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Cardiovascular Applications of Artificial Intelligence in Research, Diagnosis, and Disease Management

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Chapter 4

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ABSTRACT

Despite significant advancements in diagnosis and disease management, cardiovascular (CV) disorders remain the No. 1 killer both in the United States and across the world, and innovative and transformative technologies such as artificial intelligence (AI) are increasingly employed in CV medicine. In this chapter, the authors introduce different AI and machine learning (ML) tools including support vector machine (SVM), gradient boosting machine (GBM), and deep learning (DL) models, and their applicability to advance CV diagnosis and disease classification, and risk prediction and patient management. The applications include, but are not limited to, electrocardiogram, imaging, genomics, and drug research in different CV pathologies such as myocardial infarction (heart attack), heart failure, congenital heart disease, arrhythmias, valvular abnormalities, etc.

INTRODUCTION

Cardiovascular (CV) diseases claim the greatest number of deaths both worldwide and across the United States (Virani et al., 2021). The CV healthcare costs are enormous despite several advancements in diagnostic and therapeutic products. The CV system can be negatively impacted at various clinical levels. These broadly include heart valve abnormalities such as stenosis (narrowing) or regurgitation (backflow),

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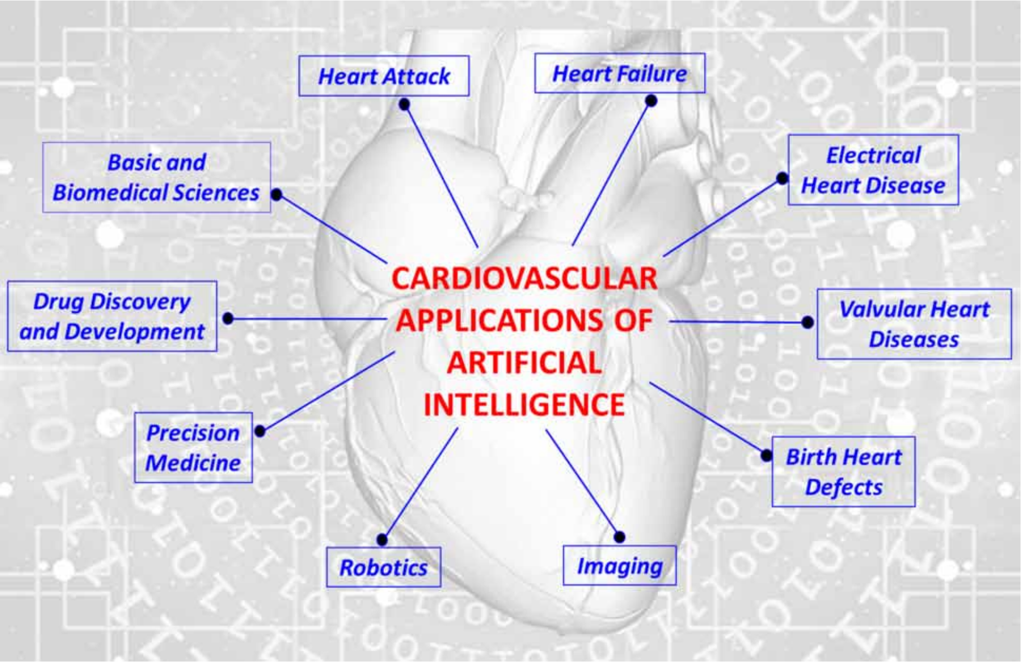
myocardial infarction (heart attack), heart failure, congenital heart disease (birth defects) and arrhythmias (electrical defects). Thus, novel technologies such as those offered by artificial intelligence (AI) has potential to enhance further progress in the field and may offer significant improvements in health outcomes along with reductions in costs.

As one of the fastest emerging technologies, AI plays major roles in practically every sector of our daily lives. For example, virtual assistants such as Alexa, Siri or Google Assistant can help customers perform searches, order products online, answer questions, set reminders, adjust local environment, etc. Many e-commerce websites improve customers' online shopping experience with personalized recommendations and more streamlined buying processes. Voice verification, facial recognition, and biometric systems have been widely used to enhance security and surveillance.

AI also plays an increasingly important role in healthcare. AI and Machine Learning (ML) techniques have been widely used to improve both patient care and administrative processing. ML and Deep Learning (DL) techniques have been successfully applied to diagnose, analyze, and predict the course of various types of diseases, and in monitoring patient health conditions as well. Natural Language Processing (NLP) techniques can be used to understand and classify unstructured clinical documentations and assist in structuring patient and medication information. AI systems and robotics are also helping with day-to-day administrative and routine functions of health facilities, thus reducing physical workload of medical personnel, minimizing human errors and maximizing efficiency.

AI and ML techniques have been applied to improve CV research and health (Figure 1). This chapter is aimed to provide an overview of AI advancements in diverse areas within the CV field, however, it is not meant be a complete resource of all developments. For a comprehensive collection, the readers are suggested to explore several published review articles (Antoniades, Asselbergs, & Vardas, 2021; Benjamins, Hendriks, Knuuti, Juarez-Orozco, & van der Harst, 2019; C. Krittanawong et al., 2019; Mathur, Srivastava, Xu, & Mehta, 2020; Quer, Arnaout, Henne, & Arnaout, 2021). AI will also be discussed in the context of aforesaid disorders along with imaging, basic and biomedical sciences, precision medicine, drug discovery and development and robotics. The Coronavirus Disease 2019 (COVID-19) pandemic has significantly affected the CV health as well, (Abu Mouch et al., 2021; Chung et al., 2021; Farshidfar, Koleini, & Ardehali, 2021; Gedefaw et al., 2021; Nishiga, Wang, Han, Lewis, & Wu, 2020; Patil, Singh, Henderson, & Krishnamurthy, 2021; Rosner et al., 2021; Wenger & Lewis, 2021; Yiangou, Davis, & Mummery, 2021), however, this chapter will not delve into the topic, as a separate chapter is dedicated for COVID-19 in this volume. Before we dive into the clinical and biomedical aspects, we shall first introduce state-of-the-art AI and ML techniques, and subsequently discuss how those techniques are applied and are beneficial in diverse CV applications.

Figure 1. Schematic of areas where Artificial Intelligence and Machine Learning impact Cardiovascular sciences and medicine.



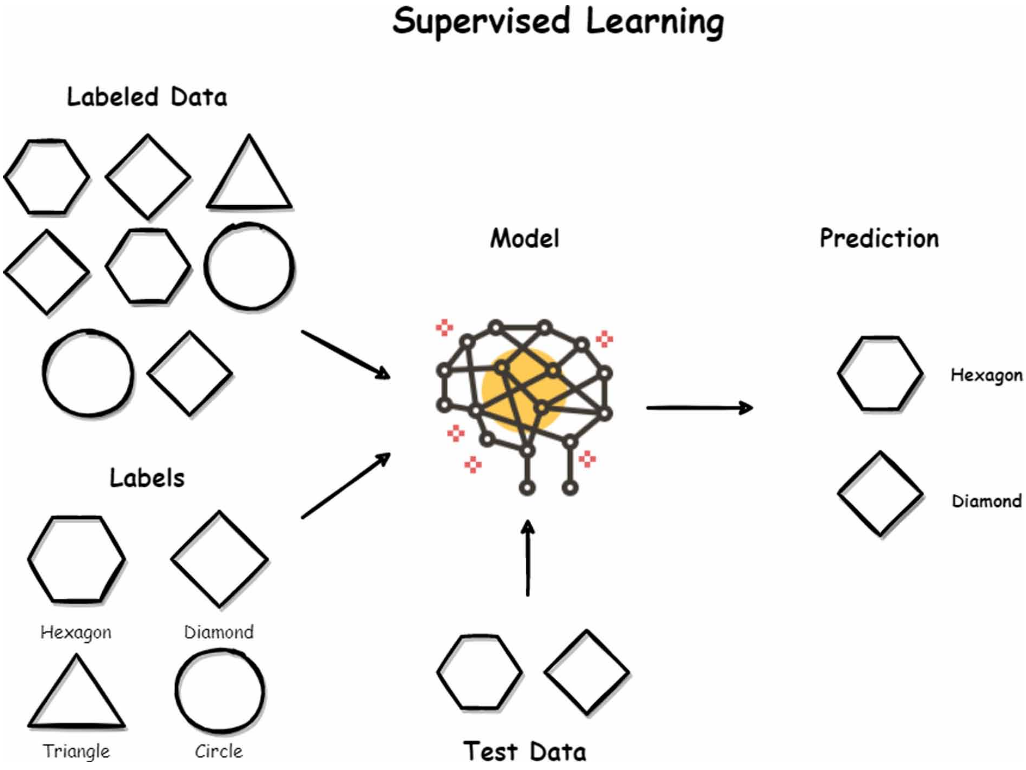
STATE-OF-THE-ART AI AND ML TOOLS

As a part of AI, ML refers to the study of computer algorithms that improve automatically through experience and by the use of data (Mitchell, 1997). Based on the nature of the signal and feedback available to the learning system, ML can be divided into different categories including supervised leaning, unsupervised learning, semi-supervised learning, reinforcement learning, etc.

Supervised Learning

Supervised learning is one of the most common methods of ML. It builds a mathematical model, i.e., a mapping function, that maps inputs to the desired outputs based on a set of training examples of input-output pairs. Here, the inputs X can be considered as features and the outputs Y can be considered as labels. Figure 2 shows a classic example of supervised learning. *Classification* and *regression* are the two major tasks in supervised learning. Classification is the process of finding the mapping function to map the input X to the categorical output Y. A model is trained on the training dataset aiming to categorize the data into different classes. For example, in a study by Sengupta et al. (P. Sengupta et al., 2016), clinical data and the imaging data have been combined together to train classifiers to discriminate cardiac abnormalities. On the other hand, regression is the process of finding the correlations between dependent and independent variables, and the task of the regression is to find the mapping function to map the input X to the continuous output Y. For example, in a study by Lee et al. (J. Lee et al., 2016), regression models have been trained to predict fractional flow reserve from coronary computed tomography (CT) angiography images.

Figure 2. Classic example of Supervised Learning. The labeled data and labels pass on to the model generating prediction of test data.



