BioRED: A Comprehensive Biomedical Relation Extraction Dataset

Ling Luo¹⁺, Po-Ting Lai¹⁺, Chih-Hsuan Wei¹⁺, Cecilia N Arighi² and Zhiyong Lu¹⁺

¹National Center for Biotechnology Information (NCBI), National Library of Medicine (NLM), National Institutes of Health (NIH), Bethesda, MD 20894, USA, ²University of Delaware, Newark, DE 19716, USA

*To whom correspondence should be addressed.

Abstract

Automated relation extraction (RE) from biomedical literature is critical for many downstream text mining applications in both research and real-world settings. However, most existing benchmarking datasets for biomedical RE only focus on relations of a single type (e.g., protein-protein interactions) at the sentence level, greatly limiting the development of RE systems in biomedicine. In this work, we first review commonly used named entity recognition (NER) and RE datasets. Then we present BioRED, a first-of-its-kind biomedical RE corpus with multiple entity types (e.g., gene/protein, disease, chemical) and relation pairs (e.g., gene-disease; chemical-chemical), on a set of 600 PubMed articles. Further, we label each relation as describing either a novel finding or previously known background knowledge, enabling automated algorithms to differentiate between novel and background information. We assess the utility of BioRED by benchmarking several existing state-of-the-art methods, including BERT-based models, on the NER and RE tasks. Our results show that while existing approaches can reach high performance on the NER task (F-score of 89.3%), there is much room for improvement for the RE task, especially when extracting novel relations (F-score of 47.7%). Our experiments also demonstrate that such a comprehensive dataset can successfully facilitate the development of more accurate, efficient, and robust RE systems for biomedicine.

Availability: The BioRED dataset and annotation guideline are freely available at https://ftp.ncbi.nlm.nih.gov/pub/lu/BioRED/.

Contact: zhiyong.lu@nih.gov

Key words: biomedical natural language processing; biomedical dataset; named entity recognition; relation extraction

1 Introduction

Biomedical natural language processing (BioNLP) and text-mining methods/tools make it possible to automatically unlock key information published in the medical literature, including genetic diseases and their relevant variants [1, 2], chemical-induced diseases [3], and drug response in cancer [4]. Two crucial and building block steps in the general BioNLP pipeline, however, remain challenging. The first is named entity recognition and linking (NER/NEL), which automatically recognizes the boundary of the entity spans (e.g., ESR1) of a specific biomedical concept (e.g., gene) from the free text and further links the spans to the specific entities with database identifiers (e.g., NCBI Gene ID: 2099). The second is relation extraction (RE), which identifies an entity pair with certain relations.

To facilitate the development and evaluation of NLP and machine learning methods for biomedical NER/NEL and RE, significant efforts have been made on relevant corpora development [5-10]. However, most existing corpora focus only on relations between two entities and within single sentences. For example, Herrero-Zazo et al. [9] developed a drug-drug interaction (DDI) corpus by annotating relations only if both drug names appear in
the same single sentence. As a result, multiple individual NER/RE tools need to be created to extract biomedical relations beyond a single type (e.g., extracting both DDI and gene-disease relations).

Additionally, in the biomedical domain, extracting novel findings that represent the fundamental reason why an asserted relation is published as opposed to background or ancillary assertions from the scientific literature is of significant importance. To the best of our knowledge, none of the previous works on (biomedical) relation annotation, however, included such a novelty attribute.

In this work, we first give an overview of NER/NEL/RE datasets, and show their strengths and weaknesses. Furthermore, we present BioRED, a comprehensive biomedical relation extraction dataset. We further annotated the relations as either novel findings or previously known background knowledge. We summarize the unique features of the BioRED corpus as follows: (1) BioRED consists of biomedical relations among six commonly described entities (i.e., gene, disease, chemical, variant, species, and cell line) in eight different types (e.g., positive correlation). Such a setting supports developing a single general-purpose RE system in biomedicine with reduced resources and improved efficiency. More importantly, several previous studies have shown that training a machine-learning algorithm on multiple concepts simultaneously on one dataset, rather than multiple single-entity datasets, can lead to better performance [11-13]. We expect similar outcome with our dataset for both NER and RE tasks. (2) The annotated relations can be asserted either within or across sentence boundaries. For example, as shown in Figure 1 (relation R5 in pink), the variant “D374Y” of the PCSK9 gene and the causal relation with disease “autosomal dominant hypercholesterolemia” are in different sentences. This task therefore requires relations to be inferred by machine reading across the entire document. (3) Finally, our corpus is enriched with novelty annotations. This novel task poses new challenges for (biomedical) RE research and enables the development of NLP systems to distinguish between known facts and novel findings, a greatly needed feature for extracting new knowledge and avoiding duplicate information towards the automatic knowledge construction in biomedicine.

![Figure 1. An example of a relation and the relevant entities displayed on TeamTat (https://www.teamtat.org).](https://www.teamtat.org)

To assess the challenges of BioRED, we performed benchmarking experiments with several state-of-the-art methods, including BERT-based models. We find that existing deep-learning systems perform well on the NER task but only modestly on the novel RE task, leaving it an open problem for future NLP research. Furthermore, the detailed analysis of the results confirms the benefit of using such a comprehensive dataset towards creating more accurate, efficient, and robust RE systems in biomedicine.
2 Overviews of NER/NEL/RE Datasets

2.1 NER/NEL

Existing NER/NEL datasets cover most of the key biomedical entities, including gene/proteins [14-16], chemicals [17, 18], diseases [5, 19], variants [20-22], species [23, 24], and cell lines [25]. Nonetheless, NER/NEL datasets usually focus on only one concept type; the very few datasets that annotate multiple concept types [26, 27] do not contain relation annotations. Table 1 summarizes some widely used gold NER/NEL datasets including the annotation entity type, corpus size and the task applications.

