Learning for Biomedical Information Extraction: Methodological Review of Recent Advances
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Abstract

Biomedical information extraction (BioIE) is important to many applications, including clinical decision support, integrative biology, and pharmacovigilance, and therefore it has been an active research. Unlike existing reviews covering a holistic view on BioIE, this review focuses on mainly recent advances in learning based approaches, by systematically summarizing them into different aspects of methodological development. In addition, we dive into open information extraction and deep learning, two emerging and influential techniques and envision next generation of BioIE.

Keywords: natural language processing; biomedical information extraction; text mining; open information extraction; deep learning

Introduction

Biomedical information extraction (BioIE) aims to automatically unlock structured semantics (e.g. entities, relations and events) out of unstructured biomedical text data. It has been successfully applied in clinical decision support [1,2], integrative biology [3,4] and biocuration assistance [5–7], and has also shown great potentials in pharmacovigilance [8].

Broadly speaking, BioIE covers a very large spectrum of research efforts, resulting in enormous publications, as shown in Figure 1. The tasks include named entity recognition [9–11], event identification[12–14], and relation extraction [10,15,16]. The text data or corpora include medical

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literature[17], biological literature[18], electronic health records[19], and healthcare related social media data[20]. The methodology includes rule-based method, knowledge-based method, statistics based method, learning-based method and hybrid method[21–23]. A thorough systematic survey covering all related work in BioIE is beyond the scope of this paper, and readers of interest can refer to several previously published survey papers[24,25,19,26,27,22,28–30,21,23,31,32]. Most recently, Gonzalez et al.[33] summarized text and data mining advances and emerging applications for biological discovery, which is domain specific and task oriented, focusing on applications of natural language processing (NLP) techniques to better understand underlying mechanisms of disease. It is IE related, but mainly for knowledge discovery. Instead this review will focus on technological advances for learning-based BioIE across different biological, medical and clinical domains, which will yet be abstracted across different types of tasks, different genres of corpora, as well as different subdomains being applied, shedding light on future research directions and providing prospective insights into next generation of BioIE.

![Figure 1](image_url)

Figure 1. The number of publications in biomedical information extraction each year (grey bar) and cumulative number since 1999 (dark bar), using the PubMed query of “(biomedical OR clinical OR medical) AND (text+mining OR text+processing OR natural+language+processing) AND (information+extraction OR named+entity+detection OR named+entity+recognition OR relation+extraction OR event+extraction)”.

**Learning for Biomedical Information Extraction**

Learning methods for BioIE have been rapidly advanced in the past 5 years. Conditional random fields(CRF) [10] and structured support vector machines(SSVM) [34] have been two representative learning methods, and deep neural networks[35] have been increasingly applied to both general domain IE and BioIE. All those methodological advances mainly fall into three categories: (1) learning from labeled data (i.e. supervised learning) which focuses on labeling more data to tackle new problems or improving model training using existing benchmark data; (2) learning from unlabeled data (i.e. semi-
supervised and unsupervised learning) which involves incorporating large amount of unlabeled data into the learning process; (3) learning scheme integration to seamlessly integrate different learning paradigms at outer system level (i.e. hybrid approach) or modeling level (i.e. joint modeling). In particular, two emerging technological advances, namely open information extraction (OpenIE) and deep learning (DL), have exerted significant influence on BioIE recently for more scalable and reliable applications. What follows will be reviewing each of the abovementioned topics in more details.

Learning from Labeled Data

Traditional learning-based systems aim to infer optimal prediction functions from labelled training data instances, which can be used for mapping new data instances to their (predicted) labels. There are mainly two types of approaches that facilitate pattern analysis on labeled data: (1) feature-based approach explicitly transforms raw data representation into feature vector space, and each feature dimension represents an individual characteristics of a data instance; (2) kernel-based approach provides an implicit way of transforming raw data into a high-dimensional space through a similarity function, called kernel function, which is defined over pairs of data instances.