Common supervised learning algorithms include logistic regression (Gortmaker, Hosmer, & Lemeshow, 2013), linear regression (Seber & Lee, 2012), naive Bayes (Zhang, 2004), decision tree (Quinlan, 2004), random forest (Cutler, Cutler, & Stevens, 2011), support vector machine (SVM) (Boser, Guyon, & Vapnik, 1996), k-nearest neighbors (KNN) (Altman, 1992), artificial neural network (ANN) (Daniel, 2013), and ensemble learning methods (Rokach, 2010).

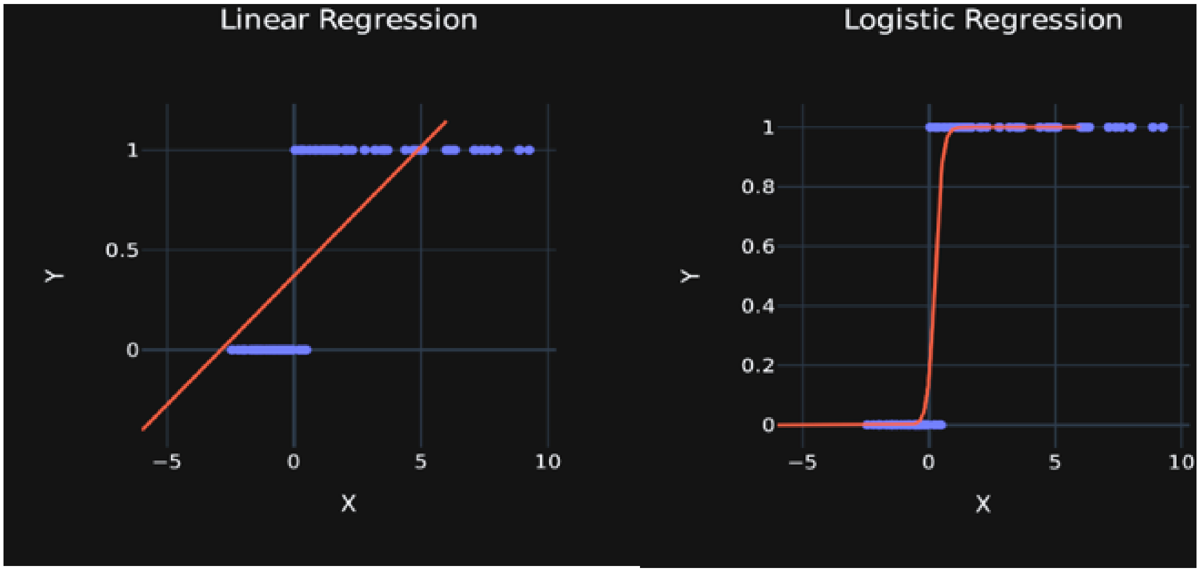
Logistic Regression

Logistic regression, also known as maximum-entropy classification, is a linear model for classification. It is a statistical model that uses a logistic function to model probability of a certain class or event such as healthy/sick. It has been successfully applied in disease prediction including prediction of CV diseases for decades.

Linear Regression

Linear regression is a linear approach to model relationship between the input variables and target variable by fitting a linear equation to observed data. It is a regression model commonly used to predict continuous values. For example, it can be used to predict the CV risk assessment score (Ismail & Anil, 2014). Figure 3 shows graphical representations of linear and logistic regression.

Figure 3. Graphical representation of Linear and logistic Regression



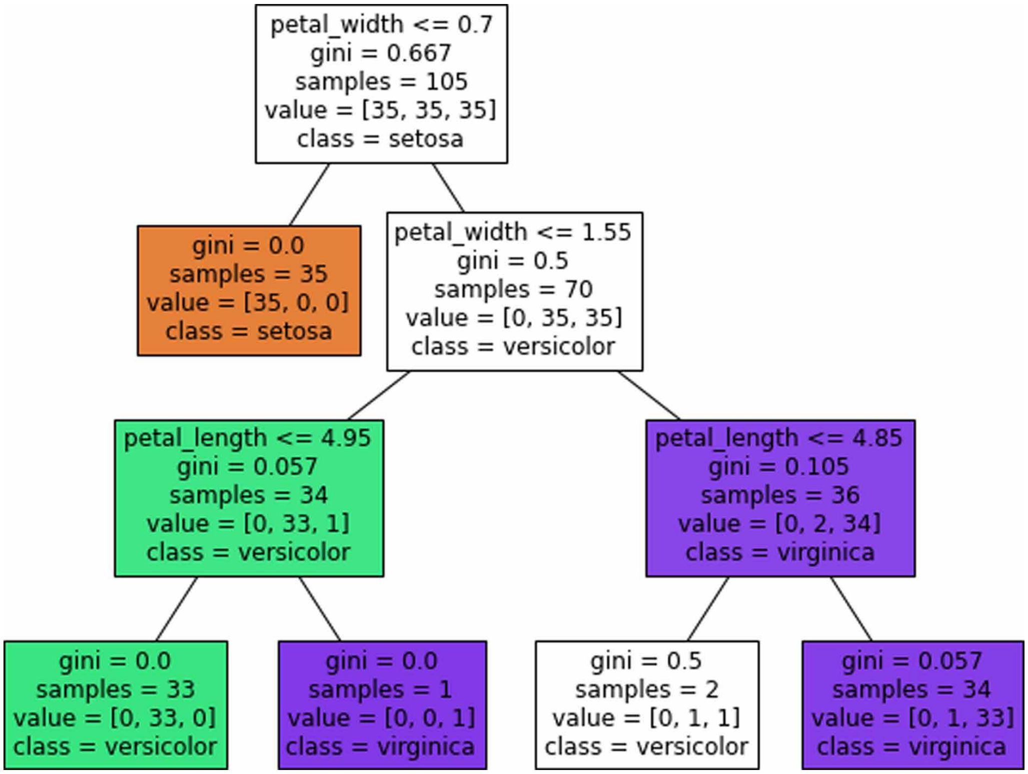
Naive Bayes

Naive Bayes are simple probabilistic classifiers based on applying Bayes' theorem with the "naive" assumption of conditional independence between every pair of features given the value of the class variable. Despite the over-simplified assumption, the naive Bayes classifiers have worked well in many complex real-world situations. They only require a small number of training data to estimate the parameters for classification, and can be trained extremely fast compared to other sophisticated learning methods. In a study by Miranda et al. (Miranda, Irwansyah, Amelga, Maribondang, & Salim, 2016), naive Bayes classifiers had shown very promising results in detection of CV disease risk's level for adults.

Decision Tree

Decision tree (DT) is one of the most popular supervised learning methods which can be used to solve both classification and regression problems. It has been widely applied in various CV applications. It is a non-parametric method that aims to create a model that predicts the value of a target variable by learning simple decision rules inferred from the data features. DT models are easily interpreted that have high accuracy and stability. DTs are also non-linear models which make them great for predicting and solving more complex problems. As shown in Figure 4, each node in the DT represents a decision binary on a feature, the branches from the nodes represent the outcome of the decision, and the last nodes of the tree (the leaves) represent the final classification/estimation of the data.

Figure 4. Architecture of a decision tree. The root and intermediate nodes test on features and the leaves predict the data.



Random Forest

Random forests are an ensemble learning method by constructing a multitude of decision trees at training time. Figure 5 shows an example of random forest ensemble learning. Similar to DT, they can be used to solve both classification and regression problems. For the classification tasks, the output of the random forest is the class selected by most trees. For regression tasks, the output is the mean or average prediction of the individual trees. Random forests generally outperform decision trees as they can help to correct the overfitting from single decision tree. They have been proven successful in many studies on CV disease classification and risk prediction (Xu et al., 2017) (Caballé, Castillo-Sequera, Gomez-Pulido, Gómez, & Polo-Luque, 2020).

Support Vector Machine

Support Vector Machines or SVMs are one of the most robust prediction methods for classification and regression based on statistical learning frameworks. Generally speaking, the objective of SVMs is to find a hyperplane in an *N*-dimensional space that has the maximum margin, i.e. the maximum distance between data points of both classes to distinctly classify the data points. Samples on the margin are called the support vectors. Maximizing the margin distance provides some safety margin such that a slight error in measurement will not cause a misclassification, and future data points can be classified with more confidence. SVMs can be used to solve both linear and non-linear problems and work well on many practical problems including the CV applications. Through non-linear transformation, SVMs can project nonlinear separable samples onto another higher dimensional space by using different types of kernel functions. Common kernel functions include linear kernel, Radial Basis Function kernel, and polynomial kernel. For example, Figure 6 shows decision boundary for a binary classification problem, with three types of kernel functions.

Figure 5. Example of Random Forest Ensemble Learning. It works by aggregating output of different decision trees via majority vote or averaging to generate a final prediction.