Table 1. Overview of gold standard NER/NEL datasets.

| Dataset          | Text size   | Entity type (#mentions)             | Task type |
|------------------|-------------|-------------------------------------|-----------|
| JBLPBA [26]      | 2,404 abstracts | Protein (35,336), DNA (10,589), RNA(1,069), cell line (4,330) and cell type (8,639) | NER       |
| NCBI Disease [19]| 793 abstracts | Disease (6,892)                      | NER, NEL  |
| CHEMDNER [18]    | 10,000 abstracts | Chemical (84,355)                    | NER       |
| CDR [5]          | 1,500 abstracts | Chemical (4,409), Disease (5,818)   | NER, NEL  |
| LINNAEUS [24]    | 100 PMC full text | Species (4,259)                    | NER       |
| tmVar [20]       | 500 abstracts | Variant (1,431)                      | NER, NEL  |
| NLM-Gene [14]    | 550 abstracts | Gene (15,553)                        | NER, NEL  |
| GNormPlus [28]   | 694 abstracts | Gene (9,986)                         | NER, NEL  |

Due to the limitation of the entity type in NER datasets, most of the state-of-the-art entity taggers were developed individually for a specific concept. A few studies (e.g., PubTator [29]) integrate multiple entity taggers and apply them to specific collections or even to the entire PubMed/PMC. In the development process, some challenging issues related to integrating entities from multiple taggers, such as concept ambiguity and variation emerged [30]. Moreover, the same articles need to be processed multiple times by multiple taggers. A huge storage space also is required to store the results of the taggers. In addition, based on clues from previous NER studies [28, 31], we realized that a tagger that trained with other concepts performs as well or even better than a tagger trained on only a single concept, especially for highly ambiguous concepts. A gene tagger GNormPlus trained on multiple relevant concepts (gene/family/domain) boosts the performance of a gene/protein significantly. Therefore, a comprehensive NER corpus can help develop a method that can recognize multiple entities simultaneously to reduce the hardware requirement and to achieve better performance. Only a very few datasets [27, 32] curate multiple concepts in the text, but no relation is curated in these datasets.

2.2 RE

A variety of RE datasets in the general domain have been constructed to promote the development of RE systems [5-10]. In the biomedical domain, most existing RE datasets focus on sentence-level relations involving a single pair of entities, such as protein-protein interactions [10], drug-drug interactions [9], and chemical-protein relations [33]. However, because many relations cross sentence boundaries, moving research from the sentence level to the document level is a popular trend, and some general-domain RE datasets (e.g., DocRED [34], DocOIE [35]) have recently been constructed with document-level relations.

In biomedicine, several sentences are often required to describe an entire biological process or relation. We highlight some commonly used biomedical relation extraction datasets in Table 2 (complete datasets review can be found in Supplementary Materials Table S4). Most of the datasets were annotated with relations in a single sentence only, and very few datasets contain relations across multiple sentences (e.g. CDR dataset [36]).
Table 2. A summary of biomedical RE and event extraction datasets. The value of “-” means that we could not find the number in their papers or websites. The SEN/DOC Level means that whether the relation annotation is annotated in “Sentence,” “Document,” or “Cross-sentence.” “Document” includes abstract, full-text, or discharge record. “Cross-sentence” allows two entities within a relation appear in three surrounding sentences.

| Dataset | # Doc./Sent. | # Entity | # Relation | SEN/DOC Level | Description |
|---------|--------------|----------|------------|---------------|-------------|
| Protein-protein interaction | | | | | |
| AImed [37] | 230 abstracts | 4,141 genes | 1,101 relations | Sentence | The AImed dataset aims to develop and evaluate protein name recognition and protein-protein interaction (PPI) extraction. It contains 750 Medline abstracts, which contain the "human" word, and has 5206 gene names. Two hundred abstracts previously known to contain protein interactions for PPI extraction were obtained from the Database of Inter-Acting Proteins (DIP) [55] and tagged for both 1101 protein interactions and 4141 protein names. Because negative examples for protein interactions were rare in the 200 abstracts, they manually selected 30 additional abstracts with more than one gene but did not have any gene interactions. A PPI dataset uses ontologies defining the fine-granted types of entities (like "protein family or group") and "protein complex" and their relationships (like "CONTAIN" and "CAUSE"). They developed a corpus of 1100 sentences containing full dependency annotation, dependency types, and comprehensive annotation of bio-entities and their relationships. |
| BioInfer [38] | 1,100 sentences | 4,573 proteins | 2,662 relations | Sentence | The BioInfer [38] PPI protein interaction pairs subtask (IPS) provides 750 and 356 full texts for training and test sets, respectively. The full text includes corresponding gene mention symbols and PPI pairs. |
| BioCreative II [9] | 1,098 full-texts | - | - | Document | The BioCreative II PPI protein interaction pairs subtask (IPS) provides 750 and 356 full texts for training and test sets, respectively. The full text includes corresponding gene mention symbols and PPI pairs. |
| Chemical-protein interaction | | | | | |
| DrugProt [48] | 5,000 abstracts | 65,561 chemicals, 61,775 genes | 24,526 relations | Sentence | The DrugProt dataset aims to promote the development of chemical-gene RE systems, an extension of the ChemProt dataset. The addressed 13 different chemical-gene relations, including regulatory, specific, and metabolic relations. |
| Chemical-disease interaction | | | | | |
| CDR [36] | 1,500 abstracts | 15,935 chemicals; 12,850 diseases | 3,106 relations | Document | CDR consists of 1,500 abstracts that chemical and disease mention annotations and their IDs. It annotates chemical-induced disease relation ID pair. There are 1,400 abstracts selected from a CTD collaboration-related dataset, and the remaining 100 articles are new curation and are used in the test set. |
| Drug-drug interaction and Drug-ADE interaction | | | | | |
| SemEval 2013 DDEExtraction [9] | 905 documents | 13,107 drugs | 5,028 relations | Sentence | It consists of 792 texts selected from the DrugBank database and 233 Medline abstracts. The corpus is annotated with 18,502 pharmacological substances and 5,028 DIDs, including both pharmacokinetic (PK) and pharmacodynamic (PD) interactions. The discharge summaries are from the clinical care database of the MIMIC-III (Medical Information Mart for Intensive Care-III). The summaries are manually selected to contain at least 1 ADE and annotated with nine concepts and eight relation pairs. The data are split into 303 and 202 for training and test sets, respectively. |
| n2c2 2018 ADE [54] | 505 summaries | 83,869 entities | 59,810 relations | - | It contains both 1000 abstracts (from RENET [57]) and 500 full-texts from PMC open-access subset. For a better quality, 500 abstracts of the dataset were refined. Authors used the 500 abstracts to train the RENET2 model and conduct their training data expansion using the other 500 abstracts. They further used the model trained on 1,000 abstracts to construct 500 full-text articles. |
| Variant/gene-disease interaction | | | | | |
| EMU [21] | 110 abstracts | - | 179 relations | Document | The EMU dataset focuses on finding relationships between mutations and their corresponding disease phenotypes. They use "MeSH + mutation" to select abstracts and use MetaMap to annotate the abstracts that are divided into containing mutations related to prostate cancer (PCa) and breast cancer (BCa). They then use rules and patterns to select subsets of PCa and BCa for annotation. |
| RENET2 [56] | 1,000 abstracts, 500 full-texts | - | - | Document | It contains both 1000 abstracts (from RENET [57]) and 500 full-texts from PMC open-access subset. For a better quality, 500 abstracts of the dataset were refined. Authors used the 500 abstracts to train the RENET2 model and conduct their training data expansion using the other 500 abstracts. They further used the model trained on 1,000 abstracts to construct 500 full-text articles. |
| Drug-gene-mutation | | | | | |
| N-ary dataset [58] | - | - | 3,462 triples; 137,469 drug-gene relations; 3,192 drug-gene mutation relations; | Cross-sentence | Authors use distant supervision to construct a cross-sentence drug-gene-mutation RE dataset. They use 59 distinct drug-gene-mutation triples from the knowledge bases to extract 3,462 ternary positive relation triples. The negative instances are generated by randomly sampling the entity pairs/triples without interaction. |
| Event extraction | | | | | |
| BioNLP ST 2013 CG [59] | 600 abstracts | 21,683 entities | 17,248 events; 917 relations | Sentence | The Cancer Genetics (CG) corpus contains annotations of over 17,000 events in 600 documents. The task addresses entities and events at all levels of biological organization, from the molecular to the whole organism, and involves pathological and physiological processes. |
| BioNLP ST 2011 GE [26, 27, 60] | 1,210 abstracts, 14 full-texts | 21,616 proteins | 18,047 events | Sentence | The GENIA event (GE) task follows the task definition of BioNLP shared task (ST) 2009, which is briefly described in this section. BioNLP ST 2011 took the role of measuring the progress of the community and generalization IE technology to the full papers. As the first BioNLP shared task, it aimed to define a bounded, well-defined bio event extraction task, considering both the actual needs and the state of the art in bio-TM technology and to pursue it as a community-wide effort. |
Besides, most of the datasets focus on single entity pair. Such like AIMed [37], BiolInfer [38], HPRD50 [39], IEPA [40], and LLL [41] datasets dedicate on the protein-protein interaction (PPI), and are widely used for developing RE systems [42-47]. Some datasets have more granular relation categories. For example, SemEval 2013 DDIExtraction [9] annotated four categories (i.e., advise, int, effect, and mechanism) of the drug-drug interaction, ChemProt [33] annotated five categories, and DrugProt [48], an extension of ChemProt, annotated thirteen categories. Recently, ChemProt and DDI are widely used in evaluating the abilities of pre-trained language models [49-52] on RE tasks.

