Pre-trained Language Models in Biomedical Domain: A Systematic Survey

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Pre-trained language models (PLMs) have been the de facto paradigm for most natural language processing (NLP) tasks. This also benefits biomedical domain: researchers from informatics, medicine, and computer science (CS) communities propose various PLMs trained on biomedical datasets, e.g., biomedical text, electronic health records, protein, and DNA sequences for various biomedical tasks. However, the cross-discipline characteristics of biomedical PLMs hinder their spreading among communities; some existing works are isolated from each other without comprehensive comparison and discussions. It expects a survey that not only systematically reviews recent advances of biomedical PLMs and their applications but also standardizes terminology and benchmarks. In this paper, we summarize the recent progress of pre-trained language models in the biomedical domain and their applications in biomedical downstream tasks. Particularly, we discuss the motivations and propose a taxonomy of existing biomedical PLMs. Their applications in biomedical downstream tasks are exhaustively discussed. At last, we illustrate various limitations and future trends, which we hope can provide inspiration for the future research of the research community.

CCS Concepts: • Computing methodologies → Natural language processing; Natural language generation; Neural networks; Bio-inspired approaches.

Additional Key Words and Phrases: Biomedical domain, pre-trained language models, natural language processing

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1 INTRODUCTION

As the principal method of communication, humans usually record information and knowledge in a format of token sequences, resulting in languages such as natural language, constructed language, and programming language. For biomedical information and knowledge, tokens in sequences could be of various types, including words, disease codes, amino acids, and DNA. Tremendous biomedical information and knowledge in nature and human history are implicitly encapsulated in these natural token sequences in nature (a.k.a., data).

Based on the abstraction degree of biomedical knowledge, we list some of these data as a pyramid in Fig. 1. The data in the top-level means it is high-level information that explicitly conveys the biomedical knowledge, which is usually small-scaled – see biomedical knowledge bases and EHR data (maybe in multi-modality). At the low level, data, such as protein and DNA sequences, may not directly convey the biomedical knowledge, e.g., one can hardly know how a short sequence really means for humans, which needs more effort for abstraction. Fortunately, data at low-level are usually tremendous. In the current stage, existing work paid more attention to data in the top and medium-level, which are relatively small but easily understood by humans. We argue that biomedical knowledge in various scales should be paid attention to. To capture and mine the biomedical information and knowledge from various data scales, there is recently growing attention in the biomedical NLP community to adopt pre-trained language models (PLMs); since PLMs could leverage these plain token sequences without human annotations (sometimes called ‘self-supervision’).

The biomedical NLP is a cross-discipline research direction from various communities such as bioinformatics, medicine, and computer science (especially a major frontier of artificial intelligence, i.e., natural language processing a.k.a. NLP). The computational biology community [110] and biomedical informatics community [38] have made a substantial effort to make use of NLP tools for information mining and extraction of widespread-adopted electronic health records, medical scientific publications, medical WIKI pages, etc. For many decades, NLP has been investigating various biomedical tasks [37, 39] such as classification, information extraction, question answering, and drug discovery. Meanwhile, the approaches in the NLP community are changing rapidly, as one can witness exponentially-increasing...
Fig. 2. Overview of selected released Biomedical pre-trained language models. One can see a more detailed list in Sec. 4. Note that there is a BERT-like language model embedded in the overall architecture of AlphaFold2.

submitted papers in top conferences like ACL, EMNLP, and NAACL. Tailoring these NLP approaches that have been evidenced effectively in the NLP community to a specific biomedical domain is beneficial.

Unfortunately, there is usually a delay for newly proposed NLP approaches being applied to the biomedical domain. Especially, since the adoption of various pre-trained language models (e.g., ELMo [183], GPT [192], BERT [45], XLNET [88], RoBERTa [144], T5 [193] and ELECTRA [35]) [190] have nearly shifted the paradigm in NLP, their biomedical variants trained using biomedical data comes sooner or later. With this hot trend of the biomedical pre-trained language model, this survey aims to bridge the gap between pre-trained language models and their applications in the biomedical domain.

Motivation of pre-trained language models in biomedical domain. The current NLP paradigm is gradually shifting to a two-stage (pre-training and fine-tuning) paradigm, thanks to recently proposed pre-trained language models. Comparing to the previous paradigm with purely supervised learning that relies on feature engineering or neural network architecture engineering [140], the current two-stage paradigm is more friendly to the scenario when supervised data is limited while large-scaled unsupervised data is tremendous. Fortunately, the biomedical domain is a typical case of such a scenario.

The motivation to use pre-trained language models in the biomedical domain are pretty straightforward. First, annotated data in the biomedical domain is usually not large-scaled. Therefore, a well-trained pre-trained language model is more crucial to provide a richer feature extractor, which may slightly reduce the dependence on annotated data. Second, the biomedical domain is more knowledge-intensive than the general domain. At the same time, pre-trained language models could serve as an easily-used soft knowledge base [184] that captures implicit knowledge from large-scale plain documents without human annotations. More recently, GPT3 has been shown to have the potential
to ‘remember’ many complicated common knowledge [27]. Lastly, large-scaled biomedical corpora and biomedical sequences (including proteins and DNAs), which are previously thought as difficult to model, can be effectively modeled by the backbone network structure in language models (such as transformers stacked in deep layers), to capture efficient information via model pre-training in the large scale data.

As shown in Fig. 3, in recent three years, we witness a rapid development of pre-trained language models (e.g., ELMo [183], GPT [192], BERT [45], XLNet [88], RoBERTa [144], T5 [193] and ELECTRA [35]) in the general NLP domain. Followed by these progress, there are efforts to tailor these pre-trained language models to their corresponding biomedical variants, via in-domain data. For example, BERT, the most typical pre-trained language, has many variants in the biomedical domain, e.g., Med-BERT [199], BioBERT [121], publicly available Clinical BERT Embeddings [10], SciBERT [16], ClinicalBERT [87], and COVID-twitter-BERT [165] et al. We draw an overview for these models in Fig. 2. It shows that the extensions of general domain pre-trained language models to the biomedical domain attract great attention from researchers in both NLP and bioinformatics communities. Interestingly, we can observe that once the general NLP community develops a new variant of PLM, it usually leads to a biomedical counterpart after some months. This parallel development between general PLMs and biomedical PLMs shows a strong demand and even necessity to summarize the existing works, which could help beginners to start their contributions on this field easily.

**Difference with existing surveys.** There are a few reviews to summarize the NLP applications in the biomedical/clinical/bioinformatics domain, such as an early one [223] and recent ones [181, 265, 289]. They cover many general methods and applications of biomedical/clinical NLP. Specifically, [223] mainly discuss either based on statistics-based NLP pipeline (including lexicon, co-occurrence patterns, syntactic/semantic parsing), or word embeddings based neural network approaches (it was mentioned that 60.8% of them are based on recurrent neural networks) [265] for NLP applications (e.g., information extraction, text classification, named entity recognition, and relation extraction et al). Especially, two reviews [99, 104] discuss the word embeddings used in biomedical NLP.

All the above reviews made thorough summarization of existing work before the pre-trained language model era of NLP. The NLP techniques in these reviews are mainly about feature engineering, or architecture engineering [140]. However, the NLP recently has been shifted to a pre-training-finetuning paradigm with large-scale pre-trained language models (see existing surveys [22, 76, 140, 141, 190] for pre-trained language model in the general domain). [22] called these pre-trained models as ‘foundation models’ to underscore their critically central. We believe the biomedical NLP applications have been benefited and will continually benefit from the development of pre-trained language models.

More recently, [98] reviews biomedical textual pre-training, especially using BERT. The difference between [98] and

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1The paper is publicly-available on the arXiv without peer review
this review is many folds. First, biomedical pre-trained language models in this review are not limited to texts like [98], but also protein, DNA, and even we envision biomedical multi-modal pre-trained language models based on the multi-modal data (e.g., in electronic health records) - in general, any data that involves biomedical information could be used in biomedical PLMs. Secondly, in contrast to [98] which only discusses Transformer-based pre-trained language models, this review also discusses RNN based language models (like ELMO [93], which is typically considered as the first pre-trained language model in NLP). Lastly, we also summarize decoder involved pre-trained language models (like GPT [114] and T5 [185]) that could enable generation tasks, while [98] mainly discusses encoder-based PLMs (BERT or BERT variants). Therefore, we believe there is a requirement for a survey paper that can review the recent progress of pre-trained language models in the biomedical domain from a multi-scale perspective.

How do we collect the papers? In this survey, we collected over a hundred related papers. We used Google Scholar as the main search engine, and also adopted MedPub, Web of Science, as an important tool to discover related papers. In addition, we screened most of the related conferences such as ACL, EMNLP, NAACL, etc. The major keywords we used including medical pre-trained language model, clinical pre-trained language model, biological language model, etc. Plus, we take Med-BERT [199], BioBERT [121], SciBERT [16], ClinicalBert [87], COVID-twitter-BERT [165] as the seed papers to check papers that cited them.

Contribution. The contributions of the paper can be summarized as follows:

• We give a comprehensive review to summarize existing biomedical PLMs models, including training data source, model variants, shared competitions, downstream tasks, etc.
• We enumerate related resources of existing PLMs and their detailed configuration, which would facilitate beginners to use them.
• We propose a taxonomy of biomedical PTMs, which categorizes existing PTMs from various perspectives. This could help to standardize the technical methods for biomedical PLMs.
• We discuss the limitation and future trends. This will be beneficial for beginners from both the computer science and bioinformatics fields.

Organization. The paper is organized as below: Sec.2 introduces the general pre-trained language models, and Sec.3 introduces the basic methodology to apply pre-trained language models in the biomedical domain and proposes a taxonomy. Sec.4 discusses the training process of language models in the pre-training phase, and their applications in the fine-tuning phase is illustrated in Sec.5. More discussions about limitations and future directions is in Sec. 6. We conclude in Sec.7.

2 BACKGROUND: Pre-trained Language Models

Pre-trained language models (PLMs) have been widely used in computer visions, natural language processing, etc., to effectively capture the linguistic information and knowledge inherited in natural languages. In this paper, we mainly discuss pre-trained language in NLP tokens 2. One can read the review paper of PLMs in [190] for more details.

Previously, there were many typical methods to build token representation (e.g., word vectors) from plain corpora. For example, [156, 180] build a one-to-one mapping between words and their vectors, which is called ‘static word embedding’ since it is static and not related to word context. However, it is well known that words often express different meanings in different contexts. Inspired by [183], many pre-trained language models adopt ‘contextualized

2Tokens usually refers to words or subwords in NLP, and also protein in the biomedical domain.

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word embedding’ to model words in a specific context. For ‘contextualized word embedding’, the vector for a word depends on its specific usage in a context. For example, the meanings of ‘bank’ in ‘river bank’ and in ‘money bank’ are supposed to have some difference. The ‘contextualized word embedding’ largely improves the quality of word representation in various tasks [45].

In this section, we will introduce three basic ingredients of biomedical pre-training models: the training objective with self-supervised tasks in Sec. 2.1 and basic neural network models in Sec. 2.2, and training paradigm in Sec. 2.3.

2.1 Pre-trained Language Models

Language models could be considered as an instance of self-supervision. Compared to data-hungry supervised learning, which usually needs annotations from humans, language models could make use of massive amounts and cheap plain corpora from the internet, books, etc. In language models, the next word is a natural label for a context sentence as a next word prediction task, or one can artificially mask a known word and then predict it. The paradigm that uses the unstructured data itself to generate labels (for example, the next word or the masked word in language models) and train supervised models (language models) to predict labels thereof is called ‘self-supervision learning’. Language models are therefore also referred as “auxiliary task” or “pre-training task”, in which the learned representations in language models can be used as an initial model for various downstream supervised tasks.

Before self-supervision was invented, neural language models [17, 156] had been proposed for decades, and their variants [156] later became the backbones of modern NLP to provide pre-trained word features. The overview of language models is shown in Table 1. [156, 180] (including Skip-Gram, CBow and Glove) typically use linear architecture to conduct calculation between word vectors, resulting in efficient training. Recently, BERT [45], and GPT [192] proposed to use multiple layers of transformers as the basic architecture, but that led to much more parameters.

Table 1. Typical ways for word vectors and language models. X = {a, b, c, d, e} is an example text sequence. ELMO, BERT, and GPT usually work on much longer sequences than neural language models (NLMs). Skip-gram and CBOW.

| Model          | Type       | Architecture | Task                             | Loss function                              |
|----------------|------------|--------------|----------------------------------|--------------------------------------------|
| NLM [17]       | static     | 1-layer MLP  | (a, b) → c) predicting the next word | − ∑_i logp(x_i | {x_{i-1},...,x_{i-1}})                     |
| Skip-Gram [156] | static     | 1-layer MLP  | b → c, b → d) predicting neighboring words | − ∑_i logp(x_i | {x_{i-1},...,x_{i-1},x_{i+1},...,x_{i+1}}) | (i is the window size) |
| CBow [156]     | static     | 1-layer MLP  | (a, c) → b) predicting central words | − ∑_i logp(x_i | {x_{i-1},...,x_{i-1},x_{i+1},...,x_{i+1}}) | (i is the window size) |
| Glove [180]    | static     | 1-layer LSTM | w_i, w_j = logp(σ(w_i w_j)) predicting the log co-occurrence count | − ∑_i,j logp(x_i | {x_{i+1},...,x_{i+1}}) | |
| ELMO [183]     | contextualized LSTM | (a, b, c, d, e) → e, (e, d, c, b) → a) bi-directional language model | − ∑_i logp(x_i | {x_{i+1},...,x_{i+1}}) + logp(x_i | {x_{i+1},...,x_{i+1}}) |
| BERT [45]      | contextualized Transformers | (a, [mask], c, [mask], e) → (e, d, c, b) predicting masked words | − ∑_i logp(x_i | {x_{i+1},...,x_{i+1}}) mask(x) are masked words, x is the rest words |
| GPT [192]      | contextualized Transformers | (a, b, c, d) → e) predicting the next word | − ∑_i logp(x_i | {x_{i+1},...,x_{i+1}}) |

training corpora for pre-trained language models (like BERT and GPT) including: 1) online text like Wikipedia ⁴, 2)

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³For example, a word acknowledge is divided to two subwords acknowledge and #ment, in which # means that the current subword is not an independent subword.

⁴https://dumps.wikimedia.org/
existing books that have been digitized like BooksCorpus \[303\], 3) crawled online corpora \(^5\). Pre-trained language models trained by these corpora are usually able to capture the common sense knowledge in the general domain. Therefore, it needs some efforts to make them be tailored to a specific domain like the biomedical domain, to capture the domain knowledge.

In this paper, we mainly discuss the pre-trained language models, \textit{e.g.}, BERT and GPT. The main difference between them is that BERT is a textual encoder to encode a given document, while GPT is a textual decoder to decode a new document. This can also be considered as the difference between the discriminative model and generative model in machine learning. BERT is mainly used for the discriminative prediction/inference for a given text, like information extraction, text classification, named entity recognition, relation extraction, and non-generative question answering, as shown in Sec. 5. The latter is to generate texts, for example, text summarization, text completions, generative question answering and translations.

2.2 Backbone Networks in Language Models

The success of pre-trained language models is also attributed to the development of their base backbone network, from LSTM [84] to Transformer. Before Transformer [242] was invented, LSTM was widely used and became the first base architecture of the pre-trained language model (ELMO). However, because of its recurrence structure, it is computationally expensive to scale up LSTM to being deeper in layers. To this end, Transformer is proposed and becomes the backbone of modern NLP. Transformers are better architecture can be attributed to: 1) efficiency: a recurrent-free architecture which could compute the individual token in parallel, 2) effectiveness: attention allows spatial interaction across tokens that dynamically depends on the input itself. In this section, we briefly introduce the two typical architecture in pre-trained language models, namely, LSTM and Transformers.

\textbf{LSTM.} Long short-term memory (LSTM) is a recurrent neural network (RNN) architecture for sequential modeling. Unlike standard feed-forward neural networks processing single data points (such as images), LSTM can deal with entire sequences of data (such as text, speech, or video). A common LSTM unit is composed of a cell, an input gate, an output gate and a forget gate. The cell learns hidden states over arbitrary time intervals and the three gates regulate the flow of information into and out of the cell. LSTM networks are well-suited for time series data and were developed to deal with the vanishing gradient problem that can be encountered when training traditional RNNs. [183] tried to adopt Long and Short term memory network (LSTM) in pre-trained language, which naturally process token sequentially.

\textbf{Transformer.} The backbone of most pre-trained language models (\textit{e.g.}, BERT and GPT) is a neural network called Transformer building upon self-attention networks (SANs) and feed-forward networks (FFNs). SAN is used to facilitate interaction between tokens, while FNN is used to refine the token presentation using non-linear transformation. Since Transformer has been the de facto backbone to replace recurrent and convolutional units, BERT and GPT adopt the Transformer as the backbone network. The transformer is superior in terms of capacity and scalability thanks to, 1) discard recurrent units and process tokens more efficiently in parallel with the position embeddings\[249, 250\], 2) relieve saturation issue of expressive power with large-scale data and very deep layers due to the well-designed architecture including residual connections, layer normalization, and etc. Interestingly, AlphaFold2 [97] also borrows some insights to design the so-called ‘Evoformer’ as the core component in its architecture. In Table 2, we introduce some typical pre-trained language models in general NLP domains, based on these two backbone neural networks.

\(^5\)https://commoncrawl.org/

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Table 2. Representative pre-trained language models in the general domain. NSP means the next sentence prediction task.

| Model      | Objective            | Backbone network               | Comments                                                                 |
|------------|----------------------|--------------------------------|--------------------------------------------------------------------------|
| ELMO [183] | bidirectional LM     | Bi-LSTM                        | the first contextualized word representation                              |
| BERT [45]  | masked LM, NSP       | Transformer (Encoder)          | the most commonly-used pre-trained language model                          |
| Roberta [144] | masked LM             | Transformer (Encoder)          | a longer-trained BERT variant using more data                              |
| ALBERT [118] | masked LM, NSP      | Transformer (Encoder)          | a BERT variant with shared weights and a factorized word embedding          |
| XLNET [282] | generalized autoregressive pretraining | Transformer (Encoder) | a generalized autoregressive pretraining using bidirectional contexts |
| Electra [35] | replaced token prediction | Transformer (Encoder) | a pre-trained based LM trained by replaced token prediction |
| GPT [192]  | autoregressive language model | Transformer (Decoder)          | a pre-trained based LM for autoregressive generation                        |
| T5 [193]   | Seq2Seq               | Transformer (Encoder)          | a pre-trained based LM for seq2seq generation                              |

**Representative Pre-trained language models.** Based on whether the input or output is a textual sequence or the label, pre-trained language models are mainly divided into three categories: **Encoder-only**, **Decoder-only**, and **En-Decoder**. Encoder-only pre-trained models are mainly for text classification and sequential labeling tasks, while pre-trained models equipped with the decoder could deal with generation-related tasks like translation, summarization, and language models. See Fig. 4 for the difference: an Encoder model predicts labels for each input tokens (the brownish yellow color), a Decoder model generates a sequence of tokens w.r.t. a probability distribution (the blue color), an En-Decoder model predicts a new sequence conditioned on a given sequence (a.k.a. Seq2Seq) (the grey color).

**2.3 Pre-training and Fine-tuning Paradigm in PLMs**

One challenge to use PLMs in downstream tasks is that there are two gaps between PLMs and downstream tasks, the **task gap** and **domain gap**. The **task gap** means the meta-task in PLMs (usually masked language model in BERT or causal language model in GPT) usually can not directly be tailored to most downstream tasks (e.g. sentimental classification). The **domain gap** refers to the difference between the trained corpora in PLMs and the needed domain in a specific downstream task. The adaptation of both **task gap** and **domain gap** is crucial.

**Adaption.** To use the pre-trained language model in a downstream task, it is suggested to adopt both the domain and task [67, 71, 204, 293], see Table. 3 for the difference. The domain adaption suggests continuing training pre-trained models trained from a general domain, in the target domain, e.g., biomedical domain. The task adaption refers to...
fine-tuning on similar downstream tasks. In this paper, without specifying, we mainly discuss the domain-adapted pre-trained models in various downstream tasks. The task adaption is not the main concern in this review. Take BERT as an example, BERT is first trained using next sentence predictions (NSP) and masked language models in the pre-training phase. Such pre-trained BERT will be used as the initial feature extractor. BERT with an additional classifier layer is then be fine-tuned to optimize the objective of down-stream tasks (like MNLI [263], NER [235], and SQuAD [194]).

| Category          | Data         | Task            |
|-------------------|--------------|-----------------|
| Pre-training      | general      | pre-training    |
| Domain adaption   | target       | pre-training    |
| Task adaption     | general      | downstream      |
| Fine-tuning       | target       | downstream      |

3 PLMS IN BIOMEDICAL DOMAIN: WHY AND HOW?

Recently, the pre-trained language models have been widely applied to various NLP tasks and achieved significant improvement in performance. The pre-trained language models are widely used because: 1) Pre-training on the huge text corpus can learn universal language representations and help with the downstream tasks. 2) Pre-training provides a better model initialization, which usually leads to a better generalization performance and speeds up convergence on the target task. 3) Pre-training can be regarded as a kind of regularization to avoid overfitting on small data [190]. Pre-trained language models are firstly trained in general plain corpora from the Internet, like Wikipedia or crawled webpages. Except for the general domain, [57] trains CodeBERT in the programming language and [16] trains SciBERT on scientific publications and biological sequence. This paper aims to discuss pre-trained language models in the biomedical domain.

3.1 Motivation

In the biomedical domain, the motivation of using pre-trained language models are manyfold.

- Firstly, the biomedical domain involves many sequential tokens (like biomedical corpora and history of electronic health records) that usually lack annotations. However, these sequential data were previously thought of as difficult to model. Thanks to pre-trained language models, it has been empirically demonstrated to train these sequential data in a self-supervised manner effectively. This would open a new door for biomedical pre-trained language models.

- Second, annotated data in the biomedical domain is usually limited at scale. Some extreme cases in machine learning are called ‘zero-shot’ or ‘few-shot’. More recently, GPT3 shows that language models have the potential for few-shot learning and even zero-shot learning [27]. Therefore, a well-trained pre-trained language model is more crucial to provide a richer feature extractor, which may slightly reduce the dependence on annotated data.

- Plus, the biomedical domain is more knowledge-intensive than the general domain, since some tasks may need some domain expert knowledge, while pre-trained language models could serve as an easily-used soft knowledge base [184] that captures implicit knowledge from large-scale plain documents without human annotations. More recently, GPT3 has been shown to have the potential to ‘remember’ many complicated common knowledge [27].
Lastly, other than text, various types of biological sequential data exist in biomedical domains, like protein sequences and DNA sequences. Using these data to trained language models has shown a great success in traditional biological tasks like protein structure predictions. Therefore, it is expected that pre-trained language models to solve more challenging problems in biology.

3.2 How to tailor PLMs to the Biomedical Domain

The pre-trained language model [45] is a new two-stage paradigm for natural language tasks. In the first phase, it trains the language model with a self-supervised meta-task in task-agnostic corpora (e.g., masked language model and casual language model), and then in the second phase, it fine-tunes the pre-trained language model to (usually small-scaled) specific downstream tasks. The trivial way to use a pre-trained language model on the biomedical domain is to fine-tune it with the domain data. However, additional adaption is usually adopted to transfer the learned domain knowledge and task characteristics to the target domain and task. In this paper, we group the usage of the pre-trained language model into the categories in Fig. 5. The adaption is basically two-fold: transfer the domain or task characteristics. The former refers to how to transfer a general pre-trained language model to a specific biomedical domain.

3.2.1 Pre-training. The main challenge in the biomedical domain is that the medical jargon and abbreviations consist of many terms that are composed of Latin and/or Greek parts, leads to a gap between the general and medical domains. Moreover, clinical notes have different syntax and grammar than books or encyclopedias. This needs to design different vocabulary, resulting in that existing pre-trained models with different vocabularies (like general BERT or GPT) probably cannot be used, and training scratch is necessary.

Continue Training or from scratch. One may reuse a pre-trained language model from the general domain (e.g., general Wikipedia pages 6 or Google books) and then continue pre-training a few epochs in the new (target) domain (i.e., biomedical domain). In the case when the corpora in the target domain are large-scale enough, one can also directly train the model from scratch since there is no need to reuse the general knowledge.

3.2.2 Fine-tuning. Based on well-trained models, one has to adapt them to downstream tasks. This is typically implemented to replace the mask language model prediction head and next sentence prediction head with a downstream prediction head, e.g., classification head, or sequence labeling heads.

Since the downstream tasks usually have much less training data than those used in pre-training, fine-tuning is an unstable process. [228] investigate different fine-tuning methods of BERT on the natural text classification tasks. [163] argue that the fine-tuning instability is due to vanishing gradients. [152] observe that fine-tuning mainly modifies the top layers of BERT. Unfortunately, the solutions (e.g. hyper-parameters of which layer to fine-tune) proposed in those papers cannot be easily translated to other settings. To automate this process, automatic hyper-parameter tuning (e.g. Bayesian optimization [26, 238]) can come into help.

3.3 Taxonomy of Usage

To better standardise the domain of biomedical pre-trained language models, we propose a systematical taxonomy from the multiple-scale perspective (e.g., data, task, and approaches.) to explain the usage of pre-trained language models in the biomedical domain.

6https://en.wikipedia.org/
Data. The data resources of PLMs range from electronic health records, scientific literature, social media, online knowledge bases, and biomedical sequences. The detail of data resources is in Sec. 4.1. In these resources, token types could be text, proteins, DNAs, etc. For textual data, most of these data are in English.

Models. The model architecture could be encoder architecture, decoder architecture, or a combination of the both. The base models Typically are Transformer, while some earlier works adopt LSTM. Finally, one could either reuse an existing model (e.g., BERT or BioBERT) and continue training, or train a new model from scratch; the choice of the two above strategies depends on the specific scenario.

Applications. The downstream tasks of biomedical PLMs include typical NLP applications such as information extraction, text classification, sentence similarity, question answering, dialogue system, summarization, and natural language inference. See Sec. 5 for more details.

We also discuss their future trends and limitations in Sec. 6.2.

4 PLMS IN BIOMEDICAL DOMAIN

Pre-trained language models are effective partially because they are not data-hungry to labeled data (sometimes called annotated data), which is essential for supervised learning. Self-supervised learning, which pre-trained language models
rely on, usually adopts plain unstructured corpora in a format of a sequence of tokens. It is believed that the pre-trained language model can always benefit from more training corpora. To achieve better performance in the domain-specific downstream tasks, it is also intuitive that the in-domain data pre-training is necessary. In the biomedical domain, the in-domain data can be text in the electronic health records, scientific literature, and online social media, or biological sequence (e.g., DNA pieces), which will be introduced in the Sec. 4.1. Next, in the Sec. 4.2, we will introduce existing pre-trained models in the biomedical domain, which are pre-trained from the in-domain data as introduced in the Sec. 4.1. We will give an overview of these models and explain some differences between them. We expect to help one from both the bioinformatics and computer science community to get knowledge of the biomedical domain specific pre-trained language model quickly.

4.1 Unstructured Data for Pre-trained Language Models

Unstructured plain data for pre-trained language models mainly include electronic health records, scientific publications, social media text, or other biological sequence like protein. An overview of EHR mining can be seen in [53, 273], and [64] discussed both health records and social media text. One can also check [99] for some systematic overview of biomedical textual corpora.

4.1.1 Electronic Health Record. Electronic health record (EHR) is a collection of patient and population electronically stored health information in a digital format that may include demographics, medical history, medication and allergies, immunization status, laboratory test results, radiology images, vital signs, personal statistics like age and weight, and billing information. One can check [219, 261] for details about EHR with deep learning. Assessing such records may be restricted to limited organizations, which hinders its widespread to the public. The reason may involve some privacy issues.

*MIMIC III.* Medical Information Mart for Intensive Care III dataset [96] 7 is one of the most popular EHR datasets that consists of the electronic health records of 58,976 unique hospital admissions from 38,597 patients in the intensive care unit of the Beth Israel Deaconess Medical Center between 2001 and 2012. In addition, there are 2,083,180 de-identified notes associated with the admissions.

*CPRD.* Clinical Practice Research Datalink (CPRD) [83] is primary the care database of anonymized medical records from 674 general physicians (GP) practices in the UK, which involves over 11.3 million patients. It consists of data on demographics, symptoms, tests, diagnoses, therapies, and health-related behaviors. It is also linked to secondary care (i.e., hospital episode statistics, or HES) and other health and administrative databases (e.g., office for national statistics’ death registration). With 4.4 million actives (alive, currently registered) patients meeting quality criteria, approximately 6.9% of the UK population are included, this shows that patients are broadly representative of the UK general population in terms of age, sex and ethnicity. As a result, CPRD has been widely used across countries and spawned a lot of scientific research output.

4.1.2 Scientific Publications. Scientific publications are another source for biomedical pre-trained language models since we expect that biomedical knowledge may be encapsulated in scientific publications. Moreover, such knowledge may not be limited to traditional common knowledge, but also involves some state-of-art research output that may be discovered by recent literature.

\[7\text{https://mimic.mit.edu/}\]
BREATHE. Biomedical Research Extensive Archive To Help Everyone (BREATHE) 8, is a large and diverse dataset collection of biomedical research articles from leading medical archives. It contains titles, abstracts, and full-body texts. The dataset collection process was done with public APIs that were used when available. The primary advantage of the BREATHE dataset is its source diversity. BREATHE is from nine sources including BMJ, arXiv, medRxiv, bioRxiv, CORD-19, Springer Nature, NCBI, JAMA, and BioASQ [30]. BREATHE v1.0 contains more than 6M articles and about 4 billion words. BREATHE v2.0 is the most recent version.

PubMed. PubMed 9 is a free search engine accessing primarily the MEDLINE database of references and abstracts on life sciences and biomedical topics. PubMed comprises more than 32 million citations for biomedical literature from MEDLINE, life science journals, and online books. Citations may include links to full-text content from PubMed Central and publisher websites. PubMed abstracts (PubMed) have 4.5B words, and PubMed Central full-text articles (PMC) have 13.5B words.

4.1.3 Social Media. Users post information on social media, which may contain biomedical information. We mainly introduce Reddit and Tweets as examples.

Reddit. Reddit is an American social news aggregation, web content rating, and discussion website. Registered members submit content to the site, such as links, text posts, images, and videos, then voted up or down by other members. Posts are organized by subject into user-created boards called “communities” or “subreddits”, which cover a variety of topics such as news, politics, religion, science, movies, video games, music, books, sports, fitness, cooking, pets, and image-sharing. Submissions with more up-votes appear towards the top of their subreddit and, if they receive enough up-votes, ultimately on the site’s front page. Despite strict rules prohibiting harassment, Reddit’s administrators have to moderate the communities and, on occasion, close them. COMETA corpus[15] crawled health-themed forums on Reddit using Pushshift (Baumgartner et al., 2020) and Reddit’s own APIs.

Tweets. Twitter is an American micro-blogging and social networking service on which users post and interact with messages known as ‘tweets’. Registered users can post, like, and retweet tweets. Tweets were originally restricted to 140 characters, but the limit was doubled to 280 for non-CJK languages in November 2017. Audio and video tweets remain limited to 140 seconds for most accounts. The COVID-twitter-BERT [165] is trained on a corpus of 160M tweets about the coronavirus collected through the Crowdbreaks platform [166] during the period from January 12 to April 16, 2020.

4.1.4 Online Medical Knowledge Sources. Other than unstructured text, there are some online medical knowledge sources that are well-organized. For example, UMLS provides biomedical concepts that may benefit biomedical pre-trained language models.

UMLS. Unified Medical Language System (UMLS) [21] (http:// umlsks.nlm.nih.gov) is a repository of biomedical vocabularies developed by the US National Library of Medicine. The UMLS has over 2 million names for 900, 000 concepts from more than 60 families of biomedical vocabularies, as well as 12 million relations among these concepts. These vocabularies include the NCBI taxonomy, the Medical Subject Headings (MeSH), Gene Ontology, OMIM and the Digital Anatomist Symbolic Knowledge Base. The UMLS knowledge sources are updated every quarter. All vocabularies are freely available for research purposes within an institution, if a license agreement is signed.

8 https://cloud.google.com/blog/products/ai-machine-learning/google-ai-community-used-cloud-to-help-biomedical-researchers
9 https://pubmed.ncbi.nlm.nih.gov/
Manuscript submitted to ACM
4.1.5 Biological Sequences. Other than text, there are various types of biomedical token sequence, for example, amino acids for proteins. Structure of each protein is fully-determined by a sequence of amino acids [12]. These amino acids are from a limited-size amino acid vocabulary, of which 20 are commonly observed. This is similar to that the text is composed of words from a lexicon vocabulary. In this subsection, we introduce a protein dataset called ‘Pfam’ and DNA sequence dataset from Human Genome Project.

Pfam Protein Dataset. The Pfam database is a large collection of protein families, in which each protein is represented by multiple sequence alignments using hidden Markov models. The newest version is Pfam 34.0 which was released in March 2021 and contains 19,179 families (or called ‘entries’) and 645 clans. The original purpose of the Pfam database is for classification of protein families and domains. It creates the database using a semi-automated method of curating information on known protein families. Pfam 34.0 contains 47 million sequences, which could be used to train protein language models.

DNA Dataset. The DNA sequence is composed of genomic sequence. The Human Genome Project was the international research effort to determine the DNA sequence of the entire human genome. Human Genome Project Results. In 2003, an accurate and complete human genome sequence was finished two years ahead of schedule and at a cost less than the original estimated budget. [90] uses the reference human genome GRCh38.p13 primary assembly from GENCODE Release. The total sequence length is about 3 Billion.

4.2 Biomedical Pre-trained Language Models

Based on the types of training corpora in the biomedical domain as introduced in the above section 4.1, we mainly introduce two groups of biomedical pre-trained language models: biomedical textual language models and protein language models.

4.2.1 Overview of Existing Biomedical Textual Language Models. Since BERT was released, various biomedical pre-trained language models have been proposed via continue training with in-domain corpora based on the BERT model or training from scratch. Tab. 4 presents existing pre-trained language models with used corpora, size, release date, and related web pages. We introduce some representative pre-trained language models including encoder-only pre-trained language models like BioBERT, ClinicalBERT, SciBERT, and COVID-twitter-BERT, decoder-only pre-trained language model like MedGPT, and encoder-decoder pre-trained language models like SCIFIVE.

- **BioBERT** [121] is initialized with the general BERT model and pre-trained on PubMed abstracts and PMC full-text articles. It is further fine-tuned for biomedical text mining tasks such as named entity recognition (NER), question answering, and relation extraction.
- **ClinicalBERT** [87] is trained on clinical text from approximately 2M notes in the MIMIC-III database [96], a publicly available dataset of clinical notes.
- **SciBERT** [16] is trained on the large scale of scientific papers from multi-domain based on the BERT. The training papers are the random sample of 1.14 M full-text papers from Semantic Scholar, in which 82% articles are from the biomedical domain.

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10http://pfam.xfam.org/
11Clans are the generated higher-level groupings of related entries in Pfam. A clan is a collection of entries which are related by sequence similarity, structure or profile-HMM.
12https://www.ncbi.nlm.nih.gov/assembly/GCF_000001405.39/
Table 4. Existing textual biomedical pre-trained models. The base setting is with 0.1B parameters and the large setting is with 0.3B parameters. Data is based on the submission in arXiv or publish data of the journal or conference proceeding.

| Model            | Corpora                          | Size       | Date        | Link                                      |
|------------------|----------------------------------|------------|-------------|-------------------------------------------|
| BioBERT          | PubMed and PMC                   | base & large | 2019.01     | https://github.com/dmis-lab/biobert       |
| BERT-MIMIC       | MIMIC-III                        | base and large | 2019.02     | -                                         |
| SciBERT          | Semantic Scholar papers          | base       | 2019.03     | https://github.com/allenai/Scibert       |
| BioELMo          | PubMed abstracts                 | 93.6 M     | 2019.04     | https://github/Andy-ja/boelmom            |
| Clinical BERT    | EHR (MIMIC-III 13)               | base       | 2019.04     | https://github.com/EmilyAI/clinicalBERT   |
| Clinical BERT    | EHR (MIMIC-III)                  | base       | 2019.05     | https://github.com/krishnang/clincalBERT  |
| BioBERT          | PubMed-MIMIC-III                 | base & large | 2019.05     | https://github.com/mol-nlp/bluebert       |
| G-BERT           | MIMIC-III                        |            | 2019.06     | https://github.com/jiahug/clincalG-Bert  |
| BEHRT            | Clinical Practice Research Datalink | -          | 2019.07     | https://github.com/deepmedicine/BEHRT     |
| BioFLAIR         | PubMed abstracts                 | large      | 2019.08     | https://github.com/ralandoresearch/flair  |
| RadBERT          | RadiCore radiology reports       |            | 2019.12     | -                                         |
| EhoBERT          | MADE corpus                      |            | 2019.12     | https://github.com/umassachusetts/ehrbert |
| Clinical XLMNet  | EHR (MIMIC-III)                  | base       | 2019.12     | https://github/lnmdalab/clinicalXLMNet   |
| CT-BERT 15       | Tweets about the coronavirus     | large      | 2020.05     | https://github.com/zhongzhou/ct-twitter-bert |
| Med-BERT         | Corner Health Facts (general EHR) | -          | 2020.05     | https://github.com/zhongzhou/med-bert     |
| onBioBERT        | PubMed                           | base       | 2020.05     | https://github.com/y-s-wada/blue_benchmark_with_transformers |
| Bio-ELECTRA      | PubMed                           | base       | 2020.05     | https://github.com/SciCrunch/bio_electra  |
| BERT-XML         | Anonymous Institution EHR system | small and base | 2020.06     | -                                         |
| PubMedBERT       | PubMed                           | base       | 2020.07     | https://huggingface.co/microsoft/BioMedNLP-PubMedBERT-base-uncased-abstract |
| MicBERT          | Chinese social media, wiki and EHR | base       | 2020.08     | https://github/allhubs-research/ChineseBLUE |
| BioAlbert         | PubMed and PMC                  | base & large | 2020.09     | https://github.com/usamaalvi/BioAlbert 15 |
| BERTLM 151       | private EHR                      | customized | 2020.09     | https://github.com/larsyenaob/bertlm      |
| BioMegatron       | Published                        | 0.3/0.6/1.2B | 2020.10     | https://nycu.ai/bio-megatron              |
| ClinicalTransformer 46 | PubMed                         | MIMIC-III | 2020.10     | https://github.com/sf-hobi-informatics-lab/ClinicalTransformerNER |
| Bioeditor-BERT    | health-themed forums on Reddit   | base       | 2020.10     | https://github.com/cambridgeellie/cometa  |
| BioRoberta 123    | PubMed, PMC, and MIMIC-III       | base & large | 2020.11     | https://github.com/facebookresearch/bio-lm |
| CODEER 157       | UMES Metathesaurus               | base       | 2020.11     | https://github.com/GanjinZero/CODEER      |
| bert-for-radiology | daily clinical reports          | -          | 2020.11     | https://github.com/xMdlance/bern-for-radiology |
| BioBERT 109       | BREATHE                          | large      | 2020.12     | https://github.com/BioMedBERT-bioedbert   |
| LBERT 227         | Published                        | base       | 2020.12     | https://github.com/warzone/LBERT          |
| ELECTRAMED 158    | PubMed abstracts                 | base       | 2021.04     | https://github/gmpoli/electramed         |
| SCIFIVE 185      | PubMed Abstract and PMC          | 220/770M   | 2021.06     | https://github.com/justinphan310/scifive  |
| MedGPT 114        | King’s College Hospital and MIMIC-III | customized | 2021.07     | https://pypi.org/project/medgpt/          |

- **COVID-twitter-BERT** [165] is a natural language model to analyze COVID-19 content on Twitter. The COVID-twitter-BERT model is trained on a corpus of 160M tweets about the coronavirus collected through the Crowdbreaks platform during the period from January 12 to April 16, 2020.

- **MedGPT** [114] is a GPT-like language model trained by patients’ medical history in the format of electronic health records (EHRs). Given the sequence of past events, MedGPT aims to predict future events like a diagnosis of a new disorder or complication of an existing disorder.

- **SCIFIVE** [185] is a domain-specific T5 model which is pre-trained on large biomedical corpora. Like T5, SCIFIVE is a typical Seq2seq paradigm to transform a input sequence to a output sequence.

### 4.2.2 Discussions on Biomedical Pre-trained Language Models

Here, we will discuss the listed models in various aspects as below:

**Training corpora: EHR, literature, social media, etc., or the hybrid?** Most pre-trained language models are based on scientific publications e.g., PubMed and EHR notes. Note that EHR datasets are usually relatively smaller than scientific publications datasets or Wikipedia. Hence pre-trained language models with only EHR datasets are typically trained from the initialization of well-trained BERT [10, 87], XLNET [88], etc. Furthermore, some pre-trained language models (e.g., BioRoBERTa [123]) adopt both scientific publications and EHRs. A few models such as CT-BERT and BioReddit-BERT [15, 165] adopt social media including Twitter and Reddit.
Extra features. Unlike typical text, EHR data usually have some extra features, for example, disease codes, personal information of patients like age, gender. Such extra features can be embedded as dense vectors used in some models such as Med-BERT and BEHRT \cite{131, 199} like word embedding, position embedding, and segment embedding that are used in the input layer of the Transformer.

Training from scratch or continue training. The standard approach to obtain a biomedical pre-trained model is to conduct continual pre-training from a general-domain pre-trained model like BERT \cite{45}, such as the BioBERT \cite{285}. Specifically, this approach would initialize the model with the standard BERT model including its word vocabulary, which is pre-trained by general Wikipedia and BookCorpus. Besides, some literature demonstrated training from scratch may fully make use of in-domain data and reduce the negative effect from out-of-domain corpora, which may be beneficial for downstream tasks such as PubMedBERT \cite{66}.

Reusing existing vocabulary or building a new one. To make use of well-trained general pre-trained language models like BERT \cite{45}, one has to reuse its vocabulary. However, Biomedical NLP is more challenging compared to general NLP because it involves jargon and abbreviations prevail: clinical notes have different syntax and grammar than books or encyclopedias. A totally new vocabulary necessarily leads to training from scratch due to different vocabularies that may be more computationally expensive.

Model size. Typically, big models usually have a bigger capacity that needs more data for training. However, the biomedical domain usually does have as many corpora as the general domain. Thus, biomedical pre-trained language models are relatively smaller than general pre-trained language models. Another reason is that most of them are based BERT or BERT-like encoder based models, while pre-trained models with decoder architecture (e.g., GPT, T5) could be bigger than encoder-based pre-trained models. To the best of our knowledge, the biggest model is Biomegatron \cite{215} with 1.2B parameters. Note that bigger models take longer for inference and this is unfriendly for those researchers without enough research computing resources.

Being publicly available. Thanks to the open-sourced tradition of computer science, most models have web pages for downloading and documents for usages. Some of them standardized its model in huggingface (https://huggingface.co), which will largely be beneficial for its wide-spreading. However, some models are not available for the public due to privacy issues even data might have been anonymized \cite{122}.

Biomedical pre-trained language models in other languages. Most of the biomedical pre-trained language models are in English. However, there is an increasing need for biomedical pre-trained language models in other languages. There are typically two solutions: a multilingual solution or a purely second-language solution. The former may be beneficial for low-resource languages the latter are usually used in some rich-resource languages like Chinese \cite{292}.

4.3 Beyond Text: Language Models for Proteins/DNA

There are various biological sequences like proteins and DNA which could be also treated like linguistic tokens in natural language. Therefore, many existing work explored training language models for these biological sequences. The most crucial difference between language models for biological sequences, and the counterparts for natural language is the tokenization (will be introduced in Sec. 4.3.1), which leads to different vocabularies like textual vocabularies. In Sec. 4.3.2, we summarize the existing language models for these biological sequences.
4.3.1 Tokenization for Proteins/DNAs. Like words in text, biological sequences such as proteins and DNA sequences could also be modeled by language models which typically aims to predict the next token in a sequence. In contrast to that words are in a relatively-big vocabulary (typically 10k-100k), the vocabularies for biological sequences are usually small.

Tokenization in Proteins. Since the structure of protein is fully determined by its amino acid sequence [12], one can represent a protein by its amino acid sequences. Roughly 500 amino acids have been identified in nature, however only 20 amino acids are found to make up the proteins in human body. The vocabulary of protein sequences consists of these 20 typical amino acids.

Tokenization in DNAs. The two DNA strands are known as polynucleotides and they are composed of simpler monomeric units *(a.k.a. nucleotides)*. Each nucleotide contains of one of four nitrogen-containing nucleobases *(i.e., cytosine [C], guanine [G], adenine [A] or thymine [T])* . The two separate polynucleotide are bound together, according to deterministic base pairing rules ([A] with [T] and [C] with [G]), with hydrogen bonds. Typically, existing work [90] usually adopts a so-called ‘\( K \)-mer’ representation for DNA sequences [18] for richer contextual information for DNAs. By doing so, the vocabulary size will increase to the \( 4^k + 5 \) which is exponential to \( k \) and additionally pluses five special tokens ([CLS], [SEP], [PAD], [MASK], [UNK]).

4.3.2 Language Models for biological sequences.

Protein language models. Since the commonly-found categories of amino acids are relatively-small, namely 20. Initially, some work applied character-level language models to protein to deal with limited-size amino acids. In the beginning, there are many efforts to training RNN-based language models [9, 18] for protein sequences. [79, 80] trains a deep bi-directional model ELMo for proteins [19]. Other than those protein sequences, protein language models usually adopt additional features for proteins, e.g., global structural similarity between proteins and pairwise residue contact maps for each protein [18]. Later, [197] introduces the Tasks Assessing Protein Embeddings (TAPE), a suite of biologically relevant semi-supervised learning tasks. The authors also train language models based on LSTM, Transformer, and ResNet on the protein sequences. Bepler et al [19] also proposed a novel framework based on the LSTM model to learning protein sequence embeddings. They make their embeddings publicly available at [20]. Rives et al. [202] trains a contextual transformer-based language model [21] on 250 million protein sequences. The representations learned by this LM encode multi-level information spanning from biochemical properties of amino acids to remote homology of proteins. Different from the above line of approaches, MSA Transformer [198] fits a model separately to each family of proteins. ProtTrans [54] trains a variety of LM models with thousands of GPUs, and also makes the trained models publicly available [22]. ProGen [146] is a generative LM trained on 280M protein sequences conditioned on taxonomic and keyword tags. ProteinLM [269] was recently proposed, which trained a large-scale pre-train model for evolutionary-scale protein sequences, and the trained model is available at [23]. More recently, DeepMind develops AlphaFold2 [97] that could predict protein structures with a high accuracy, in the challenging 14th Critical Assessment of protein Structure Prediction (CASP14). Most interestingly, there is an embedded protein language models in AlphaFold2, which makes AlphaFold2

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18 ‘\( K \)-mer’ is like a \( k \)-size convolutional window for a sequence. For example, a DNA sequence ATGGCT will be tokenized to a sequence of 3-mers (ATG TGG GCC GCT) or to a sequence of 5-mers (ATGGC TGGCC).  
19https://github.com/Rostlab/SeqVec  
20https://github.com/tbepler/protein-sequence-embedding-iclr2019  
21The trained model and code are available at https://github.com/facebookresearch/esm.  
22https://github.com/agemagician/ProtTrans  
23https://github.com/THUDM/ProteinLM  

Manuscript submitted to ACM
Table 5. Downstream biomedical tasks based on PLMs

| Tasks                        | Papers                                      |
|------------------------------|---------------------------------------------|
| Named entity recognition     | BioBERT [121], BlueBERT [179], SciBERT [16], BioELMo [93], PubMedBERT [66], BioMegatron [215], Yuan et al [286], Wei et al [258], Hafiane et al [74], Thillaisundaram et al [234], Su et al [226], Xue et al [272], Chen et al [34], Lin et al [135, 136], Guan et al [68], Liu et al [143], Sui et al [227]. |
| Relation extraction          | BioBERT [121], BlueBERT [179], SciBERT [16], PubMedBERT [66], BioMegatron [215], Yuan et al [286], Wei et al [258], Hafiane et al [74], Thillaisundaram et al [234], Su et al [226], Xue et al [272], Chen et al [34], Lin et al [135, 136], Guan et al [68], Liu et al [143], Sui et al [227]. |
| Event detection              | Trieu et al [236], Wadden et al [246], Zhang et al [288], Ramponi et al [196], Wang et al [253]. |
| Text classification          | BioBERT [121], BlueBERT [179], SciBERT [16], PubMedBERT [66], BioMegatron [215], Yuan et al [286], Wei et al [258], Gao et al [58], Mascio et al [148], Guo et al [69], Sont et al [221]. |
| Sentence similarity          | BioBERT [121], BlueBERT [179], SciBERT [16], PubMedBERT [66], BioMegatron [215], Yuan et al [286], Chen et al [33], [31], [32], Yang et al [281], Li et al [132]. |
| Question answering           | PubMedBERT [66], BioMegatron [215], Yoon et al [284], Jeong et al [89], Chakraborty et al [30], Kamath et al [100], Du et al [52], Yoon et al [282], Zhou et al [300], Akdemir et al [5], He et al [78], Amherst et al [200], Kommaraju et al [112], for COVID-19 [55, 120, 170, 201], Soni et al [222], Mairitha et al [147]. |
| Dialogue Systems             | Zeng et al. [288], DialoGPT [297], Whang et al. [262], Li et al. [127]. |
| Text summarization           | Extractive summarization: Du et al [51], Moradi et al [162], Padmakumar et al [174], Kanwal et al [101], Dan et al [44], Song et al [220]. Abstractive summarization: Wallace et al [247], Gharebagh et al [62], Both: Deyoug et al [46], Guo et al [70], Kieuvongngam et al [105]. |
| Natural language inference   | BioELMo [91], BlueBERT [179], Sharma et al [212], He et al [78], Zhu et al [302]. |
| Protein and DNA sequence     | [9], [80], [197], [202], MSA Transformer [198], ProtTrans [54], ProtGen [146], DNABERT [90], [275]. |

feasible to make use of unlabelled protein data. In detail, Alphafold2 adopts an auxiliary BERT-like loss to predict pre-masked residues in multiple sequence alignments (MSAs).

**DNA language models.** Proteins are translated from DNA through the genetic code. There are 20 natural amino acids that are used to build the proteins that DNA encodes. Therefore, amino acids cannot be one-to-one mapped by only four nucleotides. Some work also explored the potential to build language models on DNA sequences. DNA-BERT [90] is a bidirectional encoder pre-trained on genomic DNA sequences with up and downstream nucleotide contexts. Yamada and Hamada [275] pre-trains a BERT on RNA sequences and RNA-binding protein sequences. All the LMs remain largely the same as those used for human language data. Designing new architectures and pipelines tailored to protein/DNA sequences is a promising direction.

5 **FINE-TUNING PLMS FOR BIOMEDICAL DOWNSTREAM TASKS**

Similar to general domain, pre-trained language models have been widely used in many biomedical downstream tasks as shown in 5. In this section, we will introduce recent efforts of applying PLMs in various biomedical downstream tasks and also introduce some competitions and challenges in related workshops and conferences, in which pre-trained language models may help. We first introduce the downstream applications of PLMs in various classical tasks of the biomedical domain. Similar to the general domain, to evaluate the effectiveness and facilitate the research development of biomedical pre-trained language models, the Biomedical Language Understanding Evaluation (BLUE)
benchmark has been proposed in [179]. BLUE includes five text mining tasks in biomedical natural language processing, including sentence similarity, named entity recognition, relation extraction, text classification, and inference task. However, BLUE has some limitations. It does not include some important biomedical application tasks such as question answering and it mixes the applications of clinical data and biomedical literature. To improve it, [66] proposed a novel benchmark, the Biomedical Language Understanding & Reasoning Benchmark (BLURB). It includes named entity recognition (NER), evidence-based medical information extraction (PICO), relation extraction, sentence similarity, document classification, and question answering task. Moreover, there are works proposed the benchmark in other languages, such as Chinese [292]. In the following, we will introduce the recent progress of PLMs on these tasks and other critical tasks in the biomedical domain.

5.1 Information Extraction

Information extraction plays a key role on automatically extracting structure biomedical information (entities, concepts, relations and events) from unstructured biomedical text data ranging from biomedical literature, electronic health record (EHR) to biomedical related social media corpus, etc. One can check a review in [256]. It plays an important role in the applications of intelligent healthcare such as clinical decision support, biocuration assistance and health monitoring et al. In the biomedical community, it generally refers to several important sub-tasks including named entity or concepts recognition, which aims to identify the common biomedical concept mentions or entity names (such as genes, drug names, adverse effects, metabolites and diseases et al) of biomedical texts, relation extraction which determines the relationships among biomedical entities, concepts and attributes, and event extraction. Similar to the general domain, learning methods for biomedical information extraction have been rapidly advanced based on the pre-trained language models in natural language processing recently. We will next introduce the methods progress based on the pre-trained language models in each sub-tasks.

5.1.1 Named entity recognition. Biomedical named entity recognition (BioNER) is a fundamental task in the information extraction of biomedical text data. Previous deep learning methods are generally based on the sequence labeling framework, in which the word features of texts are automatically extracted with deep learning methods such as the bidirectional long short-term memory (BiLSTM) and word embeddings, and then a classification layer based on the conditional random field (CRF) is trained to predict the entity tag of each word. Recently, inspired by the effectiveness of pre-trained language models in the various NLP tasks of the general domain, much work based on PLMs has been proposed for biomedical NER. In the latest, several biomedical pre-trained language models: BioBERT [121], BlueBERT [179], BioELMo [93] and SciBERT [16], have been proposed and achieved great performance in various NLP tasks including biomedical NER. They conducted continual pre-training based on the general domain pre-trained language models including BERT and ELMo with domain-specific datasets. The BioBert model used PubMed abstracts and PubMed Central full-text articles for further domain-specific pre-training, while the BlueBERT utilized the PubMed text and de-identified clinical notes from MIMIC-III. BioBERT is only trained on the general text and non-clinical biomedical text. To meet the requirement of the specialized clinical BERT models for clinical narratives (such as physician notes), Alsentze et al [16] proposed the public available clinical embedding trained on approximately 2 million clinical notes in the MIMIC-III v1.4 database. It proved that the clinical-specific contextual embeddings trained on the clinical notes are beneficial to improve the clinical NER task. Different from them, Sci-BERT constructed its own vocabulary and pre-trains from the scratch. It is directly pre-trained on the large scale of mixed domain datasets, in which 18% texts from the computer science domain and 82% texts from the biomedical domain. In the latest, Gu et
al [66] consisted that domain-specific pre-training from scratch is more effectiveness than domain-specific fine-tuning and mixed-domain pre-training like the aforementioned methods. They proposed the PubMedBERT model, which conducted the domain-specific pre-training from scratch with the pure biomedical domain dataset: PubMed texts. It has achieved better performance than aforementioned methods on several biomedical NLP tasks including the biomedical NER task. Yuan et al [286] proposed a biomedical pre-trained language model KeBioLM to explicitly incorporate the knowledge from the Unified Medical Language System (UMLS) knowledge bases, which outperforms other PLMs in the biomedical NER task. Similar to PubMedBERT, Shin et al [215] further presented a larger BioMegatron model trained on a larger biomedical domain corpus. It has achieved the state-of-the-art (SOTA) on standard biomedical NLP benchmarks, including the named entity recognition. For the BioNER task, these models generally add an LSTM or conditional random field (CRF) based token classification layer to predict the tag of each token, on top of the transformer structures of pre-trained language models.

Besides the biomedical pre-trained language models applied in various biomedical NLP tasks, there are also many works fine-tuning pre-trained language models for only the biomedical NER task. Singh et al [206] firstly investigated the pre-trained language model on improving the performance of biomedical NER. They proposed to make use of unlabeled data: the PubMed abstract dataset to pre-train the weights of NER model and then fine-tuned the model with the supervised NER training data. Zhu et al [301] trained a domain-specific ELMo model in the mixture data of clinical reports and relevant Wikipedia pages and then utilized it for the clinical concept extraction. Si et al [216] presented an analysis of advanced word embedding methods (including ELMo and BERT) and investigate their effects on clinical concept extraction tasks. Similar to [216], Sheikhshab et al [213] also investigated the context embeddings from the language model ELMo on improving the biomedical named entity recognition. Khan et al [103] presented a multi-task transformer-based neural architecture for slot tagging and applied it to the Biomedical domain (MT-BioNER). It utilized the BioBert as the transformer encoder layer and the multiple data sets in the task-specific layers. With the development of general domain language models, Naseem [168] proposed an effective domain-specific language model bioALBERT trained on the biomedical domain corpora (PubMed abstracts and PMC full-text articles) for biomedical named entity recognition. Giorgi et al [63] proposed the end-to-end model for jointly extracting named entities and their relations using the pre-trained language model BERT. It achieved better performance in the biomedical NER task than [216] and BlueBERT. Gao et al [59] explored the effectiveness of transfer learning based on the pre-trained language models and semi-supervised self-training to improve the performance of biomedical NER with very limited labeled data. To save the memory and time consuming of domain adaption, Poerner et al [186] proposed to train Word2Vec on biomedical domain text and incorporated it into the general domain BERT to improve the performance of the biomedical NER task. Instead of treating the BioNER as the sequence labeling problem, Sun et al [229] proposed to consider the BioNER as the machine reading comprehension (MRC) problem based on BERT. Besides English, there is much work exploring the pre-trained language models on the BioNER of other languages, including Chinese [43, 91, 129, 130, 252, 272], Spanish [6, 75, 159], French [41], Korean [109], Russian [154], Arabic [23], Italian [28]. In Table 6, we summary the commonly used datasets in the BioNER task.

5.1.2 Relation Extraction. Biomedical relation extraction (BioRE) is also one of the fundamental tasks in the information extraction of biomedical texts. It aims to identify the relationship (semantic correlation) between biomedical entities mentioned (such as genes, proteins, and diseases) in texts, which has a variety of biomedical applications such as clinical outcomes prediction, protein structure prediction, and clinical diagnosis. It is generally be transformed into the classification problem, to predict the possible relation type of two identified entities in a given sentence. In the past
Table 6. Datasets used in the BioNER task.

| Dataset      | Language | Entity type                  | Text type     | Text Genre   | Size   |
|--------------|----------|------------------------------|---------------|--------------|--------|
| BC5-chem [126] | English  | Chemical                     | Abstract      | PubMed       | 1,500  |
| BC4-chem [115] | English  | Chemical                     | Full text     | PubMed       | 10,000 |
| BC5-disease [126] | English | Disease                      | Abstract      | PubMed       | 1,500  |
| NCBI-disease [48] | English | Disease                      | Abstract      | PubMed       | 793    |
| i2b2 2010 [240] | English  | Disease                      | Report        | Clinical records | 871    |
| BC2GM [217] | English  | Gene/Protein                 | Sentence      | MEDLINE      | 20,000 |
| JNLPBA [106] | English  | Protein,DNA,RNA,cell line    | Abstract      | MEDLINE      | 2,404  |
| LINNAEUS [61] | English  | Species                      | Full text     | PMC          | 100    |
| Species-800 [175] | English | Species                      | Abstract      | MEDLINE      | 800    |
| EBM PICO [171] | English  | Participants.interventions, outcomes | Abstract      | PubMed       | 4,993  |
| CCKS 2017 [24] | Chinese  | Body,disease,symptom,test,treatment | Report        | Clinical Records | 400    |
| CCKS 2018 [25] | Chinese  | Anatomy,symptom,independent,drug,operation | Report        | Clinical Records | 1,000  |
| PharmaCoNER [4] | Spanish  | Protein,chemical             | Report        | Spanish Clinical Case Corpus | 1,000  |
| CANTEMIST [159] | Spanish  | Tumor morphology             | Report        | Spanish Clinical Case Corpus | 1,301  |
| CAS [65]  | French   | Terms,negation.uncertainty   | Clinical cases | PubMed       | 100    |

Few years, deep neural networks including recurrent neural networks (RNNs), convolutional neural networks (CNNs), and graph neural networks (GNNs) have shown their effectiveness in the BioRE task, which are efficient to encode the semantic features of entities and sentences. They rely on labeled data to train the model. However, the annotated data is quite limited in the biomedical domain. In the latest, pre-trained language models have been widely explored in the BioRE. Compared with deep neural network-based methods, they are trained on a large scale of data, thus can capture more semantic information in the learned representations. In Table 7, we summarize the commonly used datasets in the BioRE task.

Wei et al. [258] conduct the first study to apply pre-trained language models on the clinical RE task. They investigated fine-tuned BERT on the clinical RE and combined additional BIO tag features. Similarly, Hafiane et al. [74] investigated two transfer learning strategies: frozen and fine-tuning to adapt BERT on the biomedical RE. Thillaisundaram et al. [234] adapted the SciBERT to the BioRE via fine-tuning the representation of the classification token (CLS). However, it only utilized partial information of the last layer due to mainly fine-tuning the classification token. To further explore the potential of utilizing full information in the last layer to improve performance, Su et al. [226] proposed to utilize the whole last layer when fine-tuning the BERT model on the BioRE task. To further learn more general representations of entities to improve the performance, Su et al. [225] propose to employ the constructive learning to improve the BERT model for biomedical relation extraction. Xue et al. [272] proposed to fine-tune BERT for joint entity and relation extraction in Chinese medical text, which used the BERT as a shared encoder and the focused attention to fuse information of NER and RE task. Chen et al. [34] combined BERT with the one-dimensional convolutional neural network (1d-CNN) to fine-tune the medical relation extraction. Lin et al. [135, 136] investigated the BERT model on the clinical temporal relation extraction. Guan et al. [68] investigated several pre-trained language models in predicting the relationships between clinical events and temporal expressions, including BERT, RoBERTa, ALBERT, XLNet, BioBERT, ClinicalBERT. They found that RoBERTa generally has the best performance. To make the biomedical relation extraction in the document with long-distance dependencies and complex semantics, Liu et al. [143] proposed to use the pre-trained self-attention structure for biomedical relation extraction in the document level with the entity replacement method. In many real application scenarios, training the medical relation extraction model generally requires collecting and storing...
privacy-sensitive data, which may conflict with privacy protection. To solve the problem, Sui et al. [227] proposed a privacy-preserving medical relation extraction method FedED based on BERT and federated learning. Moreover, similar to BioNER, several advanced biomedical domain pre-trained language models as mentioned in the last section, such as BioBERT [121], BlueBERT [179], SciBERT [16], PubMedBERT [66], BioMegatron [215] have achieved great performance on the BioRE task. They typically adapt to the BioRE task with the extra binary classification layer (linear layer or MLP).

### 5.1.3 Event Extraction
Event extraction is another important task for mining structured knowledge from biomedical data. It aims to extract interactions between biological components (such as protein, gene, metabolic, drug, disease) and the consequences or effects of these interactions [11]. It has wide applications in biomedical ranging from supporting information retrieval, knowledge base enrichment, and pathway curation. The event generally consists of event triggers and their arguments (event participants). The triggers are signal words (generally verbs or nouns) to indicate the appearance and type of events. The arguments are biomedical entities. The events will finally be formulated to the graph structures, in which the triggers are connected with the appropriate argument along with the path. Commonly used datasets are summarized in Table 8.

Many efforts have been proposed to explore the application of pre-trained language models on biomedical event extraction recently. Trieu et al. [236] proposed the neural nested event extraction model called DeepEventMine with the BERT based encoder, in which the task-specific layers are added on the top of BERT encoder to detect the nested entities and triggers, roles and nested events. Wadden et al. [246] explored combining the BERT model and graph propagation on the event extraction of a variety domain including the biomedical domain, to capture both context information in the sentence and cross-sentence dependencies. They proved that the long-range dependencies captured by the graph propagation can improve the performance of the model-based BERT alone. Zhang et al. [298] investigated transfer learning with the BERT model for Chinese clinical event detection. Moreover, there are works considering model the biomedical event extraction task as other NLP tasks. Ramponi et al. [196] modeled the biomedical event extraction as the sequence labeling problem. They proposed the neural event extraction model called BEESL, which converted the event structures into the format of sequence labeling and utilized the BERT model as the encoder. Wang et al. [253] proposed to formulate the biomedical event extraction as the multi-turn question answering problem and utilized the question answering system based on the domain-specific language model SciBERT to achieve great performance.

### 5.2 Text Classification
Text classification is an essential task in biomedical natural language processing. It aims to classify the biomedical texts into the pre-defined categories, which plays an important role in the statistical analysis, data management, retrieval of biomedical data. Compared with the general domain, text classification in the biomedical domain has more challenges.
such as data unbalancing, semantic ambiguity, and irregular data. Fine-tuning pre-trained language models on the biomedical text classification has attracted great attention recently, in which the commonly used biomedical text classification datasets are summarized in Table 9.

Gao et al. [58] investigated several different ways of adapting BERT model on the clinical single-label and multi-label document classification. However, they found that the BERT or BioBERT model generally has equal or worse performance in the text classification of clinical data such as MIMIC-III clinical notes dataset, than a simple CNN model. They suggested that this is may because BERT or BioBERT models don’t capture clinical domain knowledge due to trained on the general domain or biomedical literature datasets. Moreover, BERT model can not handle too long sentences which is longer than 512 tokens, which may influence the performance. Mascio et al. [148] made a comprehensive analysis of the performance of various word representation methods (such as Bag-of-Words, Word2Vec, GLoVe, FastText, BERT, BioBERT) and classification approaches (Bi-LSTM, RNN, CNN) on the electronic health records. They found that the contextual embeddings from BERT and BioBERT generally outperform the traditional embeddings, and the traditional deep neural networks Bi-LSTM enriched with appropriate entity information and specific domain embeddings have better performance than BERT and BioBERT. Guo et al. [69] compared the performance of three transformer-based pre-trained language models RoBERTa-base, BERTweet, and Clinical BioBERT on 25 social media classification datasets, in which 6 datasets are biomedical related. They found that RoBERTa-base and BERTweet outperform Clinical BioBERT, in which RoBERTa-base can capture general text semantic characteristics, while BERTweet captures more domain knowledge. [73] also provided an analysis of traditional deep neural networks and fine-tuning pre-trained language models including BERT and BioBERT on the performance of multi-label document classification on the COVID-19 dataset: LitCovid. They found that BERT and BioBERT models have better performance than deep neural networks such as RNN, CNN and Bi-LSTM in the datasets. They also found that BioBERT outperforms BERT model due to domain-specific pre-training. Sont et al. [221] proposed to use the character-level Bidirectional Encoder Representations from Transformers (Bert) model to enhance the text convolutional neural network, for the classification of traditional Chinese medicine cases.

Table 8. Datasets used in the Biomedical event extraction.

| Dataset                          | No. entities | No. triggers | No. relations | No. events |
|----------------------------------|--------------|--------------|---------------|------------|
| Cancer Genetics 2013 [36]        | 21,683       | 9,790        | 13,613        | 17,248     |
| EPI 2011 [172]                   | 16,675       | 2,035        | 3,416         | 2,453      |
| GENIA 2011 [107]                 | 22,673       | 10,210       | 14,840        | 13,560     |
| GENIA 2013 [108]                 | 12,725       | 4,676        | 7,045         | 6,016      |
| Infectious Diseases 2011 [189]   | 12,788       | 2,155        | 2,621         | 2,779      |
| Pathway Curation 2013 [188]      | 15,901       | 6,220        | 10,456        | 8,121      |
| Multi-level event extraction [187]| 8,291        | 5,554        | 7,588         | 6,677      |

Table 9. Datasets used in the biomedical text classification task.

| Dataset           | Label type | Text type         | Data Size |
|-------------------|------------|-------------------|-----------|
| HoC [77]          | Multi-label| PubMed abstract   | 1852      |
| MIMIC-III [96]    | Multi-label| Discharge summaries| 49785     |
| LitCovid [73]     | Multi-label| PubMed articles   | 23038     |
| CORD-19 Test [73] | Multi-label| PubMed articles   | 100       |

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Table 10. Datasets used in the biomedical sentence similarity task.

| Dataset            | Text type   | Data Size |
|--------------------|-------------|-----------|
| BIOSSES [218]     | PubMed sentences | 100       |
| MedSTS [254]      | Clinical report | 174,629  |
| MedSTS_ann [254]  | Clinical report | 1,068     |
| n2c2/OHNLP [255]  | Clinical report | 1,642     |

5.3 Sentence Similarity

Capturing the semantic similarity of sentences plays an important role in the information extraction and text mining of biomedical data, which is beneficial for many biomedical applications and downstream tasks such as biomedical search, evidence sentence retrieval, classification and question answering. It is generally be formulated into the regression problem to predict the similarity score of each sentence pair. Recent works have focused on fine-tuning various pre-trained language models to this task.

Existing pre-trained language models in the biomedical domain and general domain such as BERT, RoBERTa, BioBERT, SciBERT, ClinicalBERT, BlueBERT, PubMedBERT, and BioMegatron have achieved great performance in the task, in which the BioMegatron yielded the best performance due to domain-specific pre-training and task-specific fine-tuning. However, these models are pre-trained for yielding embeddings in the token level with the contextual information. To better capture the semantic information at the sentence level, Chen et al [33] proposed the first pre-trained open set sentence embeddings in the biomedical domain, called BioSentVec, which is trained on over 30 million documents from both biomedical literatures such as PubMed and clinical notes such as the MIMIC-III Clinical Database. Compared with existing word embeddings and sentence encoder-based methods, it yields better performance on both sentence similarity and text classification tasks, due to better capture the sentence semantic. In [31], they empirically compared the performance of traditional deep learning methods such as random forest, RNN, CNN with the pre-trained models BERT and BioBERT, which shown that pre-trained language models are more effective in capture the sentence semantic due to pre-trained in large scale of corpora. Moreover, in [32], they further employed the pre-trained sentence embedding BioSentVec to improve the traditional deep learning models: random forest and the encoder network on finding similar sentences. Yang et al [281] explored three pre-trained models including BERT, XLNet, and RoBERTa for the clinical semantic textual similarity task, in which the XLNet achieves the best performance among three models. Li et al [132] proposed to integrate the BERT models and bidirectional recurrent neural network (Bi-RNN) to capture both contextual semantic and semantic textual similarity. The commonly used sentence similarity datasets are shown in Table 10.

5.4 Question Answering

Biomedical question answering (BioQA) is a very important task for the information retrieval and knowledge acquisition of the large amount of unstructured data, which can provide service for professionals in the biomedical domain such as doctors and also general users. It aims to extract or generate the natural language answers to the given questions. It is a challenging task due to the lack of large-scale annotated data. In the biomedical domain, annotating data generally requires domain expertise, this is time-consuming and expensive. To facilitate the development of the biomedical question answering, some competitions and datasets have been proposed such as BioASQ [237] and MEDIQA 2019 [27]. Recently, motivated by the success of unsupervised pre-training models, the fine-tuning and transfer learning of

27https://sites.google.com/view/mediqa2019
pre-trained language models have been widely explored in the task. Most of them are formulated into the machine reading comprehension approach, which focuses on predicting the text span of answers with the given questions and passages containing the answers.

Much effort has investigated the BERT and BioBERT on the question answering task of biomedical literature datasets. Yoon et al [284] applied the BioBERT to answer biomedical questions such as factoid, list, and yes-no type questions. To solve the problem of limited training data in the biomedical domain, they firstly fine-tune BioBERT on the general domain question answering datasets SQuAD and SQuAD 2.0, and then further fine-tune it on the task dataset: BioASQ. Instead of the general domain question answering dataset, Jeong et al [89] proposed to transfer the knowledge of natural language inference (NLI) with BioBERT to improve the performance. Inspired by the BioBERT, Chakraborty et al [30] proposed a biomedical domain pre-trained language model BioMedBERT for question answering (QA) and information retrieval tasks. BioMedBERT is based on the BERT model pre-trained on a large-scale biomedical literature dataset BREATHE. Kamath et al [100] compared the effectiveness of pre-trained models for machine-reading comprehension and question-answering in the general domain in fine-tuning the biomedical question answering task. They found that the question answering model fits better to the task. Du et al [52] utilized the BERT model as the encoder to improve the representations of the question and passage and then used the scaled dot-product attention mechanism to capture the interaction between them. However, these models can only extract a single span of passage as the answer and can not detect multiple spans of the passage when there are multiple answers for the question. To solve the problem, Yoon et al [283] reformulated the task as the sequence tagging problem to detect multiple entity spans simultaneously. They used the BioBERT as the encoder and concatenated the Sequence Tagging Layer including the linear layer, Bi-LSTM and Bi-LSTM+CRF to predicting the tag of each token. Zhou et al [300] utilized the BioBERT and interactive transformer model to both the recognizing question entailment and question answering task. Similarly, Akdemir et al [5] also explored multi-task learning to improve the performance of BioBERT on the BioQA task. They proposed the joint BioBERT based model for biomedical entity recognition and question answering. Some works tried to incorporate the domain knowledge such as biomedical named entities, into pre-trained language models. He et al [78] proposed to infuse the domain knowledge of disease into a series of pre-trained language models including BERT, BioBERT, SciBERT, ClinicalBERT, BlueBERT, and ALBERT, to improve their performance. Amherst et al [200] incorporated the medical entity information with entity embeddings and the auxiliary task on predicting the logical form of the question to improve the accuracy and generalization of the BERT model on answering questions. Kommaraju et al. [112] also introduced the extra biomedical named entities prediction task to support the BioBERT and SciBERT on Biomedical QA. To help the prevention of COVID-19, there are works [55, 120, 170, 201] build the question answering and information retrieval system based on BioBERT and BERT.

Besides methods for biomedical literature corpora, other works have been devoted to proposing question answering models to acquire knowledge from unstructured electronic health records (EHR). Soni and Roberts [222] investigated the performance of various pre-trained language models including BERT, BioBERT, ClinicalBERT, and XLNet on the clinical question answering. They explored the fine-tuning methods with different datasets including datasets in the general domain, biomedical and clinical corpora. Mairittha [147] explored fine-tune BERT to construct the personalized EHR question answering system. The commonly used datasets in BioQA are summarized in the Table 11.

### 5.5 Dialogue Systems

Dialogue Systems (DSs) in the biomedical domain has attracted continuous attention due to the utility applications (e.g., virtual health consultants and therapists) [119]. The aim of the dialogue system is to produce a proper response in either
Table 11. Datasets used in the biomedical question answering task.

| Dataset                | Text type                        | Data Size  |
|------------------------|----------------------------------|------------|
| PubMedQA [94]          | PubMed abstracts                 | 1,000      |
| BioASQ [169]           | MEDLINE articles                 | 885        |
| CICR [231]             | Clinical case reports            | 100,000    |
| emrQA [176]            | Clinical notes                   | 400,000    |
| cMedQA [294]           | Question-answer pair from online community | 61,343   |
| COVID-19 Questions [232]| Literature review                | 124        |

a selective [262, 296] or generative [142, 288, 297] way given a dialogue context for the biomedical goals of a user. The context includes historical utterances from users and systems, biomedical knowledge base, electronic health records of users, etc. The format of a response could be various, e.g., a set of structured user goal data [259], a distribution of biomedical labels for diagnosis [138, 296] and natural language utterances [288]. For different types of contexts and responses, recent work focuses on end-to-end DS [270, 288] or parts of four typical DS modules, i.e., Natural Language Understanding (NLU) [50, 214], Dialogue State Tracking (DST) [138, 259], Dialogue Policy Learning (DPL) [259, 268] and Natural Language Generation (NLG) [288].

Recently, PLMs are well-known for natural language modeling, but it is nontrivial to pre-train on task datasets that are biased on a specific domain [262]. Pre-training DS models in biomedical can be seen as a task-specific pre-training problem [72]. It involves two essential aspects, i.e., biomedicine-domain adaptation and dialogue-task adaptation.

To adapt to the medical domain, the dominant solution is to pretrain a language model on a large-scale general/medical corpus and then fine-tune the model with a medical dialogue dataset. BERT-WWM and BERT-MED [277] first pre-train a BERT on Chinese Wikipedia and medical corpus, correspondingly, and then fine-tune on $M^2$-MedDialog dataset for understanding the intents and slots of patients. BioBERT and MIMIC-BERT [259] are pre-trained using MIMIC III dataset [216] and PubMed articles, respectively, followed by fine-tuning on MZ dataset for predicting diagnosis actions. Zeng et al. [288] pre-train Transformer, BERT-GPT, and GPT on dialog datasets and other large-scale texts, and then fine-tune models on the Chinese MedDialog dataset for generating clinically correct and human-like medical responses.

To adapt to DS tasks, the challenges are complex dialogue context modeling [178] and external knowledge (e.g., knowledge base, user profiles) enrichment [177]. Naturally, PLMs are talented for those challenges because: (i) PLMs are based on transformer architecture, which can capture longer-term dependency for learning complex dialogues effectively and efficiently [81, 242]. Yan et al. [277] unify NLU, DPL, NLG tasks into one context-to-response generation framework and use pretrained GPT2 and MT5 to model complex context for generating responses. The empirical study proves the positive impact of PLMs on $M^2$-MedDialog dataset. (ii) PLMs can incorporate external knowledge by pretraining on large-scarred corpora in a general domain [98, 127]. Shi et al. [214] use a pretrained BERT as fixed features to get a well initialized word embedding from the aspect of transfer learning. DialoGPT [297] is pre-trained based on GPT-2 [192] with a large in-domain dialogue dataset, and is able to generate more relevant, informative and coherent responses. Li et al. [127] learn to pretrain language modeling objectives (e.g., MLM and NSP) on a large-scale general corpus and then fine-tune on medical datasets with task-specific training objectives. Although recent studies have deployed PLMs models in medical DSS tasks, medical DS is still under-explored. So we summarize all available biomedical dialogue datasets in Table 12 for future research.

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Table 12. Datasets used in the biomedical dialogue system tasks.

| Dataset       | Language Domain | Evaluated Task | Text type          | # dialogues |
|---------------|-----------------|----------------|--------------------|-------------|
| MZ [259]      | EN              | Pediatrics     | DPL                | Discharge summaries | 710         |
| DX [270]      | CN              | Pediatrics     | DPL                | Patient-doctor dialogues & patient reports | 527         |
| RD [133]      | CN              | Pediatrics     | DPL                | Patient-doctor dialogues & patient reports | 1,490       |
| SD [133]      | CN              | 9 domains      | DPL                | Patient-doctor dialogues & patient reports | 30,000      |
| CMDD [138]    | CN              | Pediatrics     | NLU                | Patient-doctor dialogues | 2,067       |
| SAT [19]      | CN              | 14 domains     | NLU                | Patient-doctor dialogues | 2,950       |
| MSL [214]     | CN              | Pediatrics     | NLU                | Patient-doctor dialogues | 1,652       |
| MIE [296]     | CN              | Cardiology     | NLU                | Patient-doctor dialogues | 1,120       |
| CovidDialog [279] | CN/EN         | COVID-19       | NLG                | Patient-doctor dialogues | 1,088/603   |
| MedDG [142]   | CN              | Gastroenterology | NLG             | Patient-doctor dialogues | 17,000      |
| MedDialog [288] | CN/EN          | 29 domains | NLG                | Patient-doctor dialogues & patient reports | 3,407,494/257,332 |
| Chunyu [137]  | CN              | -              | NLG                | Patient-doctor dialogues | 12,842      |
| KaMed [124]   | CN              | 12 domains     | NLG                | Patient-doctor dialogues | 63,754      |
| M²-MedDialog-base [277] | CN | 30 domains | NLU&DPL&NLG | Patient-doctor dialogues & patient reports | 1,557       |
| M²-MedDialog-large [277] | CN | 40 domains | NLU&DPL&NLG | Patient-doctor dialogues & patient reports | 95,408      |

5.6 Text Summarization

Automatic text summarizing is an efficient task to conduct information extraction and retrieval from an ever-growing amount of biomedical texts [160]. It aims to automatically summarize the key information of single or multiple documents with shorter and fluent texts, which greatly decreases the time-consuming of acquiring important information. Similar to the general domain, existing methods generally can be classified into two categories: extractive summarization methods and abstractive summarization methods. The former methods extract correlated sentences from given long documents and concatenate them into the final summary, while the latter methods generate new sentences based on the information of given long documents. Therefore, the extractive summarization generally is formulated into the binary classification, in which the model aims to predict the sentences whether be selected into the summary, while the abstractive summarization can be deemed as the conditional text generation problem.

Pre-trained language models have been well-explored on text summarizing of the general domain. To explore the advanced pre-trained language models in the text summarizing of biomedical domain, the domain knowledge is incorporated by existing methods via domain fine-tuning. For biomedical extractive summarization, Du et al [51] proposed a novel model BioBERTSum, which used the domain-aware pre-trained language model as the encoder and then fine-tune it on the biomedical extractive summarization task. Gharebagh et al [62] utilized the domain knowledge—the salient medical ontological terms to help the content selection of the SciBERT based clinical abstractive summarization model. Moradi et al [162] proposed the unsupervised extractive summarization for biomedical extractive summarization. They proposed to use the hierarchical clustering algorithm to group the contextual embeddings of sentences based on the BERT encoder and select the most informative sentences from each group to generate the final summary. Padmakumar et al [174] also proposed an unsupervised extractive summarization model, which used the GPT-2 to encode the sentences and the pointwise mutual information (PMI) to calculate the semantic similarity between sentences and documents. The proposed method has better performance than other similarity-based models on the medical journal dataset. Kanwal et al [101] proposed to fine-tune the BERT model on the International Classification of Diseases (ICD-9) labeled MIMIC-III discharge notes for the extractive summarization of electronic health records. For abstractive summarization, Wallace et al [247] utilized the Bidirectional and Auto-Regressive Transformers (BART) as...
Table 13. Datasets used in the biomedical text summarization.

| Dataset       | Text type          | Summarization type | Data Size   |
|---------------|--------------------|--------------------|-------------|
| COVID-19 [251]| Biomedical literature | Single document   | -           |
| MS^2 [46]     | Biomedical literature | Multi-document   | 470,402     |
| CDSR [70]     | Biomedical literature | Single document   | 7,805       |
| RCT [247]     | Clinical trials    | Multi-document     | 4,528       |
| PubMed [36]   | Biomedical literature | Single document   | 215,000     |

the encoder for generating biomedical evidence summary of multiple clinical trials. For advancing multi-document summarization of biomedical literature, Deyoug et al [46] released a novel dataset of multi-document summarization on medical studies called MS^2, which contains over 470k documents and 20K summaries derived from the biomedical scientific literature. They also investigated the BART model on the proposed dataset and achieved promising results. To facilitate the development of methods for generating plain summaries toward the general public, Guo et al [70] proposed a novel task of plain language summarization task on the biomedical scientific reviews, and construct a novel dataset that contains 7805 high-quality abstract pairs. They explored the BART model for both extractive and abstractive summarization of the dataset, which was further pre-trained on general domain dataset CNN/DM and in-domain dataset PubMed and achieved the best performance.

For the information acquisition of COVID-19 related scientific literature, Kieuvongngam et al [105] proposed the BERT and GPT-2 based model for both extractive and abstractive summarization of COVID-19 research literature. There are also works to build the multi-document summarization system for the information retrieval of COVID-19 research literature with the Siamese-BERT [55], BioBERT and XLNet [44]. Besides biomedical literature and EHR, there are works that proposed BERT-based summarization methods [220] toward the understanding of the medical conversation between patients and doctors.

5.7 Natural Language Inference

Natural language inference (NLI, also known as the text entailment) is a basic task for the natural language understanding of biomedical texts. It aims to infer the relation such as entailment, neutral and contradiction, between two sentences, named as the premise and hypothesis, which can further benefit biomedical downstream tasks such as commonsense comprehension, question answering and evidence inference. In the task, the common neural network model is based on sentence pair modeling, which encodes the premise and hypothesis sentences with various neural networks and then classifies the relation between them with the softmax classifier layer.

Similar to other tasks, pre-trained language models in the biomedical domain including BioELMo [93] and BlueBERT [179], have shown their effectiveness in the task via task-guided fine-tuning. To facilitate the development of methods for text inference and entailment in the medical domain, the MEDIQA 2019 shared task [3] was organized, in which many participants investigated the SciBERT, BioBERT, and ClinicalBERT in the medical NLI task. Moreover, some works make efforts on incorporating the domain knowledge to improve PLMs on the biomedical NLI. Sharma et al [212] incorporated the embedding of knowledge graph (UMLS) in the biomedical domain into the BioELMo to improve its performance. Yadav et al [274] a novel framework Sem-KGN for the medical textual entailment task, which infused the medical entity information from the medical knowledge bases into the BERT model. He et al [78] proposed to infuse the domain knowledge of disease into a series of pre-trained language models including BERT, BioBERT, SciBERT, ClinicalBERT, BlueBERT, and ALBERT, to improve their performance in the question answering, medical inference, and
Table 14. Datasets used in the biomedical natural language inference.

| Dataset          | Text type          | Relation Type                  | Data Size |
|------------------|--------------------|--------------------------------|-----------|
| MedNLI [203]     | Clinical notes     | Entailment, contradiction, or neutral | 14,049    |
| MEDIQA-RQE [1]   | Consumer health questions | Entailment, contradiction | 9,120     |
| CMFAQ [302]      | Consumer health questions | Entailment, contradiction | 53,822    |

disease name recognition task. Zhu et al [302] utilized the neural architecture search (NAS) to automatically find a better transformer structure of the Chinese BERT-wwm-ext model [42] for better medical query understanding.

5.8 Proteins/DNAs Prediction

In this section, we only list some applications that have been well-investigated or potential, although there are much bigger spaces in biomedical domains to make use of PLMs.

5.8.1 Protein structure predictions. Proteins are essential to life, and knowing their structure can facilitate our understanding of their function. However, structure of only a small fraction of proteins is known [97]. Predicting 3D structure of a protein is based solely on its amino acid sequence, a.k.a., ‘protein folding problem’ [12]. To evaluate protein structure predictions, CASP (Critical Assessment of Structure Prediction) uses proteins with recently solved structures that have not been deposited in the PDB or publicly disclosed; it therefore is a blind test for the participants, which is the gold-standard assessment for protein structure predictions [117, 164]. In CASP14, AlphaFold 2 [97], a model designed by DeepMind achieves much more better performance than other participating methods (e.g., template-based methods). The authors claims that AlphaFold 2 could provide precise estimates and it could be confidently used for protein structure predictions with high reliability. However, predictions of existing methods including the AlphaFold 2 are more family-specific than protein-specific, and rely on the evolutionary information captured in multiple sequence alignments (MSAs). To solve these issues, Weißenow [260] proposed to use the attention head from the pre-trained protein language model ProtT5 without MSAs. Recently, Sturmfels et al [224] presented a new biologically-informed pre-training task: predicting protein profiles derived from multiple sequence alignments, which can improve the downstream protein structure prediction task.

5.8.2 DNA related applications. There are few work in DNA pre-training, among which DNABERT [86] is the representative one. DNABERT claims that ‘DNABERT could 1) effectively predicts proximal and core promoter regions; 2) accurately identifies transcription factor binding sites; 3) allows visualization of important regions, contexts and sequence motifs; 4) identifying functional genetic variants with DNABERT; 5) substantially enhances performance and generalizes to other organisms.’ Hong et al [85] proposed to pre-train DNA vectors to encode enhancers and promoters, and then Incorporated the attention mechanism to predicting long-range enhancer–promoter interactions (EPIs). Yamada et al [276] proposed a novel method based on the BERT to predict the interactions between RNA sequences and RNA-binding proteins (RBPs), in which the BERT model is pre-trained on the human reference genome. Mock et al [161] presented the BERTax based on BERT, for the taxonomic classification of DNA sequences.

5.9 Competition Venues

To facilitate the technological developments on biomedical text mining, many shared tasks and competitions are organized since several years ago, which focus on various important tasks in the biomedical domain.
• **BioNLP workshop.** The BioNLP workshop\(^{28}\) has been organized for 20 years and continually promoted the development of the biomedical domain, in which the community proposed a series of shared tasks and benchmark datasets. In BioNLP 2019, the BioNLP Open Shared Tasks (BioNLP-OST) 2019 \(^{29}\) and the MEDIQA 2019 Shared Task \(^{3}\) were organized. The BioNLP-OST 2019 proposed six tasks, including the information extraction on the bacterial biotopes and phenotypes, event extraction of genetic and molecular mechanisms, pharmacological substances, compounds and proteins named entity recognition, integrated structure, semantics and coreference task, concept extraction for drug repurposing, and the information retrieval task for neuroscience. The MEDIQA 2019 aims to explore the method development on the natural language inference (NLI), recognizing question entailment (RQE), and question answering (QA) in the medical domain. In bioNLP 2021, the MEDIQA 2021 \(^{2}\) shared tasks were organized to address three tasks related to the summarization of medical documents, including the question summarization task, the multi-answer summarization task, and the radiology report summarization task.

• **BioNLP-OST.** The BioNLP Open Shared Tasks (BioNLP-OST)\(^{29}\) has been proposed since 2009 and was motivated to facilitate the development and sharing of methods on various tasks of the biomedical text mining. It is organized every two years and organized at different conferences such as BioNLP and EMNLP. The latest BioNLP-OST 2019 is organized at the BioNLP 2019 as introduced aforementioned.

• **BioASQ.** The BioASQ\(^{30}\) organizes workshops and challenges on biomedical semantic indexing and question answering. It is held annually since 2013. In BioASQ 2019, the large-scale biomedical semantic indexing task, the biomedical information retrieval and question answering task, and corresponding benchmark datasets are proposed.

• **BioCreAtIvE.** The Critical Assessment of Information Extraction systems in Biology (BioCreAtIvE)\(^{31}\) organized challenge evaluations for the text mining and information extraction method on the biological domain since 2004. In the latest BioCreative VII Challenge, proposed five tracks, in which two tracks are related to the COVID-19, including the text mining and multi-label topic classification.

• **eHealth-KD.** The eHealth-KD\(^{32}\) organizes challenges on the structure knowledge extraction of eHealth documents in the Spanish Language. The eHealth-KD Challenge 2019 proposed the key phrases identification and classification task, and the semantic relations detection task.

• **#SMM4H.** The Social Media Mining for Health Applications (#SMM4H)\(^{33}\) held workshops and shared tasks related to natural language processing challenges in social media data for health research since 2015 annually. The shared tasks in the #SMM4H ’21 involve the information processing methods on Twitter related to COVID-19, self-report of breast cancer, adverse effect mentions, medication regimen, and adverse pregnancy outcomes.

Moreover, there are some challenges proposed recently, such as the COVID-19 Open Research Dataset Challenge (CORD-19)\(^{34}\) in response to the COVID-19 pandemic, EHR DREAM Challenge\(^{35}\) proposed in October 2019 and focusing on using electronic health record data to predict patient mortality, and ICLR 2021 workshop\(^{36}\) devoting to propose

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\(^{28}\)https://aclweb.org/aclwiki/SIGBIOMED
\(^{29}\)https://2019.bionlp-ost.org/home
\(^{30}\)http://bioasq.org
\(^{31}\)https://biocreative.bioinformatics.udel.edu
\(^{32}\)https://knowledge-learning.github.io/ehealthkd-2019/
\(^{33}\)https://healthlanguageprocessing.org/smm4h-2021/
\(^{34}\)https://www.kaggle.com/allen-institute-for-ai/CORD-19-research-challenge
\(^{35}\)https://www.synapse.org/#!Synapse:syn1405991/wiki/589657
\(^{36}\)https://mlpcp21.github.io/pages/challenge
6 DISCUSSION

6.1 Limitations and Concerns

In this subsection, we will mainly discuss the limitations of biomedical pre-trained language models and raise some concerns about them.

Misinformation. The training corpora consist of EHR and social media may include wrong information. Thus, pre-trained language models pre-trained on them may convey some misinformation. Furthermore, the biomedical domain itself may have misclassified disease definitions during its development process. Misinformation has become much more serious in the biomedical domain than general domain, since this may lead to some fatal consequences of biomedical decision-making. However, researchers must be aware of the complexity of routinely collected electronic health records, including ways to manage variable completeness. We believe that the predictions from pre-trained language models should be artificially calibrated by biomedical experts before it is used by end-uses like the patient or the public.

Interpretation issues. Along with the power of neural networks, there is a growing concern about the interpretability of deep neural networks (DNNs). While in the biomedical domain, the consequence of bad decisions/predictions may be deadly, thus a well-interpreted model is more crucial. The interpretation in the biomedical domain may come from two aspects: (1) biomedical models should be easily understood and the predictions could be simulated from the raw input, (2) a (textual) reason should be provided for each prediction. The basic example of the former (a.k.a, transparency [139]) is decision trees that could clearly illustrate the decision path. However, such a transparency goal is hardly achieved in modern natural language processing especially with pre-trained language models. More efforts could be made for the latter, one has to find some textual explanation for each prediction/decision, based on what doctors and patients could make their own decisions.

Identifying causalities from correlations. Similar to interpretability, causality may provide the underlying explanation of the model decisions. Causality is crucial in many tasks of biomedical knowledge, e.g., diagnosis, pathology, or systems biology. Causal associations between biological entities, events, and processes are central to most claims of interest, see an early review from [111]. With automatic causality recognition, it could suggest possible causal connections that may be beneficial for biomedical decisions, which hence greatly reduces the human workload [155].

Trade off between coverage or quality? There is not large-scaled and high-quality training corpora in the biomedical domain. This means one has to sacrifice its coverage to obtain a high-quality vertical application, or train a general model with large-scaled yet low-quality corpora. Pre-trained language models typically consist of many transformer layers that have many parameters, which usually requires a massive amount of plain text. This may lead to a general model with great coverage, but a smaller proportion of high-quality expert knowledge.

Heterogeneous training data. For biomedical understandings, there is heterogeneous information including tables, figures, graphs (MRI), etc. For example, tables and numbers are crucial in scientific literature. But most PLMs are unable to interpret tables and numbers well. To deeply capture the information in these heterogeneous data, both in-depth data...
prepossessing and model adaption may be needed. Especially, multi-domain pre-trained language models in biomedical should be paid much more attention.

Ethics and bias. With the rapid development of AI systems and applications in industrial products, it should be aware that they should not introduce any bias for a special groups or populations [149], and some of efforts were taken in the NLP field [20, 60, 230, 299]. This become more crucial in these sensitive environments in the biomedical domain that involves life-changing decisions, like surgery [205]. It should ensure that the decisions cannot reflect discriminatory or biased behavior toward specific groups or certain populations. In the domain of pre-trained language models, the ethics and bias issues has been quantified by a few works. [290] quantifies biases in clinical contextual word embeddings. The reason behind may due to the training itself is biased with respect to various attributes like gender, language, race, age, ethnicity, and marital status. For example, in the MIMIC-III dataset [96], one can find: 1) gender bias: males have more heart disease than females, and 2) ethnicity bias: black patients have fewer clinical studies than other groups [98]. Considering the complexity of directly reducing biases in training corpora, existing works explore to identify bias by adversarial training [290] or data augmentation [157].

Privacy. Although most corpora used in biomedical pre-training like scientific publications and social medical are open-access. Some EHRs are private since some organizations do not want to expose their data. Clinical records may contain patient visits and medical history. Such sensitive data should not be exposed as it may harm the patients physically or mentally [167]. Although sensitive information in EHR records (like MIMIC III) is de-identified before sharing for research purposes. It is possible to recover sensitive patient information from the de-identified medical records. Recent works showed that there is data leakage from pre-trained models in the general domain i.e., it is possible to recover personal information present in the pre-training corpora [122]. Due to data leakage, the models pre-trained on proprietary corpora, cannot be released publicly. Recently, Nakamura et al [167] proposed KART framework which can conduct various attacks to assess the leakage of sensitive information from pre-trained biomedical language models. Also, the federated learning [128, 278] framework may help when different organizations and end users could collaboratively learn a shared prediction model while keeping all the training data on a private side.

6.2 Future trends

We further suggest some future trends in this subsection.

Standardized benchmark. In general NLP fields, evaluation criteria and standard benchmarks are a driving force for the NLP community. For example, BERT [45] were widely accepted in benchmarks [194, 248] that makes it spread to various tasks in NLP. On the other hand, lacking effective evaluation criterion is one of the bottlenecks of text generations [29]. In the biomedical domain, various pre-trained models and their fine-tuning applications have been proposed (as introduced in Sec. 4 and Sec. 5). However, they are generally not well-compared. Although a few efforts have been done to standardize benchmarks for biomedical pre-trained models, which includes but not limits to [67, 291]. This becomes much more difficult in the cross-discipline domain like biomedical domain since papers are usually from different communities like informatics, medicine, and computer science. An open standardized and well-categorized benchmark (like in [123]) should be proposed to make use of the advantages of each work and collaboratively push the development of biomedical NLP. This survey is the first step to introduce the biomedical pre-trained language models and their applications in downstream tasks. More efforts are expected to be done to design fine-grained taxonomy and define each SOTA approach in various applications, based on what incremental work could be better evaluated.
Open culture. In general NLP fields, a lot of effort is done to make better-available resources, including open-source resources (released training data and models), fairly-implemented approaches. Open culture makes researchers could easily contribute to the community. For example, the NLP community has been largely developed thanks to the model collections [56, 264]. Most accepted papers in top conferences tend to release codes, models, and data. Biomedical NLP fields also benefit a lot from such open culture and standard systematic evaluations. For instance, pre-trained models in Huggingface largely fascinated their applications in the biomedical domain.

Efficiency on pre-trained language models. Compared to previous SOTA methods training from scratch based on neural networks such as LSTM or CNN, before Transformer, pre-trained language models are much bigger in terms of model scale and much slower due to the increasing of parameters. This is more expensive for deployment that requires more computing resources. One may have to refer to [233] for efficient transformers. For example, current work explores quantization [14, 295], weights pruning [86], and knowledge distillation [92, 207] for BERT. Therefore, in biomedical domain, pre-training language models with lower computation complexity is a direction needed to be pay more attention.

Generation based PLMs is under-investigated. Most works focused on encoder-based models, a few work is encoder-based or encoder-decoder based. This may be due to that classification tasks may be widely used in downstream biomedical tasks. Very recently, [114] proposes GPT models using temporal electronic health records and trained a T5 based biomedical pre-trained model. We believe that generation based PLMs have a great potential in biomedical domain but it is currently under-investigated. We expect that more work will be done in generation based pre-trained language models like GPT, T5, and BART.

Few-shot learning. [182] evaluates the few-shot ability of LMs when held-out examples are unavailable for choosing hyperparameters or prompts and finds that LMs do not perform well compared to random selection and under-perform selection based on held-out examples. In other words, previous methods overestimate the few-shot capability of LMs based on more realistic settings. This might be even worse for biomedical LMs.

In non-English or low-resource language. Most works in biomedical pre-trained language models are with English corpora, and a few about Chinese [292], German [25], Japanese [102, 245], Spanish [6, 7, 145, 159], Korean [109], Russian [239], Italian [28], Arabic [13, 23], French [41], Portuguese [208, 209] etc. For the non-English biomedical tasks, there are two mainstream solutions: a single non-English language paradigm and a multi-linguistic paradigm. The former uses a single language, while the latter uses multiple languages. The multi-linguistic paradigm could be more beneficial for low-resource, since biomedical knowledge itself is language-independent and information in a second language could be complementary.

Multi-modal pre-training. Multi-modal pre-training [191, 195] has attracted much attention in image classification and generation tasks, because it only needs cheap but large-scale publicly-available online resources. This shows great potential in machine learning since less human annotation is needed. It is expected that various modalities could provide complementary information. Making use of biomedical codes, medical images, waveforms, and genomics in pre-training models would be beneficial but challenging due to its multi-modal nature.

37 https://huggingface.co/
Injecting biomedical knowledge in pre-trained language model. Before the pre-training age, some works [184] have explored injecting medical knowledge into embeddings that provides potentially better machine learning features. Recently, existing work claims that pre-trained language models could be a soft knowledge base that captures knowledge. Despite this, [40, 271] also tried to explicitly inject knowledge into pre-trained language models. In the biomedical domain which is knowledge-intensive, knowledge-injected models could have great potential in the future. For example, [153] integrates domain knowledge (i.e., Unified Medical Language System (UMLS) Metathesaurus) in pre-training via a knowledge augmentation strategy.

Interpretability in biomedical PLMs. Neural networks were criticized to have limited interpretability. Pre-trained language models are typically huge neural network models, which is more challenging in terms of interpretability. One may expect to understand the working mechanism related to the medical characteristics in pre-trained language models. For example, probing pre-trained language models have been widely used to understand pre-trained language models, see [113, 134, 244, 267]. For biomedical pre-trained language models, [8] aim to evaluate pre-trained language models about the disease knowledge. [243] exhaustively analyzing attention in protein Transformer models, providing many interesting findings to better understand the working mechanisms. [93] conducts some probing experiments to determine what additional information is carried intrinsically by BioELMo and BioBERT. We believe that more efforts are expected for interpretability in biomedical PLMs.

7 CONCLUSION
This paper systematically summarizes recent advances of pre-trained language models in biomedical domain, including background, why and how pre-trained language models are used in the biomedical domain, existing biomedical pre-trained language models, data sources in the biomedical domain, application of pre-trained language models in various biomedical downstream tasks. Furthermore, we also discuss some limitations and future trends. Finally, we expect that the pre-trained language model in the general NLP domain could also help the specific biomedical domain.

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