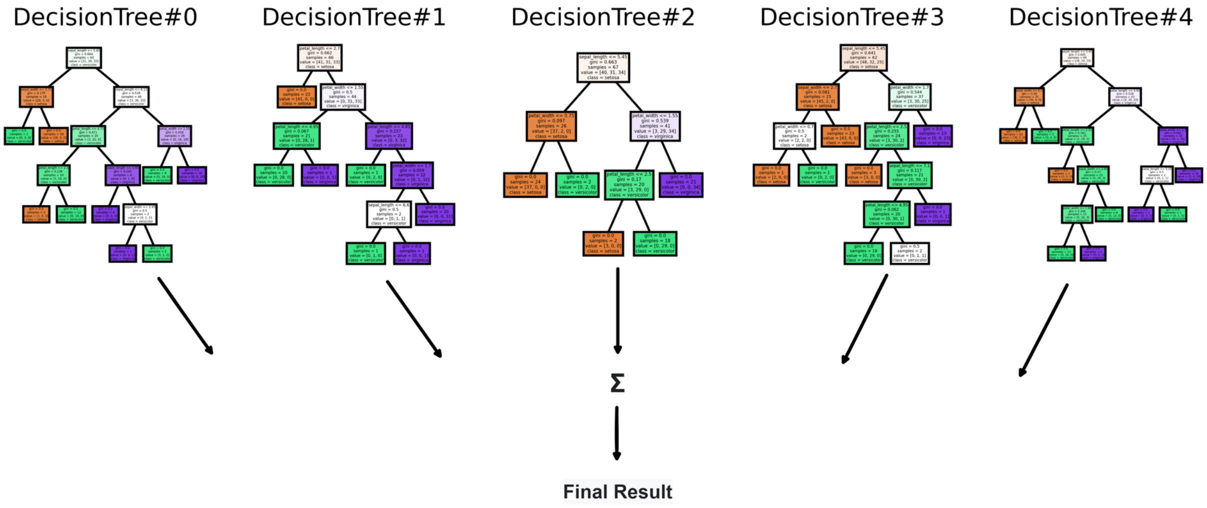
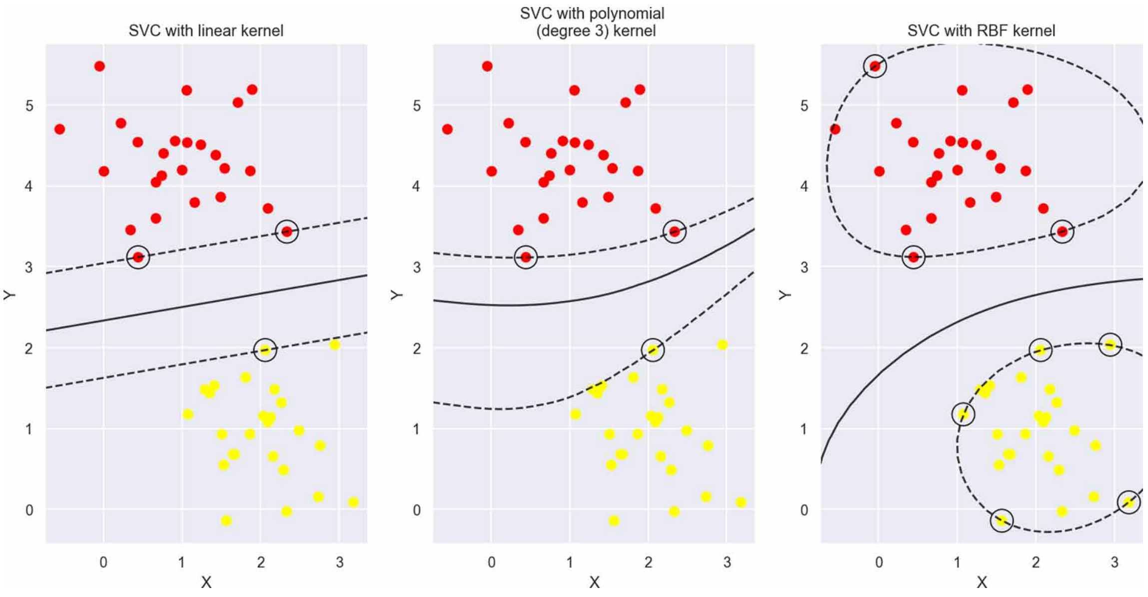


Figure 6. SVM example - Decision boundary for Different Kernels. Dash lines plot support vectors of the models and the solid lines plot decision boundaries of different models.



K-Nearest Neighbors

K-nearest neighbors (k-NN) is a non-parametric classification method which can be used to solve both classification and regression problems. In classification, the input consists of the *k* closest training examples in data set and the output is classified by a plurality vote of its *k* neighbors. While in regression, the output is the average values of the *k* nearest neighbors. The selection of the right *k* is crucial for the success of the algorithm. For example, a small value of *k* indicates that noise will have a significant impact on the result, while a large value makes it computationally expensive. One common application of k-NN on CV domain is heart disease prediction (Enriko, Suryanegara, & Gunawan, 2016). Although k-NN is a simple and easy-to-implement non-parametric algorithm, it should be noted that it gets significantly slower as the number of examples or predictors increase. In addition, it is also very sensitive to the local structure of the data.

Artificial Neural Network

Artificial neural networks (ANNs) are computing systems in accordance with biological neural networks from animal brains. They can be used to model different kinds of complex, nonlinear or discontinuous relationships. As shown in Figure 7, ANN models consist of input layer, one or more hidden layers and output layer. In each of the layers in ANN, there are nodes called neurons. These nodes are connected to each other with associated weights and thresholds and processes the data in the network through a sum and transfer function. Based on the depth of layers in neural network, ANN models can be further divided into basic neural network and DL models. Basic neural network models usually contain less than or equal to three hidden layers while DL models normally consist of deeper networks with more than three hidden layers. We will discuss various DL algorithms in detail in later sections.

Ensemble Learning

Ensemble learning methods are techniques that combine multiple learning models together to improve predictive performance, which usually produce more accurate solutions than any of the constituent learning algorithm alone. Figure 8 shows an example of the ensemble learning system. Ensemble models tend to produce better results when there is a significant diversity among the models. As a result, many ensemble methods tend to promote diversity among the models they combine (Kuncheva & Whitaker, 2003). Bagging method involves having each model in the ensemble vote with equal weight and is a common ensemble algorithm designed to improve stability and accuracy of model performance. The random forest algorithm that we introduced earlier is a bagging method. Boosting is another type of ensemble method which involves incrementally building an ensemble by training each new model instance to emphasize the training instances that previous models misclassified. Adaptive Boosting (AdaBoost) (Freund, Iyer, Schapire, & Singer, 2003), is one of the most popular boosting method. It helps to combine multiple "weak classifiers" into a single "strong classifier" by putting more weight on difficult to classify instances and less on those already handled well. Ensemble classifiers have been successfully applied in neuroscience, proteomics and medical diagnosis including clinical decision support system for CV disease (Eom, Kim, & Zhang, 2008).

Figure 7. A basic ANN example with a 5-perceptron input layer, a 10-perceptron hidden layer and a 4-perceptron output layer.

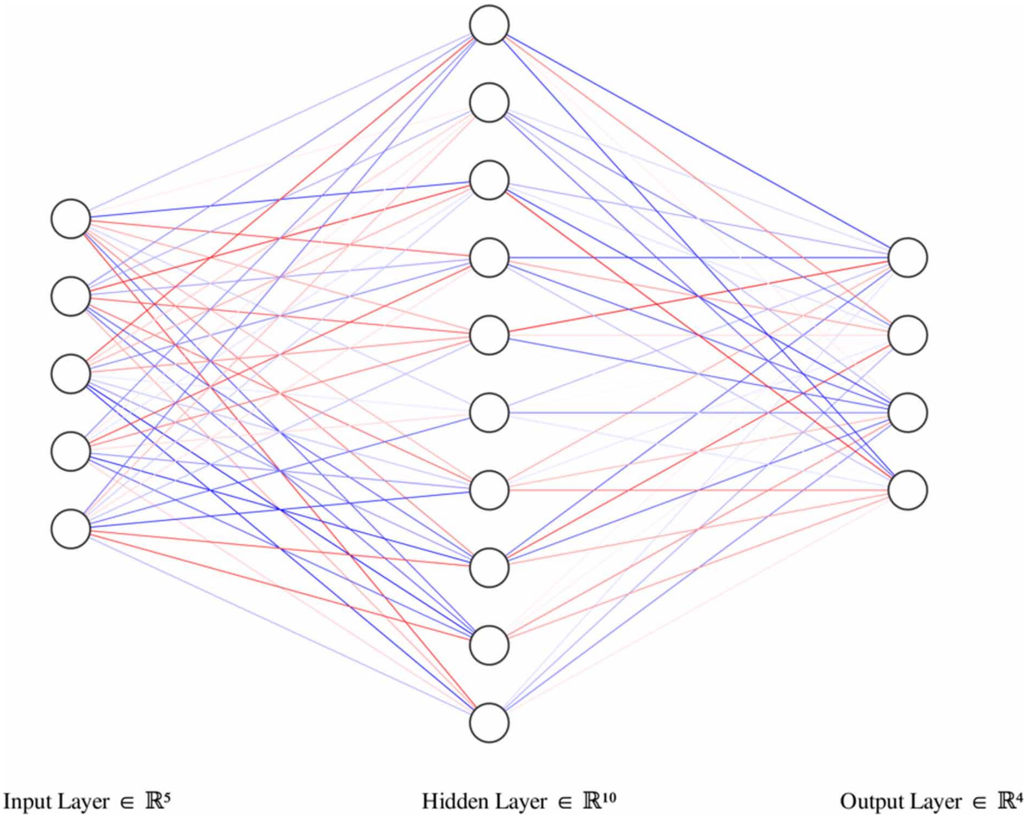
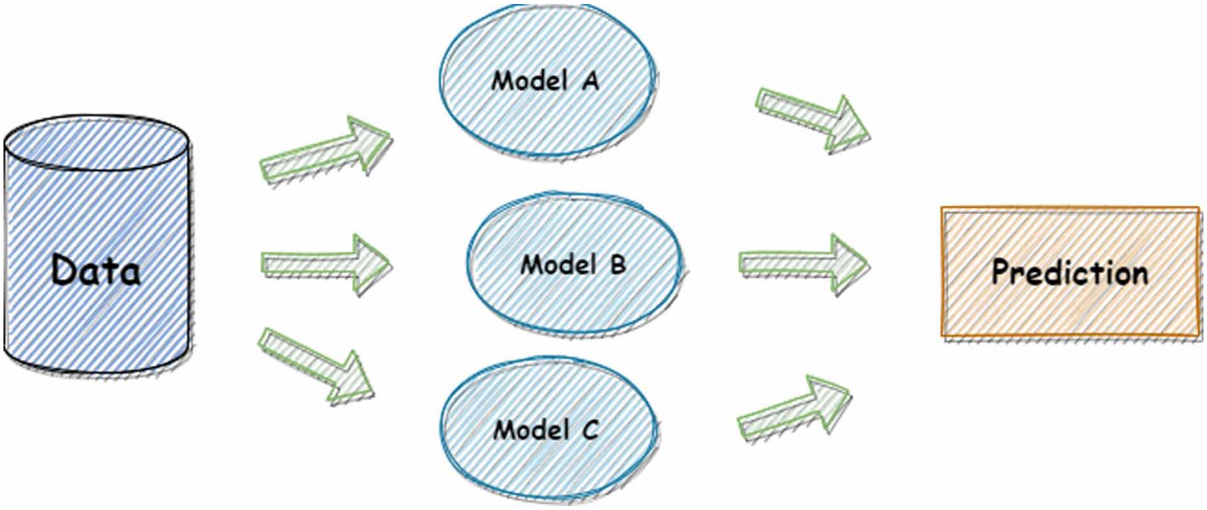


Figure 8. Example of ensemble learning output and prediction by providing same data to 3 different models and aggregating the output to final prediction.



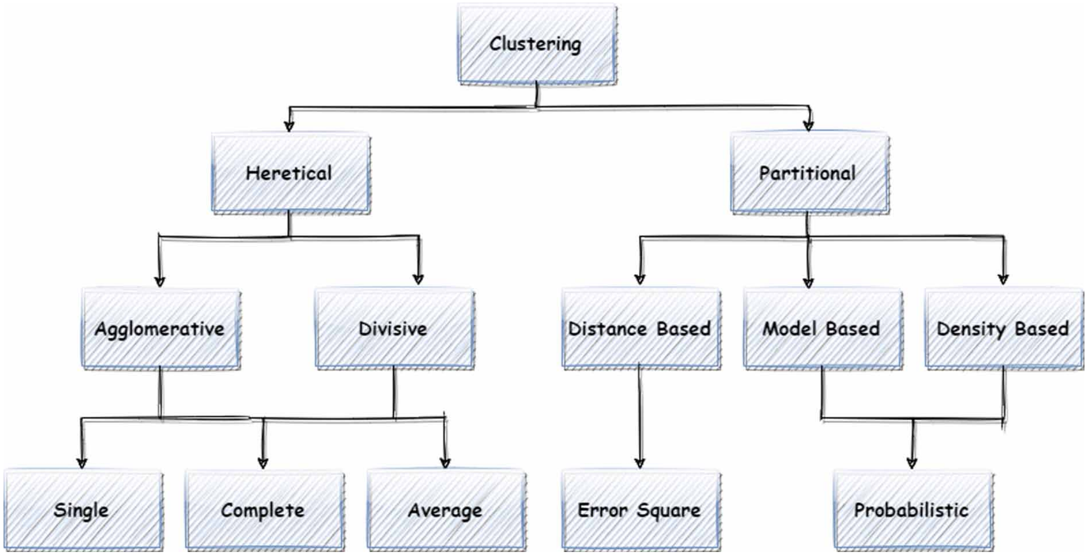
Unsupervised Learning

Unlike supervised learning that tries to fit input data with output labels, unsupervised learning works on its own to discover inherent structure within an input dataset without target labels. The three main tasks of unsupervised learning are clustering, association and dimensionality reduction (Hinton & Sejnowski, 1999).

Clustering

Clustering analysis is a task for grouping unlabeled data based on their similarities or differences such that within a group the observations must be as similar as possible, while observations belonging to different groups must be as different as possible. Figure 9 summarizes different types of cluster algorithms. Among them, hierarchical clustering and k-means clustering are the two main algorithms in clustering analysis. The k-means clustering algorithm assigns similar data points into *k* groups. The number *k* needs to be fixed in advance and it represents the size of the grouping and granularity. While hierarchical clustering is generally used for an unknown number of classes and helps to determine the optimal number. Clustering analysis has been used in many fields, including pattern recognition, image analysis, bioinformatics, etc. One common application of cluster analysis in CV research is to identify underlying risk factors for coronary artery disease (Guo et al., 2017). Unpublished data from Rajagopalan group using unsupervised hierarchical clustering showed significant alterations in expression of noncoding RNAs from left ventricles in a model of heart failure (HF) with preserved contractile function (expanded later) as seen in human disease. These findings offer enormous opportunities with potential diagnostic and therapeutic solutions in this type of HF for which there is no clear treatment available.

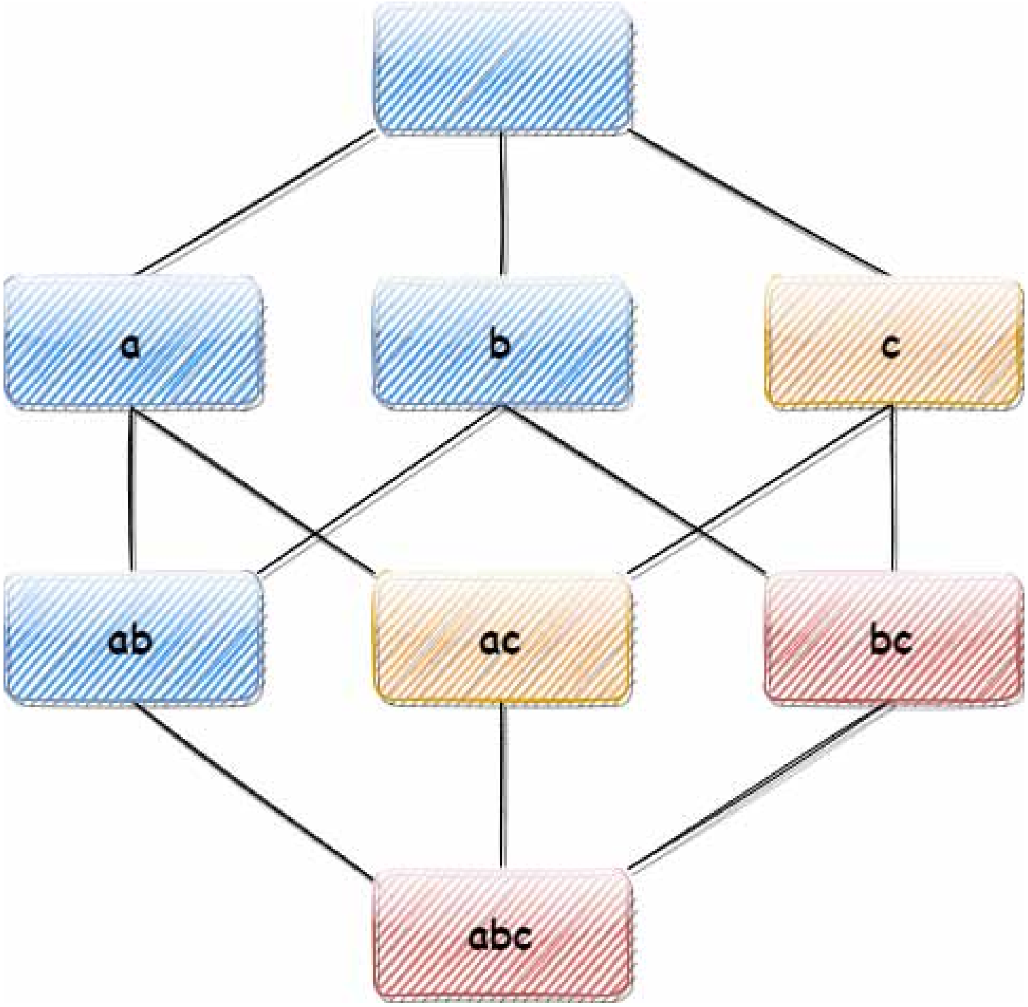
Figure 9. Types of Cluster Algorithms



Association

Association is another type of unsupervised learning method that uses different rules to find relationships between variables in a given dataset. It is frequently used to identify items that have an affinity or often appear together. Figure 10 shows downward-closure property of the association method. It can also be used for identifying dependent or associated events as seen in a study (Nahar, Imam, Tickle, & Chen, 2013) in which association rules have been used to detect factors which contribute to heart disease in males and females respectively.

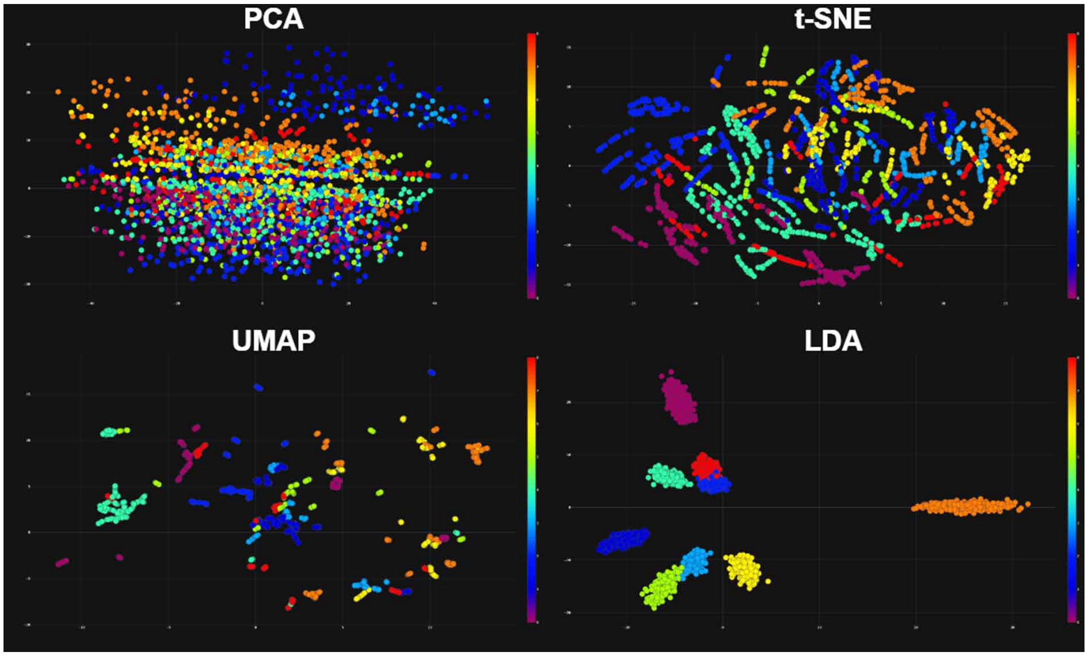
Figure 10. The downward-closure property



Dimensionality Reduction

Dimensionality reduction is a learning technique used when the number of features in a given dataset is too high. It is the transformation of data from a high-dimensional space into a low-dimensional space while still preserving data integrity. It can be divided into linear and non-linear approaches (van der Maaten, Postma, & Herik, 2007). Principal Component Analysis (PCA) is one of the most common linear techniques for dimensionality reduction. It is an orthogonal linear transformation that transforms the data to a lower-dimensional space such that the variance of the data in the low-dimensional representation is maximized. PCA has been widely used in signal processing, neuro-informatics, and bioinformatics. On the other hand, auto-encoder is a type of neural network used to learn non-linear dimension reduction functions and efficient codings together with an inverse function. It has been used in biomedical image processing, e.g., to remove noise from visual data to improve picture quality and also in drug discovery (Zagribelnyy et al., 2019).