Moreover, BioNLP shared task datasets [59, 60, 62, 63] aim to promote biological activity extraction, where the causal relationships and biological conditions should be extracted. Therefore, they provide fine-grained biological event annotations (biological relation is called “event,” and co-reference is called “relation”). For instance, BioNLP cancer genetic (CG) dataset [59] defined 22 entity types/subtypes and 38 relation type/subtypes. In the dataset, the biological relationship between entities (or their biological function) is connected with an event trigger (usually a verb). Also, the biological conditions, like location, and event modification (e.g., NEGATION or SPECULATION) are required to be identified.

In sentence-level relation where curators are usually not allowed to use external resources/databases and the context of surrounding sentences while annotating. Therefore, most sentence-level RE datasets do not provide concept identifiers (e.g., NCBI Gene ID) to the named entities. However, the development of the cross-sentence RE dataset is highly relying on the concept identifiers. However, very limited biomedical datasets provide cross-sentence relation annotations with concept identifiers, because annotating the concept identifiers is much more time-consuming than just recognizing the boundaries of the entities. CDR dataset [36] is a widely-used chemical-induced disease relation dataset, and annotated relations at the document-level. It annotates 1,500 abstracts, and each contains the chemicals, genes, IDs, and chemical-induced disease ID pairs. However, it only annotated the chemical-induced disease relation category, but not others (e.g., treatment relation). Peng et al. [58] developed a cross-sentence n-ary relation extraction dataset with drug-gene-mutation (ternary) relation and drug-mutation (binary) relation. However, the dataset is constructed via the distant supervision with inevitable wrong labeling problem [34] but not manual curation. In Table 3, we compare BioRED to representative biomedical relation and event extraction datasets.

### Table 3. Comparison of the BioRED corpus with representative relation and event extraction datasets. D = Disease, G = Gene, C = Chemical, and V = Variant.

|       | <D,G> | <D,C> | <D,V> | <C,C> | <C,G> | <G,G> | <V,C> | <V,V> |
|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| RENET2      | ✓     |       |       |       |       |       |       |       |
| CDR         |       | ✓     |       |       |       |       |       |       |
| EMU         |       |       | ✓     |       |       |       |       |       |
| DDI         |       |       |       | ✓     |       |       |       |       |
| DrugProt    |       |       |       |       | ✓     |       |       |       |
| AIMed       |       |       |       |       |       | ✓     |       |       |
| GE          |       |       |       |       |       | ✓     |       |       |
| N-ary       |       |       |       |       |       | ✓     | ✓     |       |
| CG          | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     |
| BioRED      | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     |

### 3 Methods

#### 3.1 Annotation definition/scope
We first analyzed a set of public PubMed search queries by tagging different entities and relations. This data-driven approach allowed us to determine a set of key entities and relations of interest that should be most representative, and therefore the focus of this work. Some entities are closely related biologically and are thus used interchangeably in this work. For instance, protein, mRNA, and some other gene products typically share the same names and symbols. Thus, we merged them to a single gene class, and similarly merged symptoms and syndromes to single disease class. In the end, we have six concept types: (1) Gene: for genes, proteins, mRNA and other gene products. (2) Chemical: for chemical and drugs, (3) Disease: for diseases, symptoms, and some disease-related phenotypes. (4) Variant: for genomic/protein variants (including substitutions, deletions, insertions, and others). (5) Species: for species in the hierarchical taxonomy of organisms. (6) CellLine: for cell lines. Due to the critical problems of term variation and ambiguity, entity linking (also called entity normalization) is also required. We linked the entity spans to specific identifiers in an appropriate database or controlled vocabulary for each entity type (e.g., NCBI Gene ID for genes).

![Diagram of entity types and relations](image)

**Figure 2.** Relations annotated in BioRED corpus. (a) Categorized relations between concepts. The patterns of the lines between the concepts present the categories: (▬) Popular associations: The concept pairs are frequently discussed in the biomedical literature. (═) Implied associations e.g., the name of a gene can imply the corresponding species. (---) Rarely discussed associations: Some other relation types are rarely discussed in the biomedical text (and this is why the concept Cell Line is not listed here). (b) The mapping between the concept pairs and the relation types. The frame widths of the concept pairs/relation types and the bold lines between the two sides proportionally represent the frequencies.

Between any of two different entity types, we further observed eight popular associations that are frequently discussed in the literature: \(<D,G>\) for \(<\text{Disease}, \text{Gene}>\); \(<D,C>\) for \(<\text{Disease}, \text{Chemical}>\), \(<G,C>\) for \(<\text{Gene}, \text{Chemical}>\), \(<G,G>\) for \(<\text{Gene}, \text{Gene}>\), \(<D,V>\) for \(<\text{Disease}, \text{Variant}>\), \(<C,V>\) for \(<\text{Chemical}, \text{Variant}>\), \(<C,C>\) for \(<\text{Chemical}, \text{Chemical}>\) and \(<V,V>\) for \(<\text{Variant}, \text{Variant}>\). For relations between more than two entities, we simplified the relation to multiple relation pairs. For example, we simplified the chemicals co-treat disease relation (“bortezomib and dexamethasone co-treat multiple myeloma”) to three relations: \(<\text{bortezomib}, \text{multiple myeloma}, \text{treatment}>\), \(<\text{dexamethasone}, \text{multiple myeloma}, \text{treatment}>\), and \(<\text{bortezomib}, \text{dexamethasone}, \text{co-treatment}>\) (treatment is categorized in the Negative Correlation). Other associations between two concepts are either implicit (e.g., variants frequently located within a gene) or rarely discussed. Accordingly, in this work we focus on annotating those eight concept pairs, as shown in solid lines in Figure 2a. To further characterize relations between entity pairs, we used eight biologically meaningful and non-directional relation types (e.g.,
positive correlation; negative correlation) in our corpus as shown in Figure 2b. The details of the relation types are described in our annotation guideline.

3.2 Annotation process
In order to be consistent with previous annotation efforts, we randomly sampled articles from several existing datasets (i.e., NCBI Disease[19], NLM-Gene [14], GNormPlus [28], CDR [5], tmVar [20, 64]). A small set of PubMed articles were first used to develop our annotation guidelines and familiarize our annotators with both the task and TeamTat [65], a web-based annotation tool equipped to manage team annotation projects efficiently. Following previous practice in biomedical corpus development, we developed our annotation guidelines and selected PubMed articles consistently with previous studies. Furthermore, to accelerate entity annotation, we used automated pre-annotations (i.e., PubTator [29]), which can then be edited based on human judgment. Unlike entity annotation, each relation is annotated from scratch by hand with an appropriate relation type.

Every article in the corpus was first annotated by three annotators with background in biomedical informatics to prevent erroneous and incomplete annotations (especially relations) due to manual annotation fatigue. If an entity or a relation cannot be agreed upon by the three annotators, this annotation was then reviewed by another senior annotator with background in molecular biology. For each relation, two additional biologists assessed whether it is novel finding vs. background information and made the annotation accordingly. We annotated the entire set of 600 abstracts in 30 batches of 20 articles each. For each batch, it takes approximately 2 hours per annotator to annotate entities, 8 hours for relations, and 6 hours for assigning novel vs. background label. The details of the data sampling and annotation rules are described in our annotation guideline.

3.3 Data Characteristics
The BioRED corpus contains a total of 20,419 entity mentions, corresponding to 3,869 unique concept identifiers. We annotated 6,503 relations in total. The proportion of novel relations among all annotated relations in the corpus is 69%. Table 4 shows the numbers of the entities (mentions and identifiers) and relations in the training, development, and test sets.

Table 4. Number of entity (mention and identifier) and relation annotations in the BioRED corpus, and their distribution between the training, development, and test sets. The parenthesized numbers are the unique entities linked with concept identifiers.

| Annotation       | Training | Dev  | Test  | Total |
|------------------|----------|------|-------|-------|
| Document         | 400      | 100  | 100   | 600   |
| All              | 13,351 (2,708) | 3,533 (956) | 3,535 (982) | 20,419 (3,869) |
| Gene             | 4,430 (1,141)  | 1,087 (368)  | 1,180 (399)  | 6,697 (1,643)  |
| Disease          | 3,646 (576)   | 982 (244)    | 917 (244)    | 5,545 (778)    |
| Chemical         | 2,853 (486)   | 822 (184)    | 754 (170)    | 4,429 (651)    |
| Variant          | 890 (420)     | 250 (135)    | 241 (137)    | 1,381 (678)    |
| Species          | 1,429 (37)    | 370 (13)     | 393 (11)     | 2,192 (47)     |
| Cell Line        | 103 (48)      | 22 (12)      | 50 (21)      | 175 (72)       |
| Relation         | 4,178        | 1,162        | 1,163        | 6,503          |
| Relation pair with novelty findings | 2,838 | 835 | 859 | 4,532 |
In addition, we computed the inter-annotator-agreement (IAA) for entity, relation, and novelty annotations, where we achieved 97.01%, 77.91%, and 85.01%, respectively. Figure 3.3 depicts the distribution of the different concept pairs in the relations.

![Figure 3. The distribution of concept pairs and relation types in the BioRED corpus.](image)

We also analyzed dataset statistics per document. The average document length consists of 11.9 sentences or 304 tokens. 34 entity spans (3.8 unique entity identifiers) and 10.8 relations are annotated per document. Among the relation types, 52% are associations, 27% are positive correlations, 17% are negative correlations, and 2% are involved in the triple relations (e.g., two chemicals co-treat a disease).

### 3.4 Benchmarking methods

To assess the utility and challenges of the BioRED corpus, we conducted experiments to show the performance for leading RE models. For the NER task, each mention span was considered separately. We evaluate three state-of-the-art NER models on the corpus including BiLSTM-CRF, BioBERT-CRF and PubMedBERT-CRF. The input documents are first split into multiple sentences and encoded into a hidden state vector sequence by Bidirectional Long Short-Term Memory (BiLSTM) [66], BioBERT [52], PubMedBERT [50], respectively. The models predicted the label corresponding to each of the input tokens in the sequence, and then computed the network score using a fully connected layer, and decode the best path of the tags in all possible paths by using Conditional Random Field (CRF) [67]. Here, we used the BIO (Begin, Inside, Outside) tagging scheme to the CRF layer.

We chose two BERT-based models, BERT-GT [68] and PubMedBERT [69], for evaluating the performance of current RE systems on the BioRED corpus. The first model is BERT-GT, which defines a graph transformer through integrating a neighbor-attention mechanism into the BERT architecture to avoid the effect of the noise from the longer text. BERT-GT was specifically designed for document-level relation extraction tasks and utilizes the entire sentence or passage to calculate the attention of the current token, which brings significant improvement to the original BERT model. PubMedBERT is a pretrained biomedical language model based on transformer architecture. It is currently a state-of-the-art text-mining method, which applies the biomedical domain knowledge (biomedical text and vocabulary) for the BERT pretrained language model. In the benchmarking, we used the text classification framework for the RE model development.

For both NER and RE evaluations, the training and development sets were first used for model development and parameter optimization before a trained model is evaluated on the test set. Benchmark implementation details are provided in Supplementary Materials A.1. Standard Precision, Recall and F-score metrics are used. To allow approximate entity matching, we also applied relaxed versions of F-score to evaluate NER. In this
case, as long as the boundary of the predicted entity overlaps with the gold standard span, it is considered as a successful prediction.

4 Results

4.1 NER results on the test set

Table 5 shows the evaluation of NER on the test set. The first run is evaluated by strict metrics. The concept type and boundary of the entity should exactly match the entity in the text. The second run is evaluated by relaxed metrics, which is the approximate matching. Unlike BiLSTM-CRF, the BERT-based methods contain well pre-trained language models for extracting richer features, hence achieving better performance overall. Further, PubMedBERT performs even better than BioBERT on genes, variants, and cell lines. BioBERT uses the original BERT model’s vocabulary generated from general domain text, which causes the lack of understanding on the biomedical entities. On the contrary, PubMedBERT generates the vocabulary from scratch using biomedical text, and it achieves the highest F-score (89.3% in strict metric).

Table 5. Performance of NER models on test set. All numbers are F-scores. G = Gene, D = Disease, C = Chemical, S = Species, CL = CellLine, and V = Variant.

| Metric  | Method         | All  | G    | D    | C    | S    | CL   | V    |
|---------|----------------|------|------|------|------|------|------|------|
|         | BiLSTM-CRF     | 87.1 | 87.3 | 83.3 | 88.2 | 96.3 | 80.9 | 82.9 |
| Strict  | BioBERT-CRF    | 88.7 | 89.5 | 84.8 | 89.7 | 96.7 | 83.5 | 83.9 |
|         | PubMedBERT-CRF | **89.3** | **92.4** | 83.5 | 88.6 | **97.0** | **90.5** | **87.3** |
| Relaxed | BiLSTM-CRF     | 93.2 | 93.1 | 92.8 | **92.2** | 96.8 | 85.4 | 94.4 |
|         | BioBERT-CRF    | 93.8 | 94.2 | **94.2** | 91.4 | **97.0** | 90.1 | 92.9 |
|         | PubMedBERT-CRF | **94.1** | **95.0** | 93.6 | 91.3 | **97.0** | **92.6** | **95.9** |

4.2 RE results on the test set

We also evaluated performance on the RE task by different benchmark schemas: (1) entity pair: to extract the pair of concept identifiers within the relation, and (2) entity pair + relation type: to recognize the specific relation type for the extracted pairs, and (3) entity pair + relation type + novelty: to further label the novelty for the extracted pairs. In this task, the gold-standard concepts in the articles are given. We applied BERT-GT and PubMedBERT to recognize the relations and the novelty in the test set.

As shown in Table 6, the overall performance of PubMedBERT is higher than that of BERT-GT in all schemas. Because the numbers of relations in <D,V>, <C,V> and <V,V> are low, their performance is not comparable to that of other concept pairs, especially <V,V> (the F-score is 0% for two models). In the first schema, BERT-GT and PubMedBERT can achieve performance above 72% for the F-scores, which is expected and promising in the document-level RE task. To predict the relation types (e.g., positive correlation) other than entity pairs, however, is still quite challenging. The best performance on the second schema is only 58.9%, as the number of instances in many relation types is insufficient. The performances on different relation types of our best model using PubMedBert are provided in Supplementary Materials A.2. The performance on the third schema dropped to 47.7%. In some cases, the statements of the relations in abstracts are usually concise, and the details of the relation mechanism can only be found in the full text.
Table 6. Performance on RE task for the first schema: extracting the entity pairs within a relation, second schema: extracting the entity pairs and the relation type, and the third schema: further labeling the novelty for the extracted pairs. All numbers are F-scores. The <G,D> is the concept pair of the gene (G) and the disease (D). The columns of those entity pairs present the RE performance in F-scores. G = gene, D = disease, V = variant, and C = chemical.

| Eval Schema | Method   | All | <G,D> | <G,G> | <G,C> | <D,V> | <C,D> | <C,V> | <C,C> |
|-------------|----------|-----|-------|-------|-------|-------|-------|-------|-------|
| Entity pair | BERT-GT  | 72.1| 63.8  | 78.5  | 77.7  | 69.8  | 76.2  | 58.8  | 74.9  |
|             | PubMedBERT | 72.9| 67.2  | 78.1  | 78.3  | 67.9  | 76.5  | 58.1  | 78.0  |
| +Relation type | BERT-GT | 56.5| 54.8  | 63.5  | 60.2  | 42.5  | 67.0  | 11.8  | 52.9  |
|             | PubMedBERT | 58.9| 56.6  | 66.4  | 59.9  | 50.8  | 65.8  | 25.8  | 54.4  |
| +Novelty | BERT-GT | 44.5| 37.5  | 47.3  | 55.0  | 36.9  | 51.9  | 11.8  | 48.5  |
|             | PubMedBERT | 47.7| 40.6  | 54.7  | 54.8  | 42.8  | 51.6  | 12.9  | 50.3  |

4.3 Benefits of multiple entity recognition and relation extraction.

To test the hypothesis that our corpus can result in a single model with better performance, we trained multiple separate NER and RE models, each with an individual concept (e.g., gene) or relation (e.g., gene-gene) for comparison. We used PubMedBERT for this evaluation since it achieved the best performances in both the NER and RE tasks. As shown in Table 7, both models trained on all entities or relations generally perform better than the models trained on most of the entities or relations, while the improvement for RE is generally larger. The performance on NER and RE tasks are both obviously higher in the single model. Especially for entities and relations (e.g., cell lines and chemical-chemical relations) with insufficient amounts, the model trained on multiple concepts/relations can obtain larger improvements. The experiment demonstrated that training NER/RE models with more relevant concepts or relations not only can reduce resource usage but also can achieve better performance.

Table 7. The comparison of the models trained on all entities/relations to the models trained on individual entity/relation. The <G,D> is the relation of the gene (G) and the disease (D). G = gene, D = disease, C = chemical, V = variant, S = species, and CL = cell line. All models are evaluated by strict metrics.

| Entity /Relation | Type | All entities or relations | Single entity or relation |
|------------------|------|--------------------------|--------------------------|
|                  |      | P | R | F | P | R | F |
| Entity           | G    | 92.2 | 92.5 | 92.4 | 90.8 | 91.0 | 90.9 |
|                  | D    | 80.7 | 86.5 | 83.5 | 83.2 | 85.7 | 84.4 |
|                  | C    | 87.9 | 89.3 | 88.6 | 87.3 | 92.4 | 89.8 |
|                  | V    | 88.8 | 85.9 | 87.3 | 84.7 | 87.1 | 85.9 |
|                  | S    | 95.8 | 98.2 | 97.0 | 95.2 | 96.4 | 95.8 |
|                  | CL   | 95.6 | 86.0 | 90.5 | 77.1 | 74.0 | 75.5 |
| Relation         | <G,D>| 63.6 | 71.2 | 67.2 | 75.8 | 62.7 | 68.7 |
|                  | <G,G>| 81.5 | 75.0 | 78.1 | 57.3 | 80.0 | 66.8 |
|                  | <G,C>| 74.1 | 83.1 | 78.3 | 66.7 | 68.9 | 67.8 |
|                  | <D,V>| 71.2 | 64.9 | 67.9 | 76.5 | 51.5 | 61.5 |
|                  | <C,D>| 73.3 | 79.9 | 76.5 | 78.2 | 85.2 | 81.5 |
|                  | <C,V>| 60.0 | 56.3 | 58.1 | 53.3 | 50.0 | 51.6 |
|                  | <C,C>| 75.3 | 80.9 | 78.0 | 64.2 | 72.3 | 68.0 |
4.4 Discussion

The relaxed NER results in Table 5 for all entity types are over 93% for all methods, suggesting the maturity of current tools for this task. If considering the performance of each concept individually, the recognition of genes, species and cell lines can reach higher performance (over 90% in strict F-score) since the names are often simpler and less ambiguous than other concepts. The best model for genomic variants achieves an F-score of 87.3% in strict metrics and 95.9% in relaxed metrics, which suggests that the majority of the errors are due to incorrect span boundaries. Most variants are not described in accordance with standard nomenclature (e.g., “ACG-->AAG substitution in codon 420”), thus it is difficult to exactly identify the boundaries. Like genomic variants, diseases are difficult to be identified due to term variability and most errors are caused by mismatched boundaries. For example, our method recognized a part (“papilledema”) of a disease mention (“bilateral papilledema”) in the text. Disease names also present greater diversity than other concepts: 55.4% of the disease names in the test set are not present in the training/development sets. Chemical names are extremely ambiguous with other concepts: half of the errors for chemicals are incorrectly labeled as other concept types (e.g., gene), since some chemicals are interchangeable with other concepts, like proteins and drugs.

Experimental results in Table 6 show that the RE task remains challenging in biomedicine, especially for the new task of extracting novel findings. In our observation, there are three types of errors in novelty identification. First, some abstracts do not indicate which concept pairs represent novel findings, and instead provide more details in the full text. Such cases confused both the human annotators and the computer algorithms. Second, when the mechanism of interaction between two relevant entities is unknown, and the study aims to investigate it but the hypothesized mechanism is shown to be false. Third, authors frequently mention relevant background knowledge within their conclusion. As an example, “We conclude that Rg1 may significantly improve the spatial learning capacity impaired by chronic morphine administration and restore the morphine-inhibited LTP. This effect is NMDA receptor dependent.” in the conclusion of the PMID:18308784, the Rg1 responded to morphine as a background knowledge. But it is mentioned together with the novelty knowledge pair <Rg1, NMDA receptor>. In this case, our method misclassified the pair < Rg1, morphine> as Novel.

The results in Table 7 demonstrate that training NER/RE models on one comprehensive dataset with multiple concept/relations simultaneously can not only make the trained model simpler and more efficient, but also more accurate. More importantly, we notice that for the entities and relations with lower number of training instances (e.g., cell lines and chemical-chemical relations), simultaneous prediction is especially beneficial for improving performance. Additionally, merging entity results from different model often poses some challenges, such as ambiguity or overlapping boundaries between different concepts.

5 Conclusion

In the past, biomedical RE datasets were typically built for a single entity type or relation. To enable the development of RE tools that can accurately recognize multiple concepts and their relations in biomedical texts, we have developed BioRED, a high-quality RE corpus, with one-of-a-kind novelty annotations. Like other commonly used biomedical datasets, e.g., BC5CDR [5], we expect BioRED to serve as a benchmark for not only biomedical-specific NLP tools but also for the development of RE methods in general domain. Additionally, the novelty annotation in BioRED proposes a new NLP task that is critical for information extraction in practical applications. Recently, the dataset was successfully used by the NIH LitCoin NLP Challenge (https://ncats.nih.gov/funding/challenges/litcoin) and a total of over 200 teams participated in the Challenge.

This work has implications for several real-world use cases in medical information retrieval, data curation, and knowledge discovery. Semantic search has been commonly practiced in the general domain but much less so in biomedicine. For instance, several existing studies retrieve articles based on the co-occurrence of two entities [70-73] or rank search results by co-occurrence frequency. Our work could accelerate the development of
L. Luo et al.

semantic search engine in medicine. Based on the extracted relations within documents, search engines can semantically identify articles by two entities with relations (e.g., 5-FU-induced cardiotoxicity) or by expanding the user queries from an entity (e.g., 5-FU) to the combination of the entity and other relevant entities (e.g., cardiotoxicity, diarrhea).

While BioRED is a novel and high-quality dataset, it has a few limitations. First, we are only able to include 600 articles in the BioRED corpus due to the prohibitive cost in manual annotation and limited resources. Nonetheless, our experiments show that except for few concept pairs and relation types (e.g. variant-variant relations) that occur infrequently in the literature, its current size is appropriate for building RE models. Our experimental results in Table 7 also show that in some cases, the performance on entity class with small number of training instances (e.g. Cell Line) can be significantly boosted when training together with other entities in one corpus. Second, the current corpus is developed on PubMed abstracts, as opposed to full text. While full text contains more information, data access remains challenging in real-world settings. More investigation is warranted on this topic in the future.

Acknowledgements

The authors would like to thank Dr. Tyler F. Beck, Scientific Program Officer at the NCATS and his entire research team for help with our dataset. The authors would like to thank Rancho BioSciences and specifically, Mica Smith, Thomas Allen Ford-Hutchinson, and Brad Farrell for their contribution with data curation.

Funding

This work was supported by the National Institutes of Health intramural research program, National Library of Medicine and partially supported by the NIH grant 2U24HG007822-08 to CNA.

Conflict of Interest: none declared.

References

1. Singhal, A., M. Simmons, and Z. Lu, Text mining genotype-phenotype relationships from biomedical literature for database curation and precision medicine. PLoS computational biology, 2016. 12(11): p. e1005017.
2. Lee, K., et al., BRONCO: Biomedical entity Relation ONcology CORpus for extracting gene-variant-disease-drug relations. Database, 2016. 2016.
3. Wei, C.-H., et al., Assessing the state of the art in biomedical relation extraction: overview of the BioCreative V chemical-disease relation (CDR) task. Database, 2016. 2016: p. baw032.
4. Baptista, D., P.G. Ferreira, and M. Rocha, Deep learning for drug response prediction in cancer. Briefings in bioinformatics, 2021. 22(1): p. 360-379.
5. Li, J., et al., BioCreative V CDR task corpus: a resource for chemical disease relation extraction. Database, 2016. 2016: p. baw068.
6. Hendrickx, I., et al. Semeval-2010 task 8: Multi-way classification of semantic relations between pairs of nominals. in ACL (Workshop on Semantic Evaluation). 2019.
7. Walker, C., et al. ACE 2005 Multilingual Training Corpus. in Linguistic Data Consortium. 2006.
8. Zhang, Y., et al. Position-aware attention and supervised data improve slot filling. in Proceedings of the 2017 Conference on Empirical Methods in Natural Language Processing. 2017.
9. Herrero-Zazo, M., et al., The DDI corpus: An annotated corpus with pharmacological substances and drug–drug interactions. Journal of biomedical informatics, 2013. 46(5): p. 914-920.
10. Krallinger, M., et al., Overview of the protein-protein interaction annotation extraction task of BioCreative II. Genome biology, 2008. 9(2): p. 1-19.
11. Wang, X., et al., Multitask learning for biomedical named entity recognition with cross-sharing structure. BMC bioinformatics, 2019. 20(1): p. 1-13.
12. Wei, C.-H., H.-Y. Kao, and Z. Lu, GNormPlus: an integrative approach for tagging genes, gene families, and protein domains. BioMed research international, 2015. 2015: p. 918710.
BioRED: A Comprehensive Biomedical Relation Extraction Dataset

13. Akdemir, A. and T. Shibuya, Analyzing the Effect of Multi-task Learning for Biomedical Named Entity Recognition. arXiv preprint arXiv:00425, 2020.
14. Islamaj Doğan, R., et al., NLM-Gene, a richly annotated gold standard dataset for gene entities that addresses ambiguity and multi-species gene recognition. Journal of Biomedical Informatics, 2021. 118: p. 103779.
15. Morgan, A.A., et al., Overview of BioCreative II gene normalization. Genome biology, 2008. 9(2): p. 1-19.
16. Hirschman, L., et al., Overview of BioCreAtIvE task 1B: normalized gene lists. BMC bioinformatics, 2005. 6(1): p. S11
17. Islamaj Doğan, R., et al., NLM-Chem, a new resource for chemical entity recognition in PubMed full text literature. Scientific Data, 2021. 8(1): p. 1-12.
18. Krallinger, M., et al., The CHEMDNER corpus of chemicals and drugs and its annotation principles. Journal of cheminformatics, 2015. 7(1): p. 1-17.
19. Islamaj Doğan, R., R. Leaman, and Z. Lu, NCBI disease corpus: a resource for disease name recognition and concept normalization. Journal of biomedical informatics, 2014. 47: p. 1-10.
20. Wei, C.-H., et al., tmVar: a text mining approach for extracting sequence variants in biomedical literature. Bioinformatics, 2013. 29(11): p. 1433-1439.
21. Doughty, E., et al., Toward an automatic method for extracting cancer-and other disease-related point mutations from the biomedical literature. Bioinformatics, 2011. 27(3): p. 408-415.
22. Caporaso, J.G., et al., MutationFinder: a high-performance system for extracting point mutation mentions from text. Bioinformatics, 2007. 23(14): p. 1862-1865.
23. Pafilis, E., et al., The SPECIES and ORGANISMS resources for fast and accurate identification of taxonomic names in text. PLoS One, 2013. 8(6): p. e65390.
24. Gerner, M., G. Nenadic, and C.M. Bergman, LINNAEUS: a species name identification system for biomedical literature. BMC bioinformatics, 2010. 11(1): p. 1-17.
25. Arighi, C., et al. Bio-ID track overview. in BioCreative VI Challenge Evaluation Workshop. 2017.
26. Kim, J.-D., et al. Introduction to the bio-entity recognition task at JNLPGA. in Proceedings of the international joint workshop on natural language processing in biomedicine and its applications. 2004. Citeseer.
27. Bada, M., et al. Concept annotation in the CRAFT corpus. BMC bioinformatics, 2012. 13(1): p. 1-20.
28. Wei, C.-H., H.-Y. Kao, and Z. Lu, GNormPlus: an integrative approach for tagging genes, gene families, and protein domains. BioMed research international, 2015. 2015.
29. Wei, C.-H., et al., PubTator central: automated concept annotation for biomedical full text articles. Nucleic acids research, 2019. 47(W1): p. W587-W593.
30. Wei, C.-H., et al. Biomedical mention disambiguation using a deep learning approach. in Proceedings of the 10th ACM International Conference on Bioinformatics, Computational Biology and Health Informatics. 2019.
31. Leaman, R. and Z. Lu, TaggerOne: joint named entity recognition and normalization with semi-Markov Models. Bioinformatics, 2016. 32(18): p. 2839-2846.
32. Kim, J.-D., et al., GENIA corpus—a semantically annotated corpus for bio-textmining. Bioinformatics, 2003. 19(suppl_1): p. i180-i182.
33. Krallinger, M., et al. Overview of the BioCreative VI chemical-protein interaction Track. in Proceedings of the sixth BioCreative challenge evaluation workshop. 2017.
34. Yao, Y., et al. DocRED: A Large-Scale Document-Level Relation Extraction Dataset. in Association for Computational Linguistics. 2019.
35. Dong, K., et al. DocOIE: A Document-level Context-Aware Dataset for OpenIE. in Association for Computational Linguistics. 2021.
36. Wei, C.-H., et al., Assessing the state of the art in biomedical relation extraction: overview of the BioCreative V chemical-disease relation (CDR) task. Database: The Journal of Biological Databases and Curation, 2016. 2016.
37. Bunescu, R., et al., Comparative experiments on learning information extractors for proteins and their interactions. Artificial intelligence in medicine, 2005. 33(2): p. 139-155.
38. Pyysalo, S., et al., BioInfer: a corpus for information extraction in the biomedical domain. BMC bioinformatics, 2007. 8(1): p. 1-24.
39. Fundel, K., R. Küffner, and R. Zimmer, RelEx—Relation extraction using dependency parse trees. Bioinformatics, 2007. 23(3): p. 365-371.
40. Ding, J., et al., Mining MEDLINE: abstracts, sentences, or phrases?, in Biocomputing 2002. 2001, World Scientific. p. 326-337.
41. Nédellec, C. Learning language in logic-genic interaction extraction challenge. In 4. Learning language in logic workshop (LLL05). 2005. ACM-Association for Computing Machinery.

42. Airola, A., et al. All-paths graph kernel for protein-protein interaction extraction with evaluation of cross-corpus learning. BMC bioinformatics, 2008. 9(11): p. 1-12.

43. Yadav, S., et al. Feature assisted stacked attentive shortest dependency path based Bi-LSTM model for protein-protein interaction. Knowledge-Based Systems, 2019. 166: p. 18-29.

44. Li, Y., et al. Protein-protein interaction relation extraction based on multigranularity semantic fusion. Journal of Biomedical Informatics, 2021. 123: p. 103931.

45. Yu, K., et al. Automatic extraction of protein-protein interactions using grammatical relationship graph. BMC medical informatics decision making, 2018. 18(2): p. 35-43.

46. Ahmed, M., et al. Identifying protein-protein interaction using tree lstm and structured attention. In 2019 IEEE 13th international conference on semantic computing (ICSC). 2019. IEEE.

47. Zhang, H., et al. Deep residual convolutional neural network for protein-protein interaction extraction. IEEE Access, 2019. 7: p. 89354-89365.

48. Miranda, A., et al. Overview of DrugProt BioCreative VII track: quality evaluation and large scale text mining of drug-gene/protein relations. In Proceedings of the seventh BioCreative challenge evaluation workshop. 2021.

49. raj Kanakarajan, K., B. Kundumani, and M. Sankarasubbu. BioELECTRA: Pretrained Biomedical text Encoder using Discriminators. In Proceedings of the 20th Workshop on Biomedical Language Processing. 2021.

50. Gu, Y., et al. Domain-specific language model pretraining for biomedical natural language processing. ACM Transactions on Computing for Healthcare, 2021. 3(1): p. 1-23.

51. Alrowili, S. and K. Vijay-Shanker. BioM-Transformers: Building Large Biomedical Language Models with BERT, ALBERT and ELECTRA. In Proceedings of the 20th Workshop on Biomedical Language Processing. 2021. Online: Association for Computational Linguistics.

52. Lee, J., et al. BioBERT: a pre-trained biomedical language representation model for biomedical text mining. Bioinformatics, 2020. 36(4): p. 1234-1240.

53. Xenarios, I., et al. DIP: the database of interacting proteins: 2001 update. Nucleic acids research, 2001. 29(1): p. 239-241.

54. Henry, S., et al. 2018 n2c2 shared task on adverse drug events and medication extraction in electronic health records. Journal of the American Medical Informatics Association, 2019. 27(1): p. 3-12.

55. Aronson, A.R. Effective mapping of biomedical text to the UMLS Metathesaurus: the MetaMap program. In Proceedings of the AMIA Symposium. 2001. American Medical Informatics Association.

56. Su, J., et al. RENET2: high-performance full-text gene–disease relation extraction with iterative training data expansion. NAR Genomics Bioinformatics, 2021. 3(3): p. lqab062.

57. Wu, Y., et al. Renet: A deep learning approach for extracting gene-disease associations from literature. In International Conference on Research in Computational Molecular Biology. 2019. Springer.

58. Peng, N., et al. Cross-sentence n-ary relation extraction with graph lstms. Transactions of the Association for Computational Linguistics, 2017. 5: p. 101-115.

59. Pyysalo, S., et al. Overview of the cancer genetics and pathway curation tasks of bionlp shared task 2013. BMC bioinformatics, 2015. 16(10): p. 1-19.

60. Kim, J.-D., et al. Overview of genia event task in bionlp shared task 2011. In Proceedings of BioNLP shared task 2011 workshop. 2011.

61. Kim, J.-D., et al. Overview of BioNLP’09 shared task on event extraction. In Proceedings of the BioNLP 2009 workshop companion volume for shared task. 2009.

62. Bossy, R., et al. Overview of the gene regulation network and the bacteria biotope tasks in BioNLP’13 shared task. BMC bioinformatics, 2015. 16(10): p. 1-16.

63. Pyysalo, S., et al. Overview of the ID, EPI and REL tasks of BioNLP Shared Task 2011. In BMC bioinformatics. 2012. Springer.

64. Wei, C.-H., et al. tmVar 2.0: integrating genomic variant information from literature with dbSNP and ClinVar for precision medicine. Bioinformatics, 2018. 34(1): p. 80-87.

65. Islamaj Doğan, R., et al. TeamTat: a collaborative text annotation tool. Nucleic acids research, 2020. 48(W1): p. W5-W11.

66. Hochreiter, S. and J. Schmidhuber. Long short-term memory. Neural computation, 1997. 9(8): p. 1735-1780.

67. Lafferty, J., A. McCallum, and F.C. Pereira. Conditional random fields: Probabilistic models for segmenting and labeling sequence data. 2001.
68. Lai, P.-T. and Z. Lu, *BERT-GT: cross-sentence n-ary relation extraction with BERT and Graph Transformer*. Bioinformatics, 2020. 36(24): p. 5678-5685.

69. Gu, Y., et al., *Domain-specific language model pretraining for biomedical natural language processing*. ACM Transactions on Computing for Healthcare, 2020. 3(1): p. 1-23.

70. Allot, A., et al., *LitVar: a semantic search engine for linking genomic variant data in PubMed and PMC*. Nucleic Acids Research, 2018. 46(W1): p. W530–W536.

71. Thomas, P., et al., *GeneView: a comprehensive semantic search engine for PubMed*. Nucleic Acids Research, 2012. 40(W1): p. W585–W591.

72. Dörpinghaus, J., et al. *SCAIView-A Semantic Search Engine for Biomedical Research Utilizing a Microservice Architecture*. in SEMANTICS Posters&Demos. 2018.

73. Pang, X., et al., *Accelerating cancer research using big data with BioKDE platform*. 2018, AACR.
BioRED: A Comprehensive Biomedical Relation Extraction Dataset (Supplementary Materials)

A.1 Benchmark implementation details

Here we provide the implementation details of our methods. We firstly selected the hