Chapter 1
Introduction

Humans are the only species on earth that can actively and systematically improve their health via technologies in the form of medicine. Throughout history, human knowledge is the driving force for the progress of medicine and healthcare. Humans created new technologies such as diagnostic tests, drugs, medical procedures, and devices. As the life expectancy increases, healthcare cost is growing dramatically over the years to be deemed unsustainable. For example, the US healthcare cost in 2019 alone is over 3.6 trillion dollars and accounts for 17.8% of gross domestic product (GDP). Within the gigantic spending in healthcare, there is enormous waste that should be avoided. The estimated total annual costs of waste were $760 billion to $935 billion [135].

Meanwhile, mountains of new medical knowledge are being created, making human doctors' knowledge quickly outdated. Moreover, human doctors are struggling to catch up with the increasing volume of patient visits. Physician burnout is a serious issue that affects all doctors in the age of electronic health records due to the overwhelming patient data for doctors to review and complex workflows, including tedious documentation tasks. Patients are also dissatisfied with limited interactions and attention from doctors during their short clinical visits. Quality of care is often sub-optimal, with over 400K preventable medical errors in hospitals each year [78].

With the rise of artificial intelligence (AI), can new healthcare technology be created by machine directly? For example, can machines provide more accurate diagnoses than human doctors? In the center of the AI revolution, deep learning technology is a set of machine learning techniques that learn multiple layers of neural networks for supporting prediction, classification, clustering, and data generation tasks. The success of deep learning comes from

- *Data:* Large amounts of rich data, especially in images and natural language texts, become available for training deep learning models.
- *Algorithms:* Efficient neural network methods have been proposed and enhanced by many researchers in recent years.

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- *Hardware:* Advances in parallel computing, especially graphic process units (GPUs), have enabled a fast and affordable computing engine for deep learning workload.
- *Software:* Scalable and easy-to-use programming frameworks have been developed and released via open source projects to the public. Most of them, including TensorFlow and Pytorch, have strong support from the technology industry.

This book explains the first two ingredients: rich health data and neural network algorithms that can effectively model those health data. The advance in relevant hardware and deep learning software will not be covered in this book as those topics are largely independent of healthcare applications.

Healthcare Data Among all healthcare technologies, electronic health records (EHRs) had vast adoption and a huge impact on healthcare delivery in recent years. One important benefit of EHRs is to capture all the patient encounters with rich multi-modality data. Healthcare data include both structured and unstructured information. Structured data include various medical codes for diagnoses and procedures, lab results, and medication information. Unstructured data contain (1) clinical notes as text, (2) medical imaging data such as X-rays, echocardiogram, and magnetic resonance imaging (MRI), and (3) time-series data such as the electrocardiogram (ECG) and electroencephalogram (EEG). Beyond the data collected during clinical visits, patient self-generated/reported data start to grow thanks to wearable sensors' increasing use. It was estimated over 100 Zettabytes of health-related data are being created [38].

Deep Learning Models Neural network models are a class of machine learning methods that have a long history. Deep learning models are neural networks of many layers, which can extract multiple levels of features from raw data. As large labeled data sets and modern hardware (especially GPU) become available, deep neural networks with many layers start to show significant performance advantages over other machine learning methods. For example, AlexNet using convolutional neural networks (a popular deep learning model) won the ImageNet competition by reducing the error rate to 15.3%, more than 10% points lower than that of the runner up [90]. Deep learning applications are in many domains, such as computer vision [46, 90], speech recognition [70, 128], and natural language processing [33, 79, 166]. Deep learning applied to healthcare is a natural and promising direction with many initial successes [44, 61].

1.1 Motivating Applications

Deep learning has great successes in the technology industry. Very hard technical problems had amazing performance improvements such as image classification, machine translation, and speech recognition. There are various promising deep learning applications in healthcare, including medical imaging analysis, waveform sleep analysis, inpatient outcome prediction, outpatient disease risk prediction, treatment recommendation, clinical trial matching, and molecule generation for drug discovery. Next, we briefly present some concrete healthcare applications using deep learning. More detailed applications will be presented in each chapter later.

1.1.1 Diabetic Retinopathy Detection

Diabetic retinopathy (DR) is a deadly complication of diabetes that can cause blindness. DR affects 4.2 million adults. Suppose detected early DR can be treated. However, in its early stage, patients often do not realize any symptoms. But without timely treatment, DR can cause permanent vision damage. The gold standard diagnosis is to have ophthalmologists (eye doctors) perform manual grading of retinal photographs. The cost and accessibility for such diagnoses are challenging, especially in the low resource environment. Deep learning models, in this case, convolutional neural networks, have demonstrated initial successes in the automatic diagnosis of DR based on the same retinal photographs also scored by ophthalmologists [61]. According to this study, the deep learning models trained on over 100K images can achieve expert-level accuracy over 99% area under the ROC curve (AUC)[1] Accurate automated diagnosis tools like this can potentially assist ophthalmologists in speeding up the diagnosis process and quickly identifying the patients who need the most help (Fig. 1.1).

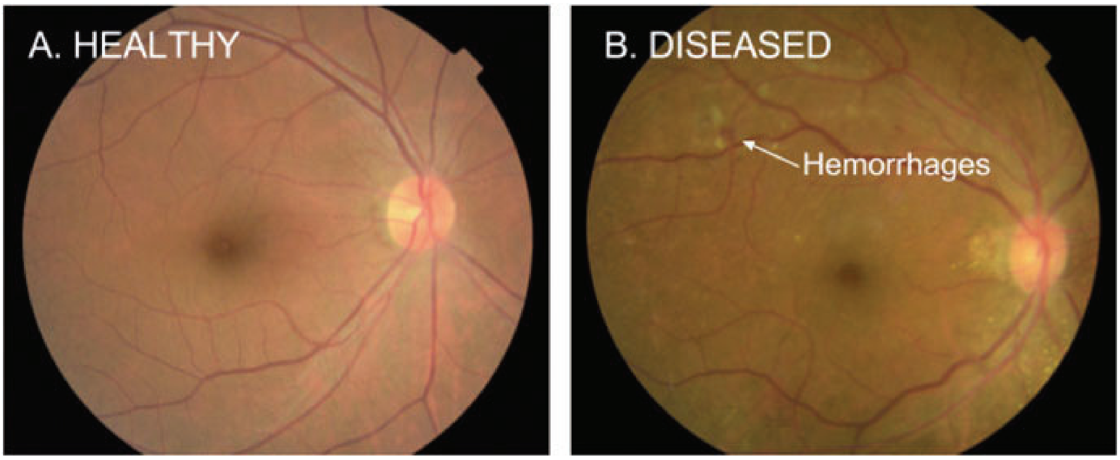

Fig. 1.1 Example retinal photos from a healthy individual and a disease patient. Credit to https://ai.googleblog.com/2016/11/deep-learning-for-detection-of-diabetic.html

[1] AUC is a common classification metric that will be described in details in Section "Real-Value Prediction for Classification".

1.1.2 Early Detection of Heart Failure

Heart failure (HF) is another deadly disease that affects approximately 5.7 million people in the United States and has over 825,000 new cases per year with around 33 billion dollars total annual cost. The lifetime risk of developing HF is 20% at 40 years of age [2]. HF has a high mortality rate of about 50% within 5 years of diagnosis [5]. There has been relatively little progress in slowing HF progression because there is no effective means of early detection of HF to test interventions. Choi et al. [30] used a deep learning model called recurrent neural networks to model longitudinal electronic health records to accurately predict the onset of HF 6 to 18 months before the actual diagnosis.

1.1.3 Sleep Analysis

Scoring laboratory polysomnography (PSG) data remains a manual task by sleep technologists. They need visually process the entire night of sleep data and annotate different diagnostic categories, including sleep stages, sleep disordered breathing, and limb movements. Attempts to automate this process have been hampered by PSG signals' complexity and physiological heterogeneity between patients. Biswal et al. [7] used a combination of deep recurrent and convolutional neural networks for assigning sleep stages, detecting sleep apnea and limb movement events. Their models achieved PSG diagnostic scoring for sleep staging, sleep apnea, and limb movements with accuracies of 87.6%, 88.2%, and 84.7%, respectively.

1.1.4 Treatment Recommendation

Medication error is the third leading cause of death in the US. The Food and Drug Administration (FDA) receives more than 100,000 reports each year related to suspected medication errors. To ensure medication safety, different medication recommendation methods have been proposed using deep learning methods. For example, researchers have attempted to build predictive models for suggesting treatments based on patient information, including diagnoses, procedures, and medication history, with the abundant longitudinal electronic health record data. LEAP [174] and GAMENet [134] are examples of such models using deep learning, particularly sequence-to-sequence models and memory networks.

1.1.5 *Clinical Trial Matching*

Clinical trials play important roles in drug development but often suffer from expensive, inaccurate, and insufficient patient recruitment. The availability of electronic health records (EHR) and trial eligibility criteria (EC) bring a new opportunity to develop computational models for patient recruitment. One key task named patient-trial matching is to find qualified patients for clinical trials given structured EHR and unstructured EC text (both inclusion and exclusion criteria). How to match complex EC text with longitudinal patient EHRs? How to embed many-to-many relationships between patients and trials? How to explicitly handle the difference between inclusion and exclusion criteria? COMPOSE [50] and DeepEnroll [176] are two deep learning models for patient-trial matching. They search through EHR data to identifying the matching patients based on the trial eligibility criteria described in the natural language.

1.1.6 *Molecule Property Prediction and Generation*

Drug discovery is about finding the molecules with desirable properties for treating a target disease. Traditional drug discovery heavily depends on high throughput screening (HTS), which involves many costly wet-lab experiments. Given large molecule databases and their associated drug properties (e.g., from drugbank), machine learning models, especially deep learning models, have shown great potentials in identifying promising drug candidates. For example, some deep learning models were proposed to predict drug property given the input molecule structures [105, 139]. Some were introduced to produce brand new molecules with desirable properties [48, 80].

1.2 Who Should Read This Book?

Most deep learning books focus on computational methods where algorithms and the underlying mathematics are described—however, few books focus on the applications in specific domains. We take a method-oriented approach with a target application domain in healthcare. The main targets are graduate students and researchers who want to learn about deep learning methods and their healthcare applications. Ideally, the audience should have a basic machine learning background, but we provide a short overview of machine learning in Chap. 3. The audience does not need to have a healthcare or medical background to read this book. The other target audience is healthcare researchers and data scientists who want to learn about the use cases of deep learning in healthcare. Finally, experienced machine learning researchers and engineers can benefit from this book if they want to learn more healthcare data and analytic problems.

This book does not require any computer programming knowledge and can be used as a textbook for the concepts of deep learning and its applications. We deliberately do not cover the programming details so that our readers can be broadened. Also, we realize the fast pace of deep learning software evolution, which will likely outdate what we wrote on that programming topic very quickly. Nevertheless, the hands-on exercises of deep learning are essential to gain practical knowledge of the topic. We encourage readers to supplement this book with other hands-on programming exercises, online tutorials, and other books on deep learning software packages.

1.3 Who Are the Authors?

When we completed the book in Apr 2021, here is our background.

Dr. Cao "Danica" Xiao is the senior director, data science and machine learning at Amplitude. Before that, she was the director of Machine Learning in the Analytics Center of Excellence (ACOE) of IQVIA, located in Cambridge, Massachusetts. Before joining IQVIA, she got her Ph.D. degree from University of Washington, Seattle and was a research staff member in IBM Research. Her work focuses on developing machine learning and deep learning models to solve real-world healthcare challenges.

Dr. Jimeng Sun is a Professor at the Computer Science Department and Carle's Illinois College of Medicine at the University of Illinois Urbana-Champaign. Before Illinois, he was an associate professor in the College of Computing at the Georgia Institute of Technology. His research focuses on artificial intelligence (AI) for healthcare, including deep learning for drug discovery, clinical trial optimization, computational phenotyping, clinical predictive modeling, treatment recommendation, and health monitoring. He was recognized as one of the Top 100 AI Leaders in Drug Discovery and Advanced Healthcare by Deep Knowledge Analytics.

1.4 Book Organization

We organize chapters based on the neural network techniques. In each chapter, we first introduce the specific neural network techniques then present concrete healthcare case studies of those techniques. We organize the book into core and advanced parts. The core part includes health data (Chap. 2), machine learning basics (Chap. 3), and fundamental neural network architectures, namely deep neural networks (DNN) (Chap. 4), embedding (Chap. 5), convolutional neural networks (CNN) (Chap. 6), recurrent neural networks (RNN) (Chap. 7), and autoencoder (AE) (Chap. 8).

- Chapter 2 covers the various healthcare data ranging from structured data such as diagnosis codes to unstructured data such as clinical notes and medical imaging data. This chapter also introduces important health data standards such as international classification of diseases (ICD) codes.
- Chapter 3 provides a primer of machine learning basics. We present the fundamental machine learning tasks, including supervised and unsupervised learning and some classical examples (e.g., logistic regression and principal component analysis). We also describe evaluation metrics for different tasks such as the area under the receiver operating characteristic curve (AUC) for classification and mean squared error for regression.
- Chapter 4 presents the deep neural networks (DNN) called a feed-forward neural network or multi-layered perceptron (MLP). In particular, we cover the basic components of DNNs, including neurons, activation functions, loss functions, and forward/backward passes. Of course, we also introduce the famous backpropagation algorithm for training DNN models. We also present two case studies: hospital re-admission prediction and drug property prediction.
- Chapter 5 illustrates the idea of embedding using neural networks, including popular algorithms such as Word2Vec and other domain-specific embeddings for EHR data such as Mec2Vec and MiME.
- Chapter 6 introduces convolutional neural networks (CNN) designed for grid-like data such as images and time series. We will present the important operation of CNNs, such as convolution and pooling, and some popular CNN architectures. We will also describe the application of CNNs on medical imaging data and clinical waveforms such as the electrocardiogram (ECG).
- Chapter 7 covers recurrent neural networks (RNN) designed to handle sequential data such as clinical text. We present important variants of RNN, including Long short-term memory (LSTM) and gated recurrent unit (GRU). The RNN case studies include heart failure prediction and de-identification of clinical notes.
- Chapter 8 describe the autoencoder model, an unsupervised neural network model. We also present case studies of autoencoder including phenotyping EHR data.

The advanced part covers the attention model (Chap. 9), graph neural networks (Chap. 10), memory networks (Chap. 11), and generative models (Chap. 12).

- Chapter 9 introduces attention models, which creates the foundation for many advanced deep learning models. We illustrate the attention model in several healthcare applications, including disease risk prediction, diagnosis code assignment, and ECG classification.
- Chapter 10 presents another foundation of advanced deep learning models, namely graph neural networks (GNN). Graph data are common in many healthcare tasks such as medical ontology and molecule graphs. GNN models are a set of powerful neural network models for graph data. The case studies focus on drug discovery.
- Chapter 11 presents memory network-based models, a set of powerful models for embedding complex data (such as text and time series). We will introduce

the idea behind original memory networks and their powerful extensions, such as Transformer and BERT models. We demonstrate memory networks on medication recommendation tasks.
- Chapter 12 presents deep generative models, including generative adversarial networks (GAN) and variational autoencoder (VAE). We show their applications in synthetic EHR data generation and molecule generation for drug discovery.

1.5 Exercises

1. Present an example data science application for lower healthcare cost, specify the datasets needed for building such machine learning models, and describe the evaluation metrics.
2. Which type of healthcare data are considered large in terms of data volume?
   (a) Genomic data
   (b) Medical imaging data
   (c) Clinical notes
   (d) Medical claims
3. Which type of healthcare data are considered fastest in velocity?
   (a) Real-time monitoring data from intensive care units
   (b) Medical imaging data
   (c) Structured electronic health records
   (d) Clinical notes
4. Which one is NOT a drug discovery and development application?
   (a) Sepsis detection
   (b) Molecule property prediction
   (c) Clinical trial recruitment
   (d) Molecule generation
5. Which one is NOT a drug discovery and development application?
   (a) Sepsis detection
   (b) Molecule property prediction
   (c) Clinical trial recruitment
   (d) Molecule generation
6. Which one is a public health application?
   (a) Mortality prediction in ICU
   (b) Patient triaging application
   (c) Treatment recommendation for heart failure
   (d) Predicting COVID19 cases at different locations in the US