Figure 11. Dimensionality Reduction via PCA, t-SNE, UMAP, LDA (reduced original data from 784 dimensions to 3 dimensions)

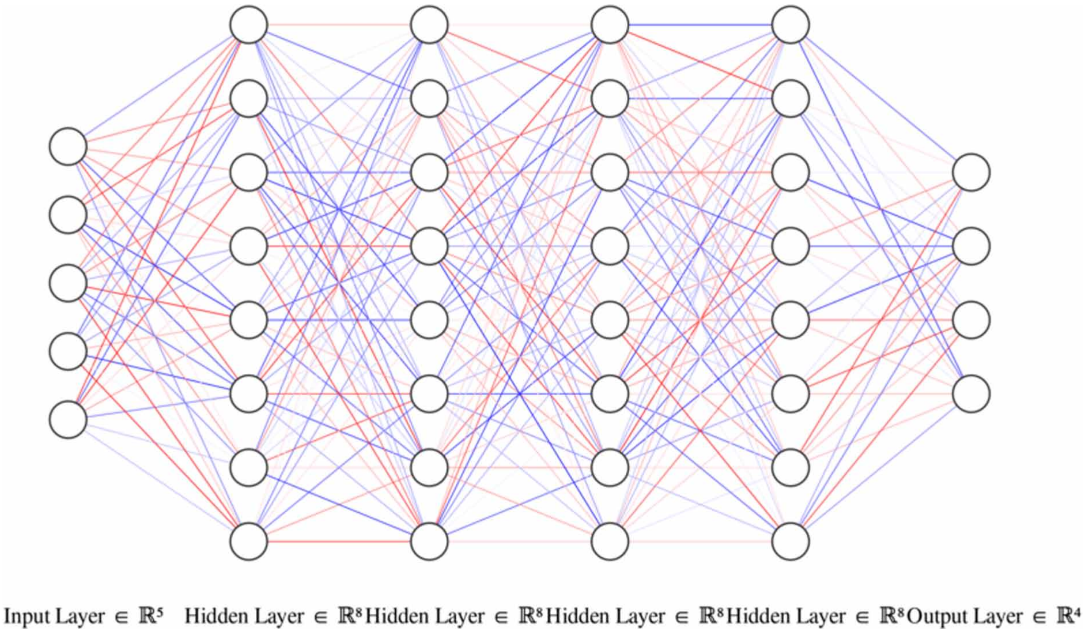


Deep Learning

Deep Learning, DL, based on ANN with representation learning, has emerged as a new area of AI over the past decade (Yoshua Bengio, Courville, & Vincent, 2013; LeCun, Bengio, & Hinton, 2015). DL techniques can be used to extract complex and concealed information from large number of raw data using multiple hidden layers, i.e., tens or hundreds, where each layer is a representation that is a high-level abstraction of the representation from the previous layer of the neural networks. The word "deep" refers to the number of layers through which the data is transformed. The greater the number of hidden layers is, the deeper the network is. For example, when we build DL models for face recognition, the input may be a matrix of pixels from raw images, the first layer may abstract the pixels and encode edges from the image, the second layer may compose and encode arrangements of edges, the third layer may encode nose and eyes, and the fourth layer may recognize that the image contains a face and match the face with registered users.

Common DL models include convolutional neural networks (CNNs), recurrent neural networks (RNNs), deep belief networks (DBNs), deep auto-encoder, etc. They have been widely used in speech recognition, computer vision, natural language processing, bioinformatics, robotics, drug design, medical image analysis and more. (Deng, 2014; Schmidhuber, 2015).

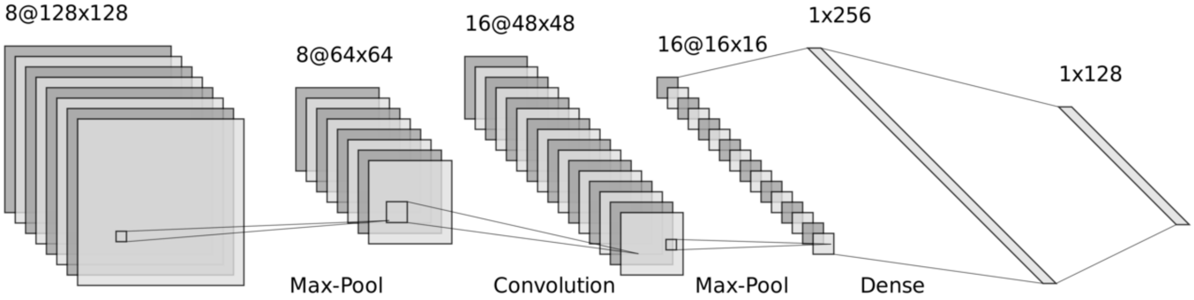
Figure 12. Classic Example of Deep Learning Neural Networks with a 5-perceptron input layer, 4 hidden layers with 8-perceptron, and a 4-perceptron output layer.



Convolutional Neural Networks (CNN)

CNNs are feed-forward neural networks inspired by mammalian visual cortex that contains very small neuronal cells sensitive to specific areas of the visual field, i.e., some neurons respond when exposed to vertical edges and some when exposed to horizontal edges (Hubel & Wiesel, 1962). All these neurons which appear to be spatially arranged in columnar structures are able to produce visual perception. Accordingly, CNNs are proposed with succession layers of convolution, activation, pooling, and fully-connected layers to obtain the final outputs. The convolution layers are the most important part of a CNN, which are composed of a set of filters to extract different features from input data. For instance, the first convolution layer extracts low-level features such as lines, edges, and corners, and higher-level layers extract higher-level features. CNNs are now the dominant approach for various computer vision tasks including medical image analysis.

Figure 13. A Comprehensive Guide to Convolutional Neural Networks. Eight convolution filters with 128×128 input, 8 convolution filters with 64×64 input, 16 convolution filters with 48×48 input, 16 convolution filters with 16×16 input followed by 2 fully connected layers with 256 and 128 units respectively.



Recurrent Neural Networks (RNN)

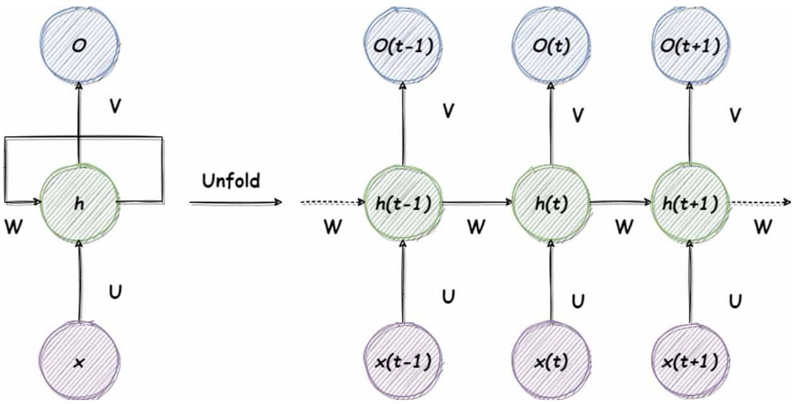
Distinct from CNNs with feed-forward networks, RNNs include feedback components that permit signals from one layer to be fed back to the previous layer (Olurotimi, 1994). Moreover, RNN is a type of deep neural network with an internal state (memory) which can be used to store long-term information and process variable length sequences of inputs (Y. Bengio, Simard, & Frasconi, 1994). In addition, RNNs can not only process single data points (such as images), but also entire sequences of data (such as speech and video). It should be noted that basic RNNs may fail to model long-term dependences of data and suffers from gradient vanishing. To overcome these drawbacks, Long-Short-Term Memories (Hochreiter & Schmidhuber, 1997) and Gated Recurrent Units (Cho et al., 2014) have been proposed. Both these models add gates and memory cells in the hidden layer to control the amount of information entering the unit, the amount that will be stored and the information that will be passed to the next units. RNNs have been introduced to various types of CV applications in the last few years. For example, in a study by Choi et al. (Choi, Schuetz, Stewart, & Sun, 2016), the RNN models were applied for early detection of HF onset.

BRIEF, SIMPLIFIED HEART ANATOMY AND PHYSIOLOGY

Human heart begins to form and function quite early in gestational period. The heart comprises 4 chambers, 2 atria (upper) and 2 ventricles (lower). The right atrium receives deoxygenated blood from all parts of the body and pumps out to the lungs for purification via right ventricle and pulmonary artery. The left atrium receives oxygenated purified blood from the lungs and delivers to left ventricle. The left ventricle pumps the blood out with greater force and pressure to all parts of the body via the Aorta. The pumping activities are the result of specialized sarcomeric protein molecules within the major heart cells called cardiomyocytes. The repetitive mechanical activities of alternating contractions and relaxations are the result of immediately preceding electrical activities elicited by specialized cells residing at different regions of heart tissues.

Before entering and leaving each heart chamber, the blood passes through specific valves. The valves are specialized tissue flaps (leaflets) that act as one-way outflow orifices and prevent backward flow of blood. While the bicuspid (mitral) valve is located between left atrium and left ventricle, the tricuspid valve is located between right atrium and right ventricle. Correspondingly, the aortic valve is located between left ventricle and aorta, and the pulmonary valve is located between right ventricle and pulmonary artery.

Figure 14. Recurrent Neural Networks (RNN). X is the input layer, h is the hidden layer, o is the output layer. W, U, and V are weighting matrices of each connection among input, hidden and output layers. The (t-1), (t), and (t+1) are the time steps.



APPLICATIONS OF AI IN CV SPACE

AI in Electrical Heart Disease

Fetal primitive human heart begins to beat towards later part of the first month of gestational period. In order for the heart to pump effectively for rest of the life, it is crucial that the beats are rhythmic and of optimal frequency. Abnormalities in electrical activities including conduction and rhythm (arrhythmias), inherited or acquired, may result in life-threatening CV anomalies such as ventricular tachycardia (VT) or ventricular fibrillation (VF).

Rogers et al. (Rogers et al., 2021) recorded 5706 ventricular monophasic action potentials during steady-state pacing in 42 patients with coronary artery disease and left ventricular (LV) ejection fraction (contractile function) £40%. Using SVMs and CNNs, they showed c-statistics of 0.90 for sustained VT/VF and 0.91 for mortality. In silico modeling also revealed higher L-type calcium current or sodium-calcium exchanger as predominant phenotypes for VT/VF. Future studies in relation to magnetic resonance (MR) imaging-determined scar or *in vivo* optical imaging would be valuable.

Atrial fibrillation (AF) is considered to be the most common rhythm disorder sometimes presenting with serious complications such as stroke. The UK DISCOVER registry comprising primary care population of greater than 600,000 individuals was studied using an ML prediction algorithm to detect AF (Sekelj et al., 2021). Results of this retrospective cohort study showed negative predictive value of

96.7% and sensitivity of 91.8% among patients aged ^{3}65 years (*n* = 117,965). Attia et al. (Attia, Noseworthy, et al., 2019) employed CNN using Keras Framework with Tensorflow backend and Python to detect electrocardiogram (ECG) signature of AF present during normal sinus rhythm using standard 10-second, 12-lead ECGs. They employed a total of more than 454,000 ECGs from almost 181,000 patients and achieved 0.9 area under the curve (AUC). These strategies can help in the development of rapid, inexpensive, point-of-care approaches to detect AF.

The widely marketed Apple Watch with proprietary AI features in conjunction with Apple iPhone was tested for its ability to detect AF. In a population of almost 420,000 participants over a median of 117 days of monitoring, the Turakhia group (Perez et al., 2019) aimed at estimating the proportion of notified participants with atrial fibrillation shown on ECG patch. Results showed that 84% of notifications were concordant with AF. To enhance the power of smartwatch towards multiple-lead ECGs, Spaccarotella et al. (C. A. M. Spaccarotella et al., 2020) placed the Watch in different body locations to obtain 9 bipolar ECG tracings that correspond to Einthoven leads I, II, III and precordial leads, V1-V6 that were compared with simultaneous standard 12-lead ECGs. In a small population set of 100 participants, the findings offer promise by demonstrating that the device was able to record multichannel ECGs in agreement with standard ECGs with comparable ST-segment changes. Taken together, such approaches may help in timely detection and potential prevention of deadly complications including those resulting from myocardial infarction (expanded later), particularly, in asymptomatic individuals. In a case report, they were also able to show ST-segment changes reflective of the rare condition, Brugada syndrome similar to that documented in standard ECG following Ajmaline infusion in an adult male patient (C. Spaccarotella, Santarpia, Curcio, & Indolfi, 2021).

AI in CV Imaging

Imaging technologies play vital role in diagnosis and prognosis of CV diseases. With the development of ML and DL, AI has made remarkable achievements in cardiac imaging (Leiner et al., 2019). This includes improvements in imaging efficiency and quality along with automation in image analyses and interpretations to further assist in the detection and management of CV disorders.

Image Acquisition and Reconstruction

Various AI techniques including compressed sensing and real-time image processing have been applied to enhance cardiac imaging methodologies such as Cardiac CT and MR imaging in the past decade (Graff & Sidky, 2015; Kido et al., 2016; Vasanawala et al., 2010). Recently, DL models have been introduced to further improve medical image acquisition and reconstruction. One study (Yang, Sun, Li, & Xu, 2016) proposed a novel deep architecture, dubbed ADMM-Net, which is defined over a data flow graph from iterative procedures in Alternating Direction Method of Multipliers algorithm for optimizing compressed sensing-based MRI models. Their proposed models can reconstruct MR images from a small number of under-sampled data in k-space, and thus accelerate data acquisition in MRI. Another study (Qin et al., 2019) proposed an advanced convolutional recurrent neural network model which can reconstruct high quality cardiac MR images from highly under-sampled k-space data by jointly exploiting dependencies of temporal sequences as well as iterative nature of traditional optimization algorithms. DL techniques have also shown high potential to reduce reconstruction time and improve visual image quality for highly accelerated 3D or 4D data. For example, Kustner et al. proposed a novel 4D (3D+time)

DL-based reconstruction network, termed 4D CINENet, for prospectively under-sampled 3D Cartesian CINE imaging (Küstner et al., 2020). The proposed model outperforms iterative reconstructions related to visual image quality, contrast, and reconstruction time.

Image Registration

ML and DL techniques have been applied to improve accuracy and speed for image registration as well (X. Chen, Diaz-Pinto, Ravikumar, & Frangi, 2020). DL models have been used to generate learnable, data-driven interpretations of similarity metrics, which outperform conventional similarity metrics in robustness and flexibility (Fan, Cao, Xue, & Yap, 2018; Haskins et al., 2018). Moreover, they have been widely used in estimating the parameters of spatial transformation for registration. In a study by Rohe et al., a novel fully convolutional network was proposed (Rohe, Datar, Heimann, Sermesant, & Pennec, 2017). It consists of contracting layers to detect relevant features and a symmetric expanding path that matches them together to output the transformation parametrization. The proposed model was used for inter-patient heart registration and has shown significant improvement over the state-of-the-art optimization-based algorithms. Another study (Sang & Ruan, 2020) proposed a convolutional auto-encoder network with a novel deformation representation model to achieve spatially variant conditioning on deformation vector field (DVF) for 3D cardiac MRIs, which can accomplish registration with physically and physiologically more feasible deformation vector fields, and improve the registration network performance significantly.

Image Segmentation

Image segmentation has a long history and various ML and DL approaches have been explored (Peng et al., 2016; Petitjean & Dacher, 2010). DL-based models such as CNNs, are currently the new state-of-the-art in the field (Ronneberger, Fischer, & Brox, 2015). Such DL frameworks have been successfully applied on segmentation of MR images involving cardiac chambers by using pixel-based classification. For example, a standard CNN model was used to segment short-axis cardiac MR images (Romaguera, Perdigón Romero, Costa Filho, & Costa, 2017). Another approach is to perform regression to produce smooth epicardial and endocardial contours rather than pixel classification. In a study by Du et al., a deep belief network based regression segmentation framework was proposed to delineate boundaries of bi-ventricle from cardiac MR images (Du et al., 2018).

Diagnosis and Prediction

AI has been widely used in image-based cardiac diagnosis and prediction as well (Martin-Isla et al., 2020). ML and DL models have been trained with conventional imaging indices, radiomics features, or raw imaging data for diagnosis of various types of CV diseases. In a study by Larroza et al., SVM models were used to predict myocardial infarction based on radiomics features extracted from MRI (Larroza et al., 2018). Wolterink et al. used random forest models for diagnosis of various cardiomyopathies by using conventional MRI imaging indices (Wolterink, Leiner, Viergever, & Išgum, 2018). Another study (Snaauw et al., 2019) proposed end-to-end DL models based on raw MR images for cardiac diagnoses.

AI in Heart Attack

AI and ML techniques have been successfully applied to predict risk of heart attack, also referred as myocardial infarction. Numerous studies have applied ML models to predict cardiac events primarily in patients presenting with acute coronary syndrome (ACS). For example, both basic ML models such as random forests and DL models have shown high accuracy in prediction of 1-year mortality after hospital discharge in patients with ACS (Barrett, Payrovnaziri, Bian, & He, 2019; Sherazi, Jeong, Jae, Bae, & Lee, 2019).

AI and ML techniques have also contributed to heart attack risk management. In a study by Mandair et al., a deep neural network model was trained to predict 6-month incident myocardial infarction based on harmonized electronic health record (EHR) data from more than 2 million individuals (Mandair, Tiwari, Simon, Colborn, & Rosenberg, 2020). Another study (Knott et al., 2020) applied AI techniques to predict heart attacks and strokes by using perfusion mapping to provide instantaneous quantification of myocardial perfusion based on magnetic resonance. Recently, researchers at the University of Oxford (Oikonomou et al., 2018), developed a new "CaRi-Heart technology", which can identify people at high risk of a fatal heart attack at least 5 years before it strikes. It applies a deeper observation into coronary CT angiogram scans based on DL models, and identifies a new biomarker, called Fat Radiomic Profile. This fingerprint detects biological red flags in perivascular space lining blood vessels which supply blood to the heart. It can more accurately identify inflammation, scarring and changes to these blood vessels, which are all pointers to future heart attack. This new AI tool measuring Fat Attenuation Index Score, FAI-Score is now reported to have received approval from the European Union, which can be used by physicians across the UK and Europe.

In another study (Poplin et al., 2018), scientists from Google Research discovered a new approach to assess risk of CV disease. They applied DL models to extract data using retinal fundus images from the back of patient's eyes, and predict their risk of suffering a major cardiac event, i.e., heart attack, with comparable accuracy as current leading methods based on blood test.

Another interesting multi-center cross-sectional study tried to associate facial features with increased risk of coronary artery disease (CAD) (Lin, li, Fu, & etc, 2020). A deep convolutional neural network model was successfully applied to detect CAD (at least one coronary lesion stenosis >/= 50% based on coronary angiography or coronary CT angiography) using facial images in diverse Chinese populations (5796 patients). Although specificity was not high, the algorithm yielded a sensitivity of 0.8 and an AUC of 0.73. It also outperformed scores typically used in assessing CAD pre-test probability, interestingly, the part of the face that contributed the most to the algorithm's predictions appeared to be the cheek. The proposed model can be used for pre-test CAD probability assessment in outpatient clinics or CAD screening in community.

AI in Heart Failure

Heart Failure (HF) is the decreased ability of the heart to provide sufficient blood to all parts of the body. In patients with HF, the incidence of all-cause hospitalizations is 63% (Tuppin et al., 2014) and can account for more than a third of CV deaths. HF is responsible for 30% of avoidable hospitalizations (Mercier, Georgescu, & Bousquet, 2015), and remains the leading cause of hospitalization for people over 65 years of age (Duflos et al., 2020). The prevalence of HF continues to rise over time, with aging of the population and is expected to increase by 46% by 2030 (Braunwald, 2013; Virani et al., 2021). The overall lifetime risks for HF range from 20% to 45% in those from 45 through 95 years of age. HF is the most frequent complication of MI associated with coronary artery diseases (the most common pathology behind adult CV disease) and also a critical prognostic factor. The chronic incidence of HF following MI is significantly high (Velagaleti et al., 2008). There are two broad types of HF—the well-studied HF with reduced ejection fraction (HFrEF) and the less well-understood HF with preserved ejection fraction (HFPEF). The former results in impaired ventricular systolic (contractile) function, while the latter is more prominently associated with impaired ventricular diastolic (relaxational) properties with systolic function not significantly impaired. HFpEF may be observed in about 55% of patients diagnosed with HF making it a major unmet need necessitating attention (Bursi et al., 2006).

Although the recent Sacubitril/Valsartan is considered as the first drug approved for HFPEF, the combination did not achieve primary endpoint of significantly lowering rate of total hospitalizations for heart failure and death from CV causes among patients with HF and an EF of 45% or higher based on PARAGON trial (Solomon et al., 2019). However, the current indication also serves patients who are sometimes referred as those with mid-range EF (Branca, Sbolli, Metra, & Fudim, 2020), but in the range adjacent to reduced EF. Such issues expose the complexity and the need to understand pathophysiology and biology of the umbrella of HFPEF, and AI offers the potential to study the patient population in a large-scale manner and may identify subgroups that are more suitable for available treatment options (Kitzman et al., 2010; Luo, Ahmad, & Shah, 2017; Pitt et al., 2014).

One study (Cole et al., 2015) concluded that reproducibility of visual grading of LV function and LVEF estimation of echocardiographic cine loops is dependent on image quality, however, individual operators could not themselves identify when poor image quality disrupts their LV function estimate. Nonetheless, coupled with the revolutionary point-of-care ultrasound and handheld imaging devices, AI may play important role in improving consistency, reproducibility, accuracy, accessibility and affordability. Using a CNN trained with Keras with a Tensorflow backend, a study from Mayo clinic was able to detect patients with suspected EF less than or equal to 35% with ECG alone (in the absence of prior transthoracic echocardiogram) (Attia, Kapa, et al., 2019). The study also suggested that false positives may be reduced by assessing NT-pro-BNP (an important biomarker for HF) after the initial "positive screen." Porumb et al. (Porumb, Iadanza, Massaro, & Pecchia, 2020) showed that their CNN model accurately (100%) identified congestive HF on the basis of single raw ECG heartbeat. The study trained and tested using publicly available ECG datasets with a total of over 490,000 heartbeats. In a small patient population, Nirschl et al. (Nirschl et al., 2018) tested a CNN classifier to detect clinical HF from Hematoxylin & Eosin stained whole-slide images. The algorithm was able to show 99% sensitivity and 94% specificity in detection of HF or severe pathology. The CNN was also reported to have outperformed two expert pathologists by nearly 20%.

Recently, Cerna et al. (Ulloa Cerna et al., 2021) showed that their CNN trained on raw pixel data in 812,278 echocardiographic videos from more than 34,000 individuals provided superior predictions of one-year all-cause mortality. The predictions outperformed the widely used pooled cohort equations, the Seattle Heart Failure score, and a ML model involving 58 human-derived variables from echocardiograms and EHR-derived 100 clinical variables. They also showed that cardiologists assisted by the model, while maintaining prediction specificity, substantially improved sensitivity of one-year all-cause mortality predictions by 13%.

AI in Valvular Heart Diseases

Another chronic and progressive condition in patients with CV diseases is valvular heart disease which presents with increasing prevalence especially in growing aging populations including in the Western world (J. Chen, Li, & Xiang, 2020). They may also be detected at later stages of disease development and needs novel approaches for earlier diagnosis and therapy.

Stenosis (narrowing or constriction) of heart valves is a relatively common and potentially fatal condition (Pawade, Newby, & Dweck, 2015). It is characterized by progressive fibro-calcific remodeling and thickening of the valve leaflets that evolve over years to can cause severe obstruction to cardiac blood flow. Aortic valves are crucial for directing blood flow from LV to aorta, and calcific aortic valve disease is considered to be the third most common form of heart disease. Diagnosis and staging of aortic stenosis are based on assessment of severity of obstruction and LV systolic function by doppler echocardiography and presence of symptoms (Lindman et al., 2016). Chang et al. (Chang et al., 2021) aimed to develop a DL-based algorithm for automated quantification of aortic valve calcium from non-enhanced electrocardiogram-gated cardiac CT scans. Their accuracy of DL-measured valve calcium volume for grading was 97.0% with AUC of 0.964 in the test set. In addition, accuracy of DL-measured Agatston score for grading was 92.9% with AUC of 0.933 in the test set thus outperforming radiologist reader group. In ML, weak supervision relies on noisy heuristics to programmatically generate large-scale, imperfect training labels. In order to overcome barriers to use of unlabeled biomedical repositories (e.g., UK Biobank) for supervised ML, Ashley, Ré and Priest groups (Fries et al., 2019) developed a weakly supervised DL model for classification of aortic valve malformations using up to 4,000 unlabeled cardiac MR sequences. In the orthogonal validation study using health outcomes data, their model identified individuals with a 1.8-fold increase in risk of a major adverse cardiac event.

Similar to the aortic valve, AI application has also been explored for disease of mitral valve (crucial for directing blood flow from left atrium to LV). One study aimed to generate an ML-based algorithm to predict in-hospital mortality after Transcatheter Mitral Valve Repair in a total of 849 patients (Hernandez-Suarez et al., 2021). Using random forest and SVM approaches, the authors showed that history of coronary artery disease, chronic kidney disease and smoking were the three most significant predictors of in-hospital mortality. Nonetheless, the study warrants additional studies with contemporary and more granular data to improve the model's discriminatory performance and applicability. Another study presented preliminary experience of an AI-based semiautomated software for analysis of tricuspid valve (crucial for directing blood flow from right atrium to right ventricle) (Fatima et al., 2020). The authors concluded that the software offered high correlation to surgical inspection throughout the cardiac cycle with higher reproducibility of data analysis, and reduces interobserver variability with minimal need for manual intervention.

In another study of 13,639 eligible patients extracted from the Chinese Low Intensity Anticoagulant Therapy after Heart Valve Replacement database (all 3 valves above) from 15 centers across China, the authors reported that Back Propagation Neural Network model showed promise for predicting warfarin maintenance dose after heart valve replacement compared with multiple linear regression model (Li et al., 2020). The former presented a higher ideal prediction percentage in external validation group, best prediction accuracy in intermediate-dose subgroup, high predicted percentage in high-dose subgroup and poor performance in the low-dose subgroup.

Furthermore, mobile AI-enabled stethoscopes and FDA-approved softwares used with digital stethoscopes in smartphones or computers are useful for automated detection of cardiac murmurs (unusual sounds across heart valves) including automated heart rate detection. Although they may not offer complete explanation for the decision provided and are more expensive than conventional stethoscopes (Thoenes et al., 2021), they can serve as cost-effective screening tools and reduce over-referrals to echocardiography, and can be more user- and telemedicine-friendly.

AI in Birth Heart Defects

Congenital Heart Diseases (CHD) are defects in one or more structures of the heart and associated anatomy and are generally present from birth. These can be life-threatening with significant negative impact on function of the heart, especially directionality of blood flow and oxygen saturation, and are mainly seen in pediatric population with significant hereditary component. Diagnostic and therapeutic advancements have enabled newborns with CHD to survive through childhood and well into adulthood. In addition, some disease conditions may not manifest until later in adult life. AI tools can be used for diagnostic imaging (classification and segmentation), clinical outcomes prediction and also disease prevention (Orwat, Arvanitaki, & Diller, 2021).

Diller et al. (Diller et al., 2019) studied over 10,000 patients with adult CHD from a single institution with neural network architecture designed in R using Keras and Tensorflow. Algorithms based on over 44,000 medical records categorized diagnosis, disease complexity and NYHA class with all their accuracies above 90% in the test sample. Cardiac MR offers reliable analysis of cardiac function and anatomy in CHD; however, analysis can be time-consuming. To circumvent this issue, Karimi-Bidhendi et al. (Karimi-Bidhendi et al., 2020) developed an automated deep fully convolutional network-based model showing strong agreement with manual segmentation, and no significant statistical difference was found by two independent statistical analyses.

Chest radiography with X-rays is one of the most widely used diagnostic tools across the world for CV and related disorders including CHDs. However, their predictive value can be limited by subjective and/or qualitative nature of interpretation. In a study using deep CNN approach developed by Google already trained with everyday color images from ImageNet, the diagnostic concordance rate of the DL model was significantly high (Toba et al., 2020). Although the model was not highly sensitive for detecting a high pulmonary to systemic flow ratio, the specificity was 0.95, and the AUC was 0.88.

While several genes associated with CHD have been identified and characterized so far, many more are yet to be discovered (Pierpont et al., 2018; Sifrim et al., 2016). Bicuspid aortic valve (aortic valve with only two cusps/flaps instead of three) is the most common congenital valvular heart disease (0.6%–1.0% of adult population), and is attributed to be the primary cause of about half of isolated severe aortic stenosis discussed earlier requiring aortic valve replacement. It is also frequently associated with aortic aneurysm and aortic dissection (LeMaire et al., 2011; Yutzey et al., 2014). The Srivastava group (Theodoris et al., 2021) developed a K-nearest neighbors ML algorithm approach to identify small molecules that broadly correct gene networks dysregulated in N1 haploinsufficiency in isogenic human induced pluripotent stem cell-derived endothelial cells from patients with aortic valvular stenosis and calcific aortic valve disease relevant to bicuspid valves. Gene network correction by the most efficacious therapeutic candidate (XCT790) generalized to patient-derived primary aortic valve cells and was sufficient to prevent and treat N1-dependent aortic valve disease *in vivo* in a mouse model.

AI in Basic and Biomedical CV Sciences

AI technologies have been successfully employed in the understanding of biological, developmental and preclinical aspects of CV sciences. Ahmad et al. (Ahmad et al., 2014) combined ML sequence features with chromatin immunoprecipitation data for key cardiac regulators to computationally classify cell type-specific cardiac enhancers of *Drosophila melanogaster* (fruit flies). Using these strategies, the authors identified heart regulatory elements on a genome-wide scale, their shared and unique sequence motifs, and novel cardiogenic transcription factors. They also validated computational predictions using *in vivo* experiments. In addition, they identified novel cardiac and cell type-specific regulatory motifs by clustering top-scoring classifier sequence features.

Stem cells have had a resurgence in CV research over the past two decades and development of pluripotent stem cell-derived cardiomyocytes and engineered cardiac tissues have made significant progress. The potential for applications in cardiac regeneration and drug screening is enormous. In a recent study, Lee et al. (E. K. Lee et al., 2017) described use of supervised ML to comprehensively analyze several functional parameters from force readouts of human pluripotent stem cell-derived ventricular cardiac tissue strips electrically paced at a range of frequencies and exposed to a library of drug compounds. Each contraction of the myocytes was considered as an individual data point for the ML analysis. They developed a classification model that can not only automatically determine if a compound is cardioactive, but can also predict mechanistic action of unknown cardioactive drugs.

Imaging at histological, cellular and molecular levels are becoming inevitable aspects of fundamental research in CV biology. Improvements in automating detection, localization and analyses of cellular organelles and molecules are crucial for better efficiency and quality of research. In a study by Orita et al., (Orita, Sawada, Matsumoto, & Ikegaya, 2020) the authors optically detected contractility of confluent cultured human-induced pluripotent stem-cell-derived cardiomyocytes using bright-field microscopy. They reported discrimination between functionally normal and abnormal contractions of the stem cell-derived cardiomyocytes using data preprocessing, data augmentation, dimensionality reduction and SL.

Ali et al. (Ali, Nguyen, Wang, Jiang, & Sadek, 2020) developed a proof-of-principle methodology to detect cardiomyocyte nuclei and distinguish from nonmyocyte nuclei using a global nuclear stain (DAPI) along with cardiomyocyte structural protein (troponin T) immunostained images from 8 µm-thick, frozen sections. Ground truth nuclei labeling was accomplished by immunostaining young adult alpha myosin heavy chain promoter-driven transgenic mouse cardiac tissues for Cre recombinase. Using an image-to-image DL U-net style architecture model with TensorFlow, the authors showed that the prediction closely matched expectations with an AUC of about 0.94. Further development of such models will also help in the assessment of pathological clinical samples routinely used for CV patients.

AI in CV Drug Discovery and Development

AI plays crucial roles in current drug discovery and development strategies. Many biopharmaceutical companies, including Bayer, Roche, and Pfizer have worked very closely with information technology companies from drug discovery to pharmaceutical product management (Mak & Pichika, 2018). ML algorithms such as random forest, naive Bayes, SVM as well as DL models including CNN, RNN, and autoencoder have been included in diverse sectors in CV drug discovery including drug design, chemical synthesis, polypharmacology, drug repurposing, and drug screening (Jing, Bian, Hu, Wang, & Xie, 2018; Patel, Shukla, Huang, Ussery, & Wang, 2020; Paul et al., 2020; Vamathevan et al., 2019; Yeung, Benjamins, van der Harst, & Juárez-Orozco, 2021).

In drug design, AI techniques and ML models can be used to determine drug activity, predict 3D structure of target protein and drug-protein interactions and improve the molecular de novo design. For example, studies using deep generative adversarial autoencoder or generative adversarial network with transcriptomic data have shown their potential to generate new or hit-like molecules (Kadurin, Nikolenko, Khrabrov, Aliper, & Zhavoronkov, 2017; Mendez-Lucio, Baillif, Clevert, Rouquie, & Wichard, 2020). In polypharmacology, DL models have been successfully applied to help the design of bio-specific and multi-target drug molecules. ML and DL models have been widely used in chemical synthesis studies as well such as predicting retrosynthesis pathways and designing synthetic routes. In drug screening, AI has shown advantages in prediction of toxicity, identification and classification of target cells, etc. (Lavecchia, 2019).

In late 2020, the Google AI offshoot, DeepMind presented a revolutionary breakthrough in the world of fundamental biology by developing DL algorithm to accurately predict three-dimensional structure of protein using physical and geometric constraints that determine how a protein folds (Callaway, 2020). Instead of predicting relationships between amino acids, the network predicts a target protein sequence's final structure. This, AlphaFold, has huge implications and offers optimism in the ability to develop drugs to combat numerous pathologies including CV diseases. The methodology has recently been published (Jumper et al., 2021; Tunyasuvunakool, et al., 2021) as open source code, and this could open enormous opportunities both for industry and academia to advance various fields forward.

AI in Precision CV Medicine

Precision medicine is a relatively new approach to disease prevention and treatment, which try to optimize medical care provided to individual patients by considering factors such as their genetics, environment, and lifestyle. AI and ML play especially important roles in advancing precision medicine (Ho et al., 2020; Subramanian et al., 2020). By integrating existing medical variables, multi-omics, lifestyle, and environmental data together, AI techniques have great potential to digitize future clinical trials, and discover novel therapies (Chayakrit Krittanawong, Johnson, Hershman, & Tang, 2018). They have been applied in CV medicine to explore novel genotypes and phenotypes in existing diseases, enable cost-effectiveness, improve the quality of patient care, and reduce readmission and mortality rates (Chayakrit Krittanawong, Zhang, Wang, Aydar, & Kitai, 2017).

In a study by Choi et al., RNNs with gated recurrent units were used to model temporal relations among events in EHRs, which can improve model performance in predicting initial diagnosis of HF (Choi et al., 2016). Another study (Juhola, Joutsijoki, Penttinen, & Aalto-Setälä, 2018) showed that it was possible to separate different genetic cardiac diseases on the basis of Ca^{2+} transients by using basic ML methods including KNN, Random Forest and SVM models. AI and ML techniques are commonly used in high throughput differential gene expression analyses as well, which can be used to identify genes that are altered in patients but not in controls. For example, PCA and logistic regression models were used to investigate relationship between familial hypercholesterolemia mutations and high polygenic score, to early-onset myocardial infarction (Khera et al., 2018).

In addition, ML and DL techniques have been used to advance risk prediction and patient management. For example, in a study by Zhao et al., different types of ML models including logistic regression, random forest, gradient-boosted trees, CNN, and Long-Short-Term Memories, have been applied to predict 10-year CV events, by using the features extracted from longitudinal EHRs (Zhao et al., 2019). The prediction results show that all ML models perform significantly better than the American College of Cardiology and the American Heart Association pooled cohort risk equation. Another study (Bellot & Schaar, 2018) investigated the problem of personalizing survival estimates of patients in heterogeneous populations for clinical decision support. A novel probabilistic survival model which can flexibly capture individual traits through a hierarchical latent variable formulation was proposed to enable survival prognosis in heterogeneous populations.

AI in CV Robotics

Robotic surgeries have attracted a lot of attention recently. Many systems including the laparoscopy-based Da Vinci robot, the endovascular catheter platforms such as the Corpath system, and the more electro-mechanically advanced Magellan robot, have been developed for CV surgery in the past decade. AI techniques can be used to enhance productivity and minimize scope of errors in robotic surgeries (Daglius Dias, Shah, & Zenati, 2020; Feizi, Tavakoli, Patel, & Atashzar, 2021; Jones, Reed, & Hayanga, 2020).

AI techniques can be used to improve surgical decision making by combining diverse sources of information including patient risk factors, anatomy and disease natural history. Rapid developments of computer vision, automatic control, and reinforcement learning make usage of autonomous and semi-autonomous robotic systems more realistic, which may have great potential to reduce trauma to patients, improve surgical safety and shorten hospital stays (Moustris, Hirides, Deliparaschos, & Konstantinidis, 2011). For instance, autonomous and semi-autonomous robots can provide faster and higher-accuracy procedures than surgeons, particularly for simple surgeries involving standard and repetitive operations (Shademan et al., 2016; Sousa et al., 2020). A retrospective analysis of 300 surgeries showed that integration of robotic-assisted minimally invasive direct coronary artery bypass procedures in the surgical landscape can be safely achieved and complication rates can quickly be reduced below those expected in traditional coronary artery bypass grafting (Van den Eynde et al., 2021)

Social robotics and our understanding of human-robot interactions are improving (Darling K, 2021). A recent study (Céspedes et al., 2021) investigating benefits of using socially assistive robots for long-term cardiac rehabilitation suggested that robots increase adherence and faster completion of rehabilitation program. The patients had more rapid improvement in their recovery heart rate, better physical activity performance and higher improvement in cardiovascular functioning.

Moreover, use of autonomous robots can reduce radiation exposure for clinicians performing remote procedures associated with use of digital subtraction angiography or for infectious exposures during crisis such as the COVID-19 viral pandemic.

FUTURE DIRECTIONS AND CONCLUSION

The potential of AI towards progress in CV sciences and health can be best realized by comprehensive integration of big data from various sources and aspects of both individual subjects and the environment. This could span across genomics, epigenomics, transcriptomics, proteomics, metabolomics, microbiomics, physiomics, radiomics, foodomics, etc. Realistically, even algorithms well-designed for clinical applications may face executional challenges associated with availability of high-quality, annotated and structured data for algorithm training and validation, and of data that are representative of real-world conditions.

In addition, some countries may have regulatory barriers in data sharing, privacy restrictions, intellectual property considerations or incomplete reporting. To overcome some of these challenges including improving reproducibility and credibility of ML studies, standards have been developed by different groups ("Machine learning in translation," 2021; Topol, 2020). These include Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT), Consolidated Standards of Reporting Trials (CONSORT), Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines, Checklist for Artificial Intelligence in Medical Imaging (CLAIM) best-practice guide and Proposed Requirements for CV Imaging-Related Machine Learning Evaluation (PRIME) (Cruz Rivera et al., 2020; Liu et al., 2020; Mongan, Moy, & Kahn, 2020; P. P. Sengupta et al., 2020; Sounderajah et al., 2020). The Butte group (Norgeot et al., 2020) also developed Minimum Information about Clinical Artificial Intelligence Modeling (MI-CLAIM).

The future is bright for incorporation of AI in day-to-day aspects of the CV space both in healthcare practice and continuing research. Simplification and automation using AI protocols can allow CV experts to focus their energies on more pressing questions towards the universal goal of reducing mortality and morbidity and accelerate novel biological, diagnostic and therapeutic advancements.

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KEY TERMS AND DEFINITIONS

Arrhythmia: Arrhythmias are heart rhythm abnormalities that occur when electrical impulses that coordinate heartbeats are anomalous and can lead to impaired heart contraction or relaxation or both.

Artificial Intelligence: Artificial intelligence is the ability of computer systems to perform tasks that normally require human intelligence.

Deep Learning: A class of machine learning based on artificial neural networks that include multiple hidden layers to progressively extract higher level features from the raw data.

Genome: Complete set of genetic instructions needed to build and sustain an organism. This may include interactions of genes with one another and the environment (epigenome).

Heart Failure: Heart failure occurs when heart muscle does not pump sufficient blood to meet the demands of the body secondary to several conditions including heart attack, hypertension, heart valve disease, congenital (birth) heart defects, etc.

Machine Learning: A study of computer algorithms that can access data and use the data to learn by themselves.

Myocardial infarction: Sometimes referred as heart attack, myocardial infarction occurs when blood flow to the heart tissues is interrupted secondary to obstruction from buildup of fat and other substances within blood vessels called coronary arteries.

APPENDIX

Table 1. Summary of Neural Network or Machine Learning Features of References

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