- Feature-based Approaches

Advanced feature engineering has proven to be successful in many machine learning based BioIE applications. In addition to common features, such as lexical (e.g., words), orthographic (e.g., capitalization, character n-grams), syntactic (e.g., part-of-speech, chunking), semantic (e.g., semantic category of a word by dictionary or ontology) and local context (e.g., n-grams, neighboring words) features [36–39], discourse-level features (e.g., sentence length, section headings, writing patterns) [36,37] and dependency tree based features [39–42] have also been explored. Different systems also leverage task specific features using external resources or other domain knowledge, e.g. chemical elements, amino acid sequences and chemical formulas were used to derive features for recognizing chemical named entities[43]; features derived from event occurrence pattern were designed to detect the causal relation in a clinical problem-action relation extraction system[44]. To improve the performance of feature-based system, combining multiple types of features is a widely used strategy, e.g. a drug-drug interaction (DDI) system[45] was developed to combine heterogeneous features, including lexical, syntactic, semantic and negation features derived from sentences and their corresponding parse trees.

Word features are prone to the data sparseness challenge (i.e., insufficient training data vs. a huge amount of features). To overcome such challenge, vector-based word representations have been exploited, including clustering-based word representation (i.e., representing a word by its hard cluster(s)) [36,46], distributional representation (i.e., representing a word by its semantically related words as calculated on word co-occurrence statistics) [37,46], and distributed representation (i.e., word embedding) [46,47]. Tang et al. [48] combined clustering-based word representation and distributional word representation into a structural SVM learning scheme, showing better performance than using either single type of representation feature. More on word embedding will be described later in deep learning section.

However, a richer set of features may not guarantee better performance, as features that are irrelevant, redundant or have limited discriminative power may cause adverse effects on model learning, leading to increased computational complexity and over-fitting. As a result, feature selection is of paramount importance for any learning-based approaches, especially with high-dimensional features.
Simple additive or subtractive feature selection strategies (adding or removing each feature class one by one to evaluate feature contribution) work well for many BioIE applications (e.g. [49]). New feature selection approaches were also proposed, e.g. Leaman [50] applied multivariate feature selection with filters and false discovery rate analysis to biomedical NER; Xia et al. [51] evaluated an accumulated effect evaluation (AEE) algorithm for feature selection and showed improved performance in the GENIA bioNLP shared task 1 (event detection); Campos et al. [52] described an optimization algorithm to find the feature set that better reflect the characteristics of each event type for biomedical event trigger recognition; and Fang et al. [53] introduced an improved feature selection method by combining mutual information and class separability criteria for identifying non-redundant optimal features on multidimensional time series clinical data. In addition, a partition-specific feature selection method was successfully applied on both protein-protein interaction[54] and drug-drug interaction [45] tasks, where candidate relation pairs are partitioned into groups based on syntactic properties and features are optimized for each group, achieving the state-of-the-art system performance.

- **Kernel Approaches**

Kernel-based approaches are becoming more and more popular for learning algorithms including perceptron and support vector machines, as sometimes data can’t be easily represented with explicit feature vectors (e.g. sentences are better characterized by trees or graphs). In the last few years, many task specific kernels have been proposed or applied on many BioIE tasks. Patra et al. [55] proposed a novel kernel named “sliding tree kernel”, which is an improved tree kernel specific to named entity recognition(NER) task. It considers a substructure of trees in the form of sliding window, leading to a better way to model local context of a word. A hash subgraph pairwise(HSP) kernel was introduced for protein-protein interaction extraction[56], which can efficiently make use of the full dependency graph that represents sentence structure and particularly capture the contiguous topological and label information.

In addition to single-kernel-based approaches, ensemble approach combines outputs from different kernel-based systems and multiple kernel learning (MKL) approach constructs a hybrid kernel by linearly or polynomially combining individual kernels. Thomas et al. [57] reported the best performing drug-drug interaction system in the DDI extraction 2011 challenge, which combined outputs from two kernel-based systems and a case-based reasoning system using majority voting. Yang et al. [58] presented a weighted MKL approach for protein-protein interaction(PPI) from biomedical literature, where different kernels (feature-based, tree, graph and part-of-speech path) were combined linearly and the shortest path-enclosed tree(SPT) and dependency path tree were extended to capture richer contextual information, achieving better performance than counterpart systems. Following this strategy, Li et al. [59] further improved the state-of-the-art performance on PPI by incorporating a semantic kernel characterizing the protein-protein pair similarity using Medical Subject Heading and the context similarity using WordNet. Similarly, the best system [60] in SemEval’13 DDI extraction applied a MKL approach linearly combining a feature-based kernel, a shallow linguistic kernel and a path-enclosed tree kernel. Another hybrid kernel, which consists of an entity kernel and convolution parse tree kernel combined via polynomial expansion, was showing promising result on biomedical event extraction[61].

Tikk et al. [62] conducted an analytical study on the performance of 13 types of kernels for PPI extraction, which suggests that the system performance benefits more from novel features than from novel kernel functions. Rich features have been explored to improve kernel-based systems. For instance, Zhou et al. [63] showed a novel framework for biomedical event trigger identification, where word embedding features were combined with syntactic and semantic contextual features using MKL method, achieving the state-of-the-art performance. Similarly, Li et al. [64] showed improved performance when
integrating word embedding features in a kernel based PPI extraction system, and Ma et al. [65] improved PPI extraction by proposing a new tree kernel where processing rules were defined to better handle the parsing error of modal verb phrases and noise interference by appositive dependency. In contrast, Kim et al. [66] showed that a simple linear kernel that integrates a rich set of lexical and syntactic features is able to achieve a competitive performance for DDIs, suggesting that linear kernel may perform as well as complex kernels.

- **Cost-effective Ground Truth Acquisition**

Supervised machine learning approaches depend on annotated corpora, which are frequently expensive to obtain, especially in the medical/clinical domain. Semi-supervised annotation, active learning, and crowd-sourcing approaches have been developed to create large-scale annotated corpora.

Pre-annotation or computer-aided annotation gives human annotators the machine-annotated data for potentially better efficiency. Recent studies, however, reported mixed results in terms of how much pre-annotation helps. Lingren et al. [67] created a dictionary for pre-annotation on clinical NER task, showing reduced time needed for review by 13.85-21.5% compared with fully manual annotation. However, in an experiment on clinical text de-identification task by South et al. [68], it has been shown that machine-assisted annotation didn’t improve annotation quality for most PHI classes and didn’t provide statistically significant time-savings compared to manual annotation of raw documents. By further combining iterative machine learning approach in pre-annotation, RapTAT [69], a semi-automated semantic annotation tool, was shown capable of reducing the annotation time by up to 50% on 401 clinical notes, as well as improving the inter annotator agreement.

Active learning aims to alleviate annotation efforts by reducing annotated sample size. It selects informative samples via actively involving the learning algorithms. Various studies have investigated the effects of using active learning to achieve less learning cost without compromising learning performance of associated predicative models, such as assertion annotation for medical problems [70], semantic annotation for medical abbreviations and terms [71], clinical NER annotation [72], clinical coreference resolution [73], pathological phenomena labeling in MEDLINE [74] and phenotype annotation [75]. Two recent studies on medical concept extraction show that: (1) incorporating external knowledge resources within active learning query strategies [76] can further reduce annotation efforts; (2) incremental active learning [77] is promising in building robust medical concept extraction models while significantly reducing the burden of manual annotation.

Crowdsourcing has been widely explored in biomedical and clinical domain [78]. Studies have demonstrated that crowdsourcing is an inexpensive, fast and practical approach for collecting high-quality annotations for different BioIE tasks, e.g. medication NER in clinical trial documents [79], disease mention annotation in PUBMED literature [80], relation extraction between clinical problems and medications [81], etc. Different techniques have been explored to improve the quality and effectiveness of crowdsourcing, including probabilistic reasoning [82] to make sensible decisions on annotation candidates and gamified techniques [83] to motivate a continuous involvement of the expert crowd. More recently, a method called CrowdTruth [84] was proposed for collecting medical ground truth through crowdsourcing, based on the observation that disagreement analysis on crowd annotations can compensate lack of medical expertise of the crowd. Experiments of using CrowdTruth on medical relation extraction task show that the crowd performs just as well as medical experts in terms of quality and efficacy of annotation, and also indicate that at least 10 workers per sentence are needed to get the highest quality annotation for this task.
Learning from Unlabeled Data

In contrast to relying on the costly labeled data, freely available unlabeled data have been explored for BioIE. Approaches include unsupervised, semi-supervised, and distant supervision.

Unsupervised biomedical NER systems described in [85] are based on phrase chunking and distributional semantics, showing competitive results on both clinical notes and biomedical literature. Quan et al. [86] explored kernel-based pattern clustering and sentence parsing to tackle the PPI extraction and gene-suicide association extraction from biomedical literature. More recently, Alicante et al. [87] reported an unsupervised system for both entity and relation extraction from clinical records written in Italian.

Semi-supervised methods aim to incorporate unlabeled data in a supervised manner. Recent semi-supervised approaches in BioIE mostly differ in the approximation methods used to obtain labelling for unlabeled data as well as the ways to handle uncertainty when adding unlabeled data, including self-training, also known as bootstrapping (e.g. [88] for medical risk event extraction and [89] for drug-gene relation extraction), transfer learning (e.g. [90] for clinical concept extraction), and manifold regularization (e.g. [91] for medical relation extraction). To obtain higher quality labelling for unlabeled data, several strategies have been proposed for semi-supervised learning, such as combining active learning for PPI extraction [92], introducing event inference mechanisms to detect more event mentions from unlabeled text [93], and exploiting topic analysis to identify similar sentences for automatic labeling [94]. From feature representation point of view, feature coupling generalization (FCG) has been explored to generate new features directly from unlabeled data, e.g. [95] for gene NER and PPI extraction and [96] for biomedical event extraction.

Different from abovementioned semi-supervised methods, distant supervision approach typically doesn’t require any labeled data, which makes use of weakly labeled data derived from a knowledge base [97], or some seed data points [98] but without finer-grained sentence level annotations. Recently it has been widely used in DDI and PPI extraction [97,99,100] with different strategies to deal with training challenges due to noisy data, as well as later work on the BioNLP Gene Regulation Network task [98], gene expression relation extraction [101] and cancer pathway extraction [102]. Most recently, the DeepDive system [103] was employed to scaled up the distant supervision method on biomedical text mining without limiting the application to a specific process or pathway, achieving promising results for extracting gene interactions from full-text PLOS articles.

Learning Scheme Integration

- **Hybrid Approach**

Hybrid approaches integrate heuristics/rule/pattern-based method, domain knowledge, and learning-based method. One ensemble strategy is to develop multiple independent models, and then combine the results of each model for a final output, either through rules or by using some classification/regression model, e.g. combining rule-based model with SVM classifiers for biomedical event detection [104]; integrating pattern recognition into learning for DDI extraction [105]; algorithmically fusing results from two approaches for temporal relation extraction in patient discharge summaries [106]. Another ensemble strategy is to run different models sequentially for further filtering and refining to a better system output, e.g. extracting disorder mentions from clinical notes [107]; extracting disease-treatment relations from MEDLINE corpus [108]; identifying Genia events by learning-
based classifiers with rule-based post-processing [109]; and similar post-processing was also used in a hybrid system of recognizing composite biomedical named entities[110].

- **Joint Modeling**

A BioIE system typically involves different subtasks with embedding and inter-dependent characteristics. To overcome cascading errors in a multi-step pipeline framework, joint models (e.g. a Markov Logic Network(MLN) based approach [111]) have shown improved performance. But due to complexity of inference for joint modeling, rich features previously used in the pipeline framework may be compromised to make inference tractable. Therefore, many efforts have been made to relieve the computational bottleneck of joint inference in biomedical event extraction. For instance, Riedel and McCallum [112] proposed three joint models of increasing complexity to make the system more robust and applied dual decomposition to make joint inference tractable; Vlachos and Craven [113] applied the search-based structured prediction framework (SEARN) for high modeling flexibility and fast joint inference; Venugopal et al.[114] presented an MLN-based join model which employs an SVM model to encode high-dimensional features; and more recently Li et al.[115] exploited dual decomposition based joint inference, dependency parsing based rich features, and word embedding for event extraction. From a different perspective, Wei et al.[116] proposed to use dependency chain tagging to extract embedded semantic relations from biomedical literature, which avoided complex inference but kept the hierarchy feature of entities.

In addition to the abovementioned work focusing on BioNLP shared event extraction task, joint modeling has been increasingly introduced in other specific subdomains. To effectively extract adverse drug event(ADE), Li et al.[117] designed a transition-based model to extract drugs, disease and ADEs jointly, which leverages the structured perceptron for training and the multiple-beam search algorithm for decoding.

**Open Information Extraction (OpenIE)**

OpenIE [118] has been emerging as a novel information extraction paradigm in the last couple of years. It doesn’t presuppose a predefined set of relations but aims to identify any possible relations from unlabeled data with no or limited supervision.

OpenIE systems typically consist of four main components: (1) Automatic Labeling of data using heuristics or distant supervision; (2) Extractor Learning using relation-independent features on noisy self-labeled data; (3) Tuple Extraction on a large amount of text by the Extractor; (4) Accuracy Assessing by assigning each tuple a probability or confidence score. Based on features used in extractor learning, we can roughly group existing OpenIE systems into two categories: Light Open Extractors (e.g. [118–121]) which only use shallow language processing, e.g. part-of-speech tagging and chunking, and Heavy Open Extractors (e.g. [122,123]) which use deep linguistic analysis, e.g. dependency parsing. Typically, the former is much more efficient but is much lower in either recall or precision, while the latter improves the overall performance significantly with the hit on system efficiency. OpenIE requires no or little supervision and its extractor is trained on automatically labelled data using heuristics or distant supervision, which is the same as traditional bootstrapping system in this regard. However, it lends itself well to contributing to next generation information extraction systems due to its particularly advantageous aspects, as summarized in Table 1.

| Table 1. Advances of OpenIE Compared with Traditional self-learning |
### OpenIE vs. Traditional self-learning

| OpenIE                                      | Traditional self-learning |
|---------------------------------------------|---------------------------|
| Highly scalable to size and diversity of the WEB | Relatively small and homogeneous corpus |
| Not dependent on relation specific features | Relation dependent features |
| Avoid lexical features for generalization   | Use lexical features for better precision |
| Domain independent                          | Domain dependent          |
| No predefined relation schema               | Targeted to specific types of relations |
| Label all the data                          | Selectively label data    |
| Redundancy-based accuracy assessing         | Confidence derived from the learned model |

One major challenge is that the massive facts OpenIE systems extract are in purely textual surface form which cannot be directly used by applications. There are several directions to address this issue: (1) Building knowledge resources to make sense of OpenIE extractions, e.g. dynamic knowledge graphs[124], web-scale knowledge repository[125], taxonomy of textual relational patterns[126]; (2) Harnessing semantic web technologies to enable information fusion and semantic reasoning[127]; and (3) Integrating ontological resources, e.g., linking OpenIE to world knowledge[128,129] and aligning multiple ontologies[130]. In addition, Riedel et al. [131] proposed a universal schema, which unites surface form relational patterns from OpenIE with relations defined in knowledge bases. By using matrix factorization and collaborative filtering, this approach is able to reason about unstructured and structured data in mutually-supporting ways.

The great potential of applying OpenIE techniques to BioIE has been recognized. For instance, Attias et al. [132] adapted the Never Ending Language Learner (NELL) [133] to biomedical domain and proposed a Rank-and-Learn methodology to effectively prevent semantic drift, achieving promising results on learning biomedical lexicon of open categories. Nebot et al. [134,135] presented a scalable method that extracts surface-form biomedical relations without pre-specified types, and then infers abstract relations and their signature types by clustering these extracted relations.

### Deep Learning

Deep learning refers to “a class of machine learning techniques that exploit many layers of non-linear information processing for supervised or unsupervised feature extraction and transformation, and for pattern analysis and classification”[136]. Deep learning networks can be roughly categorized into (1) unsupervised/generative, e.g., restricted Boltzmann machines (RBMs)[137], deep belief networks (DBNs)[138]; (2) supervised/discriminative, e.g., deep neural networks (DNNs)[139], convolutional neural networks (CNNs)[140] and recurrent neural networks (RNNs)[141]; and (3) hybrid, e.g., DBN-DNN[142] models that combine unsupervised pre-training and supervised fine-tuning.

There have been a surge of interest of applying deep learning techniques in common NLP tasks, such as semantic parsing[143], information retrieval[144,145], semantic role labeling[146,147], sentimental analysis[148], question answering[149–152], machine translation[153–157], text classification[158], summarization[159,160], text generation[161], as well as information extraction, including named entity recognition[162,163], relation extraction[164–168], event detection[169–171]. CNNs and RNNs are two popular models employed by these work. Despite of the difference in network architecture, they share the key motivation to avoid task-specific, knowledge-centric feature engineering by leveraging the word embedding technique.
More recently, remarkable progress has also been made in BioIE due to the widely propagated application of deep learning techniques. One popular technique from deep learning is word embedding, which have been widely used in biomedical named entity recognition[46,172], medical synonym extraction[173], medical semantics modeling[174], relation extraction including chemical-disease relation [175], Protein-Protein interaction[176], and relation between pharmaceuticals and diseases/physiological processes. In terms of event extraction, Li et al.[177] reported comparable state-of-the-art performance when applying word embeddings on BioNLP event extraction task; Nie et al.[178] presented an embedding assisted neural network prediction model to conduct biological event trigger identification; Henriksson et al.[179] leveraged distributed semantics to detect adverse event signals from clinical notes. Furthermore, Wu et al.[180] utilized neural word embeddings for disambiguating clinical abbreviation mentions; similarly Liu et al.[181] exploited task-oriented resources to learn word embeddings for clinical abbreviation expansion. Ghassemi et al.[182] employed distributed stochastic neighbor embedding (tSNE) to extract clinical sentiment information (positive vs. negative).

Instead of using standard word embedding training strategy, Jiang et al.[183] proposed a biomedical domain-specific word embedding model by incorporating stem, chunk, and entity information, and used them for DBN-based DDI extraction and RNN-based gene mention extraction. Similarly in clinical domain, Choi et al.[184] presented a novel neural word embedding tool, Med2Vec, which can not only learn distributed representations for both medical codes and visits in electronic health record (EHR), but also allow interpreting the learned representations confirmed positively by clinical experts. Then an extensive and comparative study[185] has been performed among medical concept embeddings learned from medical journals, medical claims and clinical narratives respectively, evaluating their similarity and relatedness properties.

Different deep learning architectures have also been explored to predict clinical events, e.g. Choi et al.[186] applied RNNs to longitudinal EHR data to predict future disease diagnosis and medication prescription. Following that, they further explored two gating mechanisms Long Short-term Memory (LSTM)[187] and Gated Recurrent Units (GRUs)[153] on RNN models, incorporating patient static data to extract early signs from EHR data for predicting kidney transplantation endpoint events, Jagannatha and Yu[188] employed a bidirectional LSTM RNN structure to extract adverse drug events from electronic health records, and Miotto et al.[189] explored a three-layer stack of denoising autoencoders to learn a general-purpose patient representation from EHR data, resulting in improved clinical predictions. In addition to using textual data, Liu et al.[190] proposed a recurrent self-evolving fuzzy neural network (RSEFNN) to leverage brain dynamics data to predict driving fatigue event; Lehman et al.[191] combined CNNs with dynamical systems to model physiological time series for prediction of patient prognostic status.

Due to the big success of deep learning on computer vision, information extraction/detection from medical imaging has been substantially influenced, such as pulmonary nodule detection in computed tomography scans using CNN features[192], a successful application of CNN trained on a large-scale non-medical image dataset for chest x-rays pathology detection[193], automated detection of posterior-element fractures on spine CT based on deep CNN [194], an interleaved text/image deep learning system for extracting and mining the semantic interactions of radiology images and reports[195]. More recently, Shin et al.[196] exploited and extensively evaluated three important factors of applying deep CNN to medical image classification, i.e., network architecture, dataset characteristics and transfer learning, in the context of two different computer-aided diagnosis applications: thoraco-abdominal lymph node detection and interstitial lung disease classification. Other successful examples of applying deep learning techniques include genomic information extraction[197–199], protein structure prediction[200] as well as drug discovery[201].
Challenges and Future Directions

Recent innovated methodology development has significantly advanced biomedical information extraction, giving rise to a broad spectrum of improved biological and clinical applications. However, a number of limitations and problems at the frontiers of BioIE continue to impose additional challenges and present new opportunities for more accurate, efficient, reliable, scalable and sustainable BioIE research.

Data-driven approaches will continue to be a mainstream strategy. OpenIE techniques have been drawing more and more attention to enhance and scale BioIE systems by utilizing large, complex and heterogeneous data (different genres of textual data, structured vs. unstructured, text data vs. high throughput biological data) and extracting all meaningful relations and events without any restriction. Although in general domain several efforts have recently been made along this line, such as joint embedding of text and knowledge base (e.g. [202–205]) and unsupervised Web-scale event extraction[206], adapting current OpenIE techniques into BioIE applications is still at an early age. In addition, confidence based quality control and information normalization/fusion will be two remaining challenges for OpenIE platforms.

Joint inference models have been proposed to overcome the error propagation problem in pipeline approaches, by making predictions for multiple IE tasks simultaneously [207,208]. However, these models are complex and difficult to design. Exact inference is usually impossible and even inexact inference can be computationally expensive. Important questions remain to be answered in order for joint models to play a bigger role in BioIE, such as to what extent do we want a joint modeling? Which model architectures and learning methods better suit a specific IE problem? How to balance the computational efficiency and accuracy?

Evidently, deep learning techniques have played an unprecedented role in recent BioIE advances, which brought significant improvements across various subtasks. It is also signifying its continuous great potential for more advanced BioIE applications. Yet many issues remain to be investigated to take full advantage of deep learning for BioIE. Firstly, although deep learning can learn an internal distributed feature representation automatically from the data, combining domain knowledge and biomedical knowledge resources into deep learning architecture may lead to greater accuracy and flexibility. Collobert et al. [209] showed that by integrating linguistic and domain features, their DNNs improved over the original model (which does not use any feature engineering) and also outperformed benchmark systems in POS tagging and NER. The same strategy can be explored for BioIE. Secondly, deep learning models provide a natural way to learn distributed representations of entities and relations from knowledge bases [210,211]. Such approaches can be extended to fuse knowledge from multiple resources (e.g., knowledge bases, annotated corpora, and output from automatic systems). Finally, optimizing deep learning architecture to scale for big data processing and enable learning transferable features[212] will arouse increasing interest in the near future.

BioIE involves complex events, and those events are dependent. Better utilizing those inter-event dependencies[213] will be beneficial for further improving BioIE system performance, as well as for developing more integrative next-generation biomedical event extraction system through interconnecting biological reaction networks[214].

The big-data-driven BioIE research is rapidly evolving and projecting a bright future equipped with both learning-based algorithmic advances and multiple level model integrations.
Key Points

- Learning-based data-driven approaches have become and will continue to be the mainstream strategy for BioIE applications.
- Methodological development evolves into joint modeling, system integration and embracing a variety of linguistic knowledge and domain-specific semantics.
- Utilizing abundant unlabeled data presents promising results for tackling all kinds of BioIE challenges in a cost-efficient way, and will remain an active research area.
- OpenIE and deep learning have shown significant potential in further advancing BioIE research, and are foreseen to be more involved for building cutting-edge BioIE solutions in the big data era.

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