the generated molecules match the distributions of the lengths
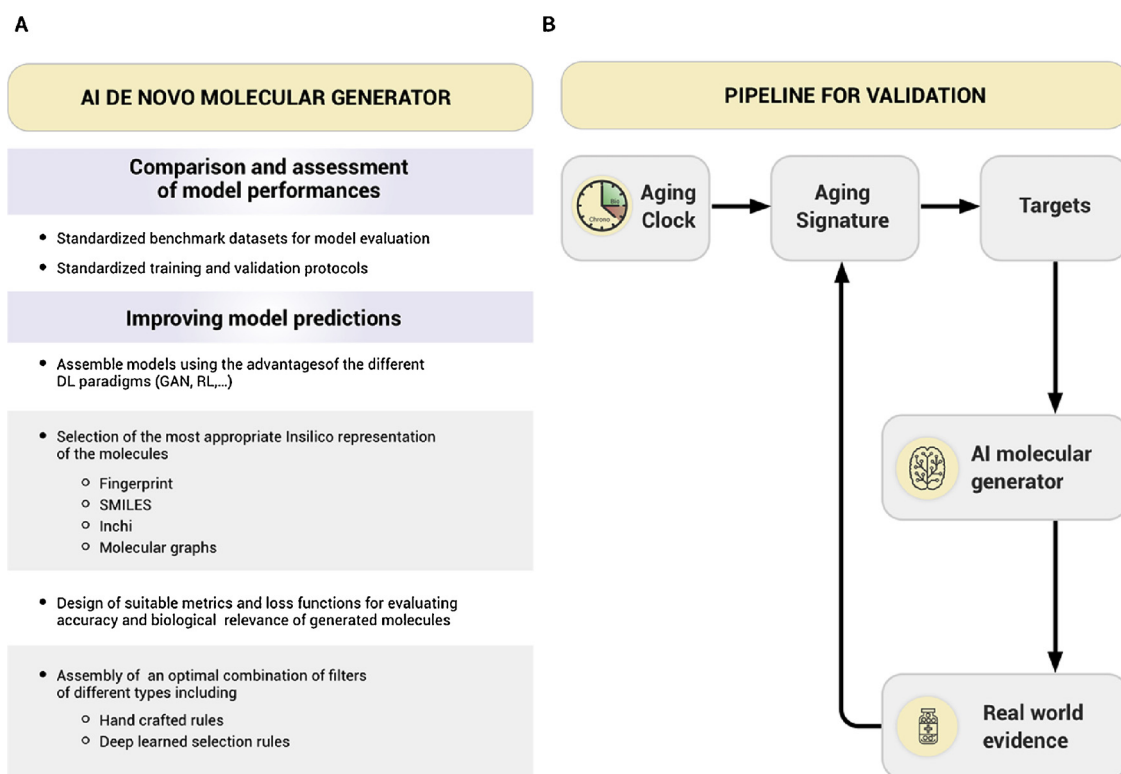
Fig. 4. (A) AI de novo molecular generators offer interesting opportunities to optimize the identification and selection of molecules with desired properties. However, a systematic use of such approaches requires the establishment of standardized procedures and protocols for the training and validation of the models. Furthermore, systematic studies could be performed to better understand how the model performances depend on the specific architecture, loss functions, and combination of filters used. (B) AI-molecular generators are best used in combination with aging clocks. Targets identified from aging signatures and features used by aging clocks are used to define appropriate properties of molecules generated by AI generators. As for any computational methods, predictions obtained from AI-based generators must go through various phases of testing. Feedbacks obtained from these critical steps can help improve the global pipeline.

and the key molecular descriptors of the training molecules. Furthermore, comparisons with ORGANIC showed that RANC performed better in terms of number of unique structures, Muegge criteria, QED scores and number of generated molecules passing the medicinal chemistry filters (MCFs).

Another variant of molecular generator called Adversarial Threshold Neural Computer (ATNC) was also designed (Zhavoronkov et al., 2018b). Like the RANC and ORGANIC models, ATNC is based on the GAN and RL paradigms and, like RANC, it also uses DNC as generator. However, ATNC includes a supplementary computational unit, called adversarial threshold (AT). The AT unit acts as a filter between the agent (generator) and the environment (discriminator and objective reward functions). In order to generate more diverse molecules, a new objective reward function named Internal Diversity Clustering (IDC) was introduced. The performances were compared with ORGANIC and both models were trained on the SMILES string representation of the molecules. Four objective functions, the internal similarity, the Muegge druglikeness filter, presence or absence of sp3-rich fragments, and the IDC were used. The distributions of four molecular descriptors—number of atoms, molecular weight, logP, and tpsa—were analyzed and five supplementary chemical statistical features were also computed (internal diversity, number of unique heterocycles, number of clusters, number of singletons, and number of compounds that have not been passed through medicinal chemistry filters). The analysis of these molecular descriptors and chemical statistical features demonstrated that the molecules generated by ATNC elicited better druglikeness properties. One of the limitations of the ATNC emphasized by the authors concerns the architecture itself. It was suggested that replacing the GAN part by an AAE can provide the model with a mechanism to control the percentage of correctly reconstructed molecules. Other main limitations are related to the method used for representing the molecules. ATNC, RANC and ORGANIC are SMILES-based models and cannot properly employ fragment-based objective reward functions. This is due to the fact that SMILES string of a fragment cannot be found in a SMILES string of a molecule because of the SMILES format notation. The authors suggested that using other molecule representation, for example graph representation of molecules, where each molecule will be represented in a unique way, could overcome this issue. Finally, they suggested that using modern, multi-objective RL techniques could allow the environment to optimize the scoring of the molecules by using several objective rewards simultaneously (Fig. 4A).

The examples discussed in this section illustrate this growing field of research still lacks a unified set of benchmarks which could be used to provide a framework to evaluate and compare different generative models. Furthermore, it is necessary to formulate best practices for this emerging industry of 'AI molecule generators' at different levels, including how much training data is required, for how long the model should be trained, and what kind of metrics and loss functions are the most appropriate for monitoring the performance and assessing the validity of the outputs of these models. For example, replacing handcrafted rules commonly used in the context of de novo drug design with rules learned from data. DiversityNet is a promising initiative to address this issue. DiversityNet is a data science collaborative challenge which asked participants to collaborate to design the most appropriate set of tasks, metrics, and select suitable datasets to evaluate generative molecule generators. AI-molecular generators have already been successfully integrated in extended pipelines where their prediction power and accuracy are improved by using biologically relevant features selected through the use of aging clocks and other dimensionality reduction techniques (Fig. 4B).

4.4. Regenerative medicine

The field of regenerative medicine aims to provide patients with improved treatment and faster recovery through, for example, the use of induced pluripotent stem Cells (iPSCs) (Takahashi and Yamanaka,

2006; Takahashi et al., 2007) which can differentiate into different cell lineages and ultimately, to any kinds of cell types (Scudellari, 2016; Yamanaka, 2012). Therefore, one could control iPSC differentiation to treat various diseases (Jiang et al., 2014). For example, by creating beta islet cells to treat diabetes or neurons to treat neurological diseases. These techniques could also be used to grow tissues and organs and transplant them into the body, eliminating potential organ transplant rejection. If applied at a larger scale, this could help to address the shortage of organs available for transplants.

However, the use of iPSC potentials requires fully controlling the differentiation process itself. In past decades, much progress has been made to understand the complex dynamics taking place during the stem cell fate decision at the genetic and epigenetic levels. At the genomic level, pluripotency maintenance is regulated by transcription factors (Thomson et al., 2011; Walker et al., 2007; Walker and Stanford, 2009; Tantin, 2013) which act as master regulators of gene regulatory networks (GRNs) (Iglesias-Bartolome and Gutkind, 2011; Ng and Surani, 2011; Dalton, 2013). From a dynamical point of view, GRNs are organized following various dynamical motifs which act together and contribute to improving the adaptation abilities and robustness of the system (Yeo and Ng, 2013; Saint-André et al., 2016). Transcription factors have been shown to continually attempt to specify differentiation to their own lineage. Consequently, direct external interventions, through activation or inhibition of one or several signaling pathways, are necessary to reinforce the pluripotency state or to control the differentiation to a specific lineage (Silva and Smith, 2008; Nowick and Stubbs, 2010; Loh and Lim, 2011). From this point of view, the pluripotency state could be considered a metastable state whose maintenance depends on the properties of the external environment of the cell. These discoveries explain why differentiating iPSCs into specific cell types can only be achieved by following a rather complex differentiation protocol, usually specific to each kind of cell (Malik and Rao, 2013).

Although significant efforts and progresses have been accomplished to establish standardized sets of differentiation protocols for various cell types (Si-Tayeb et al., 2010; Takeda et al., 2017; Dai et al., 2015; Daniel et al., 2016), large scale applications are still difficult. Within this context, computational methods could be used to design AI automated systems to create and adjust custom protocols to optimize the success of stem cells differentiation processes. The opportunities offered by AI techniques in the development of predictive models for personalized treatments with engineered stem cells, immune cells, and regenerated tissues in humans were recently reviewed in (Sniecinski and Seghatchian, 2018). For instance, AI can be used to identify the state of development of embryonic cells (Fig. 1C). An example of this kind of application was recently published in (West et al., 2018). In this study, a DNN ensemble was trained on transcriptomic data of 12,404 healthy, untreated tissue samples from Affymetrix (4822 samples) and Illumina (7582 samples) microarray platforms to be able to classify samples according to five categories: embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), embryonic progenitor cells (EPCs), adult stem cells (ASCs) and adult cells (ACs). The DNN outperformed traditional ML methods (kNN, SVM, GBM) and achieved a mean 0.99 F1 score—the probability that the guesses are correct—on the Affymetrix microarray training dataset, and 0.75 F1 on the external validation dataset. Interestingly, prediction performances of the DNN were improved with dimensionality reduction using the pathway level analysis approach iPANDA. Further feature importance analysis identified repression of COX7A1 as a novel marker associated with the mammalian embryonic-fetal transition (EFT). The computational methods developed in this work have been made available through an online platform called embryonic.ai (http://embryonic.ai). The AI-based platform was developed by Insilico Medicine Inc. in collaboration with the company Biotime Inc., (http://www.biotimeinc.com/). It gives access to the first deep learned transcriptome-based classifier designed to compute the embryonic score of a sample, an integrative metric of cell development

stage. Embryonic AI is an ensemble of DNNs trained and validated on transcriptomics data representative of healthy ESC, iPSC, EPC, ASC and AC types. Using data provided by the user, the system will output an embryonic score.

Another example of application of AI technology is the recent introduction of an online catalog of 3D stem cell images produced using DL analyses and cell lines altered with the gene-editing tool CRISPR (Maxmen, 2017). This tool, called Allen Cell Explorer (https://www.allencell.org/), will be used in the near future by scientists to better understand iPSC structures and their relationships to functions, and ultimately to diseases like cancer.

At a larger scale, AI can also offer practical solutions to other types of challenges faced in regenerative techniques with the prediction of tissue engineering results with ANN (Xu et al., 2005; Shaikhina et al., 2015) or with the development of computational model-based neural networks for more elaborated tissue engineering applications. One can expect the current trend toward AI-guided regenerative medicine will bring impactful benefits in the near future.

Applying such regenerative technologies to design anti-aging drugs or treatments targeting age related diseases is an appealing perspective. Several companies focus on developing such treatments but most of the clinical applications will require years of development and clinical trials before potential FDA approval. Nevertheless, several near-term applications are already undergoing clinical trials. This is the case for a regenerative product for age-related macular degeneration which is developed by AgeX Therapeutics (http://www.agexinc.com/), a subsidiary of BioTime, Inc. AgeX Therapeutics is also developing pluripotent stem cell-derived therapies for manufacturing brown fat cells. These cells contribute to the regulation of metabolism as they burn calories rather than store them. The amount of brown fat cells within the body decreases with age and restoring them might help maintain the metabolic balance at the same level as younger individuals.

4.5. Gene therapy

Gene therapy is an experimental technique that uses genes to treat or prevent diseases, including inherited disorders, some types of cancer, and certain viral infections. In practice, this technique is designed to introduce genetic material into cells to compensate for abnormal genes or to make a beneficial protein. Although promising, gene therapy is currently being tested only for diseases that have no other cures (Soleimani et al., 2015). However, in recent years gene therapy has gained more attention due to several successes. The FDA has recently approved the first gene therapies for treating forms of leukemia, lymphoma and retinal dystrophy—an inherited disease. Although these initial successes did not benefit from the emergence of AI techniques, the rapidly growing amount of genomic data available has, like in other fields of life science, triggered the interest applying AI for improving gene therapies and as a consequence, the potential of personalized medicine as both of them rely on matching the appropriate drug with the right patient population. A task for which AI technologies are perfectly adapted (Fig. 5). More specifically, one sees AI as a key ingredient to improve the precision of the gene editing process. Although the development of gene editing has provided new opportunities for exploring personalized cures and treatments by providing scientists with the ability to alter patient DNA, the ability to perform gene editing accurately is still challenging. Several companies have developed AI-based platforms to answer the needs of this specific sector. For example, ATUM (https://www.atum.bio/), a California-based bioengineering service organization, and the largest US-based provider of synthetic genes, is applying AI to gene synthesis and has developed a technology called Leap-In transposase which enables any recombinant DNA sequence to behave as a transposon. Synpromics (http://www.synpromics.com/), an Edinburgh-based company, uses AI to identify patterns between genomic sequences and their involvements in cell type-specific regulation of gene expression. Elevation, the project

developed by Microsoft, uses genomic data and AI to predict the optimal position to edit a strand of DNA to alleviate side effects and speed up the editing process (Listgarten et al., 2018).

Gene therapies also offer tremendous opportunities for designing efficient anti-aging treatments. It is known that mitochondrial oxidative stress may contribute to human aging. For example, increased expression of catalase in the mitochondria results in much more potent protection against oxidative stress (Bai et al., 1999; Arita et al., 2006). To take advantage of this discovery, it has been suggested that an adeno-associated virus vector expressing the mitochondria-targeted catalase gene could be used as a gene therapy to prevent aging-related pathology (Li and Duan, 2013). Telomerase gene therapy is another possible application. This approach is based on the observation that telomere shortening is linked with aging and disease and that the genetic manipulation of lengthening telomeres through increased telomerase expression may result in increased longevity. Telomerase gene therapy is a possible therapeutic intervention against aging and age-related diseases (Boccardi and Herbig, 2012; Bär et al., 2016; Muñoz-Lorente et al., 2018). One can expect that the use of AI technologies to optimize the design of gene therapies will greatly help the future development of anti-aging treatments.

4.6. Immuno oncology and immunosenescence

Cancer is currently one of the main causes of death. This is due to an aging population but also possibly related to unhealthy food habits, changing lifestyle, and increasing consumption of tobacco-related products. According to the National Cancer Institute, around 1.6 million new cases of cancer were diagnosed in the USA in 2016. As these numbers are expected to grow in the future, there is an increasing and pressing demand for identifying new oncology drugs that can be used as a part of anti-cancer treatments. Normally, the immune system is able to recognize tumor cells and distinguish them from their normal counterparts. However, in cancer patients, tumor cells escape from immune system surveillance by dodging immune checkpoints (inhibitory pathways to inactivate T-cells). Oncology drugs, also called anti-cancer drugs or anti-neoplastic drugs, are agents that can be used alone or in combination to control or destroy neoplastic cells. These agents can be either systemic or targeted. In systemic, the drug spreads throughout the body, whereas in targeted, the drug or substance identifies the specific location causing less harm to the growth of neighboring healthy cells. There are several types of Cancer Immunotherapies using either Immune Checkpoint Modulators, Immune System Modulators or Therapeutic antibodies, Immune Cell Therapy, or Cancer Vaccines, usually made from a patient's own tumor cells or from substances produced by tumor cells.

A specific challenge when treating cancer comes from the fact that each cancer and every cancer patient are different and tumor cells within a specific tumor site can vary in diversity. For that reason, a strategy pursued in oncology research is to identify small subsets of cancer patients that can benefit from a specific treatment. However, this targeted approach has encountered limited success until recently, because although researchers and doctors had access to large sets of data from imaging, genomics, co-morbidities and previous treatments, they did not have the adapted methods to make an efficient use of them.

With its ability to learn, predict, and advice based on vast amounts of data, AI technology can identify patterns that can be used to predict the prognosis of patients and advise medical practitioners with different options available ranging from available personalized medicine to clinical trials with experimental therapies (Fig. 5). For example, convolutional neural networks (CNNs) were trained to classify cancer patients using immunohistochemistry of tumor tissues (Vandenberghe et al., 2017). A ML-based tumor classifier was presented in (Capper et al., 2018) and works using ML methods specifically for breast cancer pattern classification and forecast modeling. These methods were also reviewed in (Yue et al., 2018). Applications of standard ML-techniques
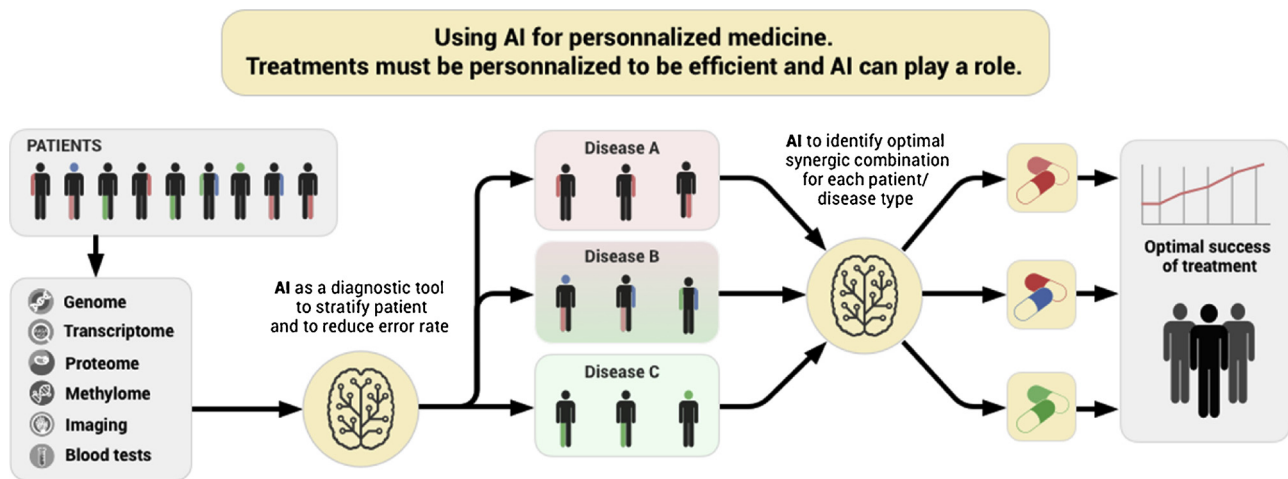
Fig. 5. AI can be used in different ways for designing personalized treatments. AI platforms can be used as a diagnostic tool to reduce error rate. It is also useful to stratify patients according to their specific health condition. By combining more accurate diagnostics and a better knowledge of the health conditions of the patients, AI platforms can be applied to design more effective treatments.

for cancer diagnosis have been covered in (Kourou et al., 2015) and DL-based cancer diagnosis approaches were recently reviewed in (Hu et al., 2018). As in the case of regenerative medicine, applying AI technology as a diagnostic tool in oncology (detection of cancer) can significantly reduce the error rate of diagnosis and also contribute to reducing time-consuming activities. There are many initiatives to support the application of AI within oncology. For example, the open research initiative called EPIDEMIUM aims to bring together multiple players and apply AI to the research of new cancer therapies. Many companies are working to develop AI-based platforms to address challenges faced in oncology and cancer research. For instance, AI is used by the company Sophia Genetics to pinpoint the gene mutations behind cancer to assist doctors in the prescription of the best treatment. The company Freenome developed an AI genomics platform to predict patients' responses to immuno-oncology therapies by observing changes in biomarkers circulating in the bloodstream. In addition to being used to stratify patients, AI can also be applied to identify synergistic combinations of cancer targets in order to develop drugs against those targets; this strategy is followed by Sanofi and GSK which have partnered with Exscientia. These efforts, although in their infancy, begin to generate results with the case of the company BenevolentAI which, in partnership with Janssen, has shown concrete results, leading to a drug candidate now moving to a Phase II trial.

In non-cancerous cells, the immune system also undergoes alterations with age. The most important alterations occur in the adaptive immune system and involve T cells. Many of these alterations are assumed to decrease capacity of the immune system to combat the emerging or progressing tumor (Pawelec et al., 2010; Fulop et al., 2010; Pawelec, 2017). The declining function of the immune system is known as immunosenescence and leads to a higher incidence of infection, cancer, and autoimmune disease related mortalities in the elderly population (Pawelec, 2018). For these reasons, various strategies have been suggested to combat immunosenescence, including cellular and genetic therapies (Xu and Larbi, 2017). Immunosenescence involves a shift in function of both adaptive and innate immune cells, leading to reduced capacity to recognize new antigens and widespread chronic inflammation (Stahl and Brown, 2015; Ventura et al., 2017). This state can be assessed by measures of different immune biomarkers that are different in younger and older individuals and are associated with a detrimental clinical outcome. Many other biomarkers were assessed in studies of younger and older adults. Well established markers of immunosenescence include CD45RO, CD45RA (Neuber et al., 2003), CD27 (Bulati et al., 2011; Xu and Larbi, 2017) CD57 (Xu and Larbi, 2017) and CD28 whose downregulation occurs in response to chronic immune

stimulation in older individuals (Kennedy et al., 2016; Tu and Rao, 2016). CD31 is known as a good marker of CD41 + T cells (Larbi and Fulop, 2014; Douaisi et al., 2017) whereas CD79 A is a highly reliable marker for B-cells. Downregulation of several genes has been associated with a decrease in immune functions. For example, KLF4 whose expression may wane with age is known to control immune function (Kennedy et al., 2016). TSPAN33 also wanes with age and plays a role in red blood cell differentiation (Kennedy et al., 2016). Interleukin-7 (IL-7) plays a central, critical role in the homeostasis of the immune system (Nguyen et al., 2017a,b). Immunosenescence is also correlated with a lower expression level of IL-2 as highly differentiated T cells accumulate with age and are unable to produce IL-2 (Henson and Akbar, 2009). Other examples of genes whose expression is positively or negatively correlated with the onset of immunosenescence are described elsewhere (Bellavista and Franceschi, 2009; Opal et al., 2005; Xu and Larbi, 2017; Rosenstiel et al., 2008). There have been several studies where computational methods were applied to investigate the mechanisms behind the onset of immunosenescence, especially its interconnection with inflammation (Morrisette-Thomas et al., 2014; Bektas et al., 2017). However, in the near future, our understanding of immunosenescence and its interconnection with other processes could take advantage of similar methodologies rather than the ones used for predicting biological ages. AI technology could identify key regulators involved in the onset of immunosenescence and reveal the complexity of the interplay with other key biological processes. These regulators could, in turn, become targets for developing appropriate treatment.

5. AI for cross-species aging research

Demographic data, or life tables, such as the ones from the Human Mortality Database (http://www.mortality.org) provide information to analyze demographic trends including mortality and fertility rates. Using life tables, one can extract survival curves showing the proportion of individuals surviving to each age for a given species. The analysis of these curves demonstrate that they elicit specific topological features which provide information about the specific aging patterns of each species (Jones et al., 2014). As described in (Demetrius, 1978), survival curves can be broadly classified into three types. The Type-I survival curves change at early and middle ages and then decline at late ages, as seen for humans. The Type-II curves almost linearly decrease with age, as seen for short lived birds. Type-III curves quickly decrease at early ages, as seen for most plants. Nevertheless, major, non-trivial topological features of these curves are still poorly understood and a current challenge in fundamental aging research is to find how aging

patterns and mortality curves are shaped. To that end, it is necessary to identify the mechanisms responsible for the observed shapes. Currently, there are several causal and relatively complex mechanistic models which have been built to describe some of these topological features (National Research Council (US) Committee on Population, 2012). Although, some of the models successfully predict several curves for species, they do not provide a complete framework for explaining the diversity of aging patterns observed through the tree of life (Liu, 2015; Dolejs, 1997; Kogan et al., 2015). The difficulty comes from the fact that the mortality curves are the result of complex relationships between living styles, effects of natural selection, environmental conditions, and fine-tuning of cellular mechanisms. Many of these parameters are specific to each species (Vanhaelen, 2015; Vanhaelen, 2018). Although these models can include variables such as resource availability, reproduction rate, and the effects of competition between species, considering the effects of fine-tuning of cellular mechanisms is still challenging. This requires having a detailed description of these mechanisms, that is, a description of how aging occurs and propagates with the living system. It is well known that there are many mechanisms contributing to aging, including inflammation, apoptosis, oxidative stress, accumulation of DNA damage, cell cycle deregulation, mitochondrial dysfunction, and telomere shortening, to name a few. A classical modeling approach would be to elaborate models combining the effects of accumulation of mutations, senescence, effects of natural selection and any other parameter and process supposed to intervene in the onset and propagation of aging. Such a task presents tremendous technical challenges (Tarkhov et al., 2017) that is made even more complex by the fact that one can reasonably assume many of the mechanisms or biological parameters which should be included in such models are still either poorly understood or even completely unknown.

Another approach (Fig. 6) would take advantage of the ability of AI techniques to design specific algorithms whose goal should be to systematically analyze the demographic data available for various species in order to identify and extract the major features behind the shape of survival curves. In addition, AI platforms could be designed to perform cross-species analysis of such data. This could allow the examination of common and distinct features of the aging process through different species. The results of such investigations could lead to the identification of generalized aging biomarkers. This approach could also be used

to analyze how evolution has shaped different species' aging patterns.

6. Generative adversarial networks (GANs) for generation of synthetic data and target identification

As previously described, GANs represent a powerful new tool for the generation of synthetic data. In situations where patient-specific datasets are scarce, it is possible to use GANs to significantly augment the original data set by producing new data across the broad spectrum of ages. It is also possible to simulate patient cases that did not exist in nature by generating patients older than the current record of 122.5 years. This powerful technique can also be used to infer causality and identify actionable biological processes or targets. By generating the "older" or "younger" representation of the individual patient or patient subpopulations, it is possible to identify the most important features responsible for this change and explore the dependencies between these features. The illustration in Fig. 7 (A) demonstrates this concept using photographic data. It is clear from the photographs that the generated 130 year old subject looks older than the original or synthetic 20-year old subject. The applications of GANs to the generation of shorter and longer-lived subjects depicted in Fig. 7 (B) may help identify the drivers of the aging process as well as the protective mechanisms.

7. Aging research for advancing artificial intelligence

While advances in AI are already making substantial contributions to research in aging, the computational solutions specifically developed for aging research could substantially advance research in AI. For optimal use in aging research, AI should not only provide correct predictions, but also give information about the features used to obtain the predictions. The results provided should be interpretable in terms of initial inputs, which can be of highly diverse origins. There have already been several breakthroughs in making AI systems more interpretable, contributing to the development of new memory systems capable of capturing multi-modal continuous data and efficiently forgetting unnecessary information.

Improving the interpretability of AI-based algorithms can be done using two different complementary approaches. First, the complex data collated in many biological databases are well suited to DL but also
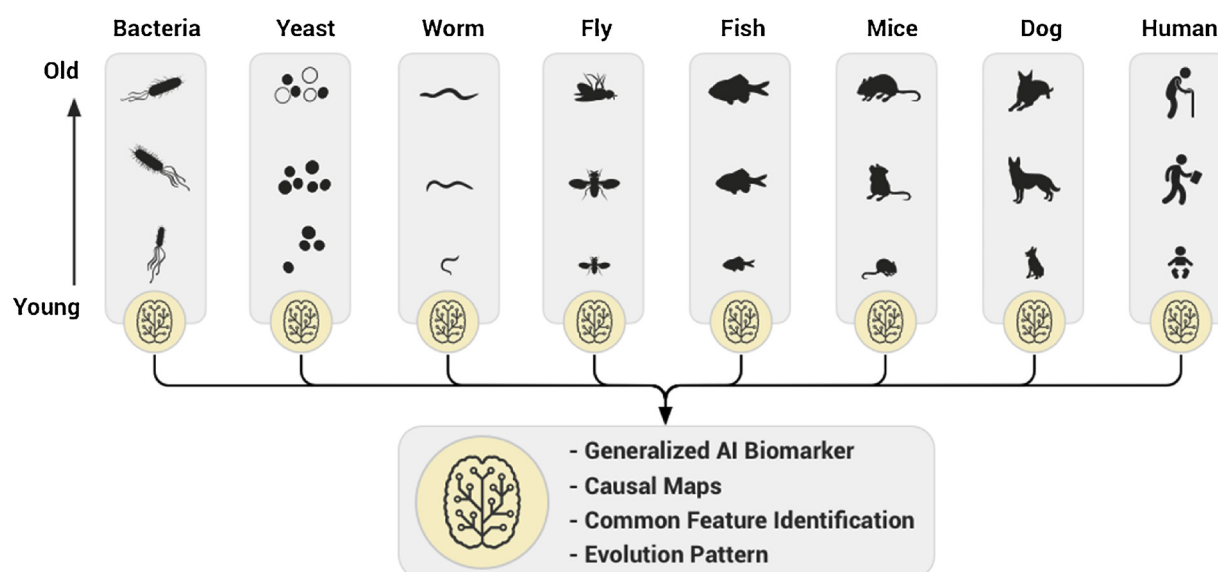
Fig. 6. AI algorithms are capable of handling large amounts of data and identify relevant patterns without prior information about the related phenomena. For this reason, AI algorithms are adapted to analyze the complexity of demographic data. Analysis can include the extraction of the most important features used to reproduce the topology of species. Specific curves can give an overview of the most important mechanisms involved. Cross species analysis could provide explanations about the origins of the huge diversity observed through the tree of life. The information gathered could be used to design generalized aging biomarkers, identify common features of aging across species, and improve the understanding of how evolution shaped aging across species.
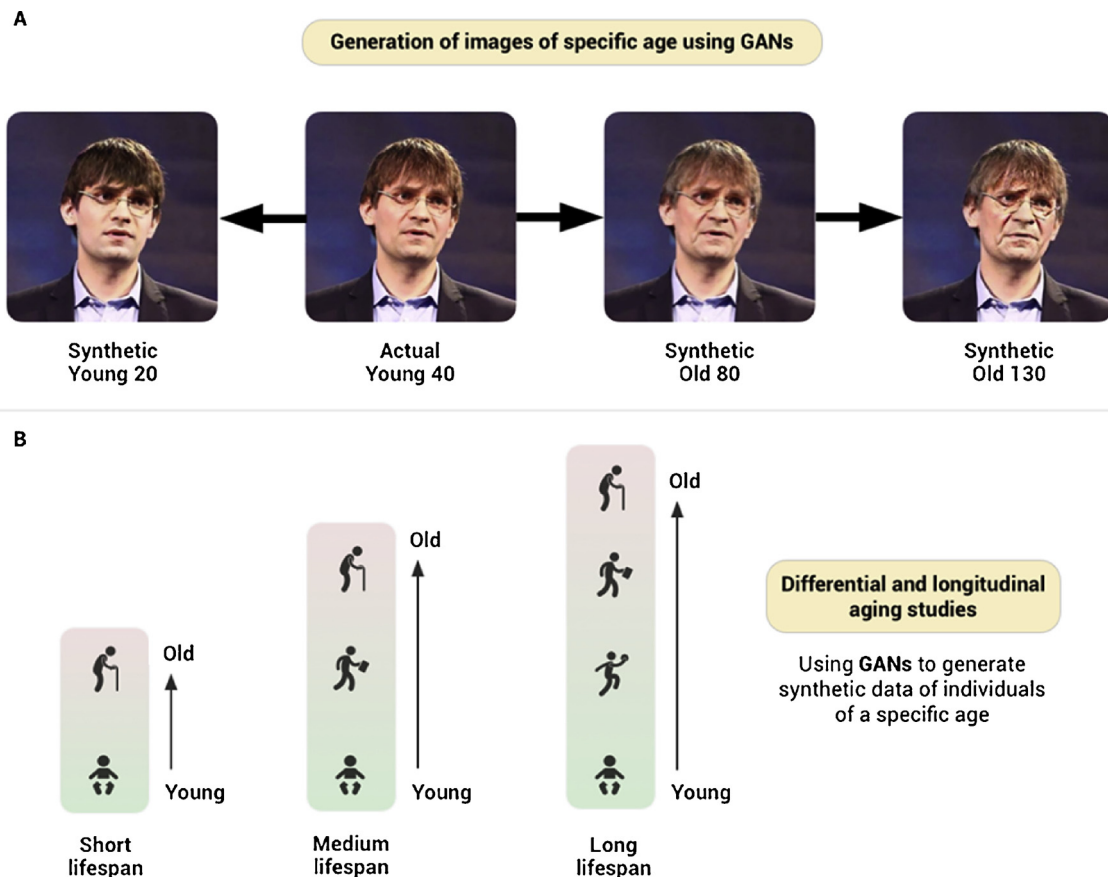
Fig. 7. GANs are well known for their abilities to generate models from data. These features have been largely used for image generation. Combining this ability with the capabilities of GAN to handle large sets of data to capture complex features across individuals at different age, one can build GAN-based architecture to generate synthetic health data and pictures of individuals at any age using the health data at a known given age.

contain challenging features, including high dimensionality, noise, and multiple, often incompatible, platforms. Consequently, while AI architectures are able to extract features from the data automatically and usually outperform other ML approaches in feature extraction tasks, it is recommended to select a set of relevant features before training DL models. Feature selection and extraction can involve dimensionality reduction. Generic methods such as principal component analysis or clustering methods can be applied. However, other feature extraction methods preserving the biological function can also be used. In practice, the appropriate reduction and feature extraction methods heavily depend on the context of the study. For instance, when dealing with transcriptomic data, dimensionality reduction should be applied prior to training DNNs because the dataset contains a number of samples much smaller than the number of genes. Supervised, knowledge-based approaches such as the gene aggregation method, like pathway analysis, are the most suitable tool to that end. The list of the most relevant perturbed pathways is then taken as the new list of features. The strategy is to ensure that the features are relevant with respect to the biological problem under study. Besides the appropriate selection of feature prior to the training of the model, the predictions obtained from AI algorithms can be better interpreted by using methods such as the permutation feature importance (PFI) technique (Altmann et al., 2010) which allows evaluating the relative importance of features to DNN prediction accuracy. Specific type of architectures, like DFS models (Li et al., 2016), automatically implement similar procedures. These ranked lists of features can be used as a starting point to investigate the mechanisms behind the observed biological behavior and to put the prediction of the algorithm in context.

8. Artificial general intelligence (AGI) for aging research

While there are multiple efforts to develop artificial general intelligence (AGI), also referred to as the sentient AI, and even transfer of the human memory and capabilities into computers, there is no proof of concept demonstrating the feasibility of any of these approaches (Wallach et al., 2010; Deca and Koene, 2014). However, there is substantial debate on AI safety and ethics. Regardless of the winning approach to AGI and the probability of AGI emerging in the near future, it may be important to develop a values-based rules book to train AGI to maximize the number of quality-adjusted life years (QALY) for everyone in the population. Maximizing global longevity and human health span should be taught as the ultimate form of altruism to AGI.

9. Conclusion

The revolution in deep learning which started with deep neural networks outperforming humans in ImageNet competition (He et al., 2015) and RL in video games (Mnih et al., 2015) is rapidly propagating into aging research. These efforts are driven by academia and industry with the influx of government funding and venture capital. Aging is a universal feature possessed by most living organisms, and therefore, most of the advances in deep learning in the context of aging research are in the field of biomarker development. Many age predictors are commonly referred to as "aging clocks" developed for multiple data types ranging from basic clinical blood tests, photos, videos, voice, retinal scans, and medical imaging to microbiome data. These feature selections, feature importance analysis, multimodal data analysis efforts and causal model development efforts not only help estimate the biological relevance of these data types but also help advance research in
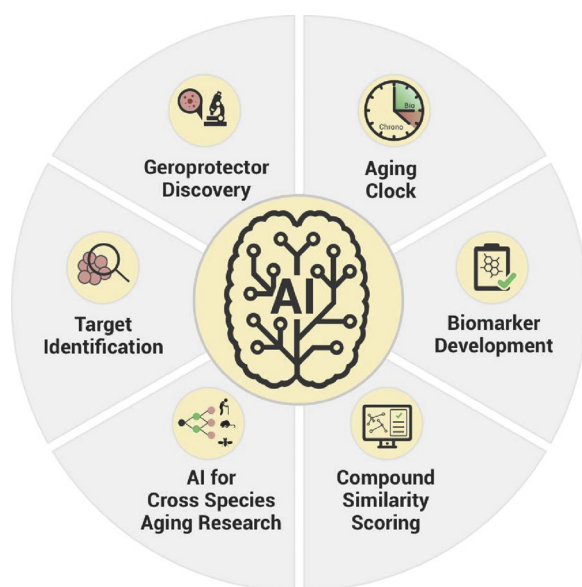
Fig. 8. AI is progressively deployed in aging research. AI-based methods have already been applied in different areas and contribute to optimize research and development pipelines. AI-based methods can either be used as standalone approaches or integrated within wider end-to-end learning pipelines solving complex tasks from hypothesis generation and target identification to real world evidence analysis. These pipelines can include computational methods used for more efficient features selection and prior dimensionality reduction. Both of these steps are likely to lead to more accurate and biologically relevant outputs and substantially accelerate aging and disease research.

AI by making the DNNs more interpretable.

The applications of AI presented in this work illustrate that AI technologies are rapidly emerging and are starting to deliver promising results in different fields of aging and longevity research (Fig. 8). One can expect that multidisciplinary approaches combining the ability of modern AI to generalize, learn strategy, generate new models, objects and data from learned features with accurate methods for feature extraction and causality analysis will lead to new applications in every area of preventative, regenerative and restorative medicine. AI progressively moves from the status of an overhyped technology with only a few proof-of-concept examples to a massively-adopted and accepted trend in healthcare. An example of this trend happened in early 2017 when the first DNN based platform, Arterys Cardio DL, was officially approved by the FDA. This platform is now widely used in the clinic. Systems like Young.AI (http://young.ai) and aging.ai (http://aging.ai) which estimate the predicted biological age of a person using multiple data types may provide valuable insights into the person's health status and evolve into disease-specific applications. Multi-modal integration of the multiple aging clocks using modern AI will lead to a more holistic approach to the understanding of biology and provide a unified theory of aging and repair.

Encouraging progress can be seen from regulatory institutions. Many regulatory authorities have initiated the development of a regulatory framework to promote innovation and support the use of AI technologies in healthcare. The first cloud-based DNN has recently been approved by the FDA under the category of medical devices. In the EU, a legislative proposal for regulations related to software for medical devices for prediction and prognosis is currently under review.

In addition to the many technical challenges still faced by AI technologies, another major concern in the application of AI technologies within healthcare is related to the acquisition, generation, and use of health data. Many people consider their health information private and agree that it should be protected, accordingly. Patients usually want to know how their information is being handled. The fact that the transfer of medical records from paper to electronic formats could increase the

chances of individuals accessing, using, or disclosing sensitive personal health data, has triggered a lot of privacy concerns.

To address these concerns, regulatory efforts are underway to ensure proper flow and use of healthcare records. The most recent development is the General Data Protection Regulation (GDPR) enforcement established in Europe which has strong implications for the development of AI-based platforms. Although these regulations are welcome and necessary to avoid abusive practices, regulatory institutions should ensure that they do not become barriers to meaningful technological development. The ability of AI to make accurate predictions is heavily dependent on data availability. Access and regulation should take into account that collaboration between healthcare and AI-based companies is necessary to establish an efficient pipeline for data acquisition.

The population specificity of the many aging biomarkers demonstrates the need for international collaborations and consortiums focused on data economics, generation, and exchange, model exchange and validation as well as meta-analysis, clinical trials and educational programs.

Competing interest

Alex Zhavoronkov, Polina Mamoshina, Quentin Vanhaelen and Alex Aliper are affiliated with Insilico Medicine, Inc., a company engaged in aging research, which designs and uses AI-based algorithms for de novo molecules generations and is also involved in biomarker development and hence may have competing financial interests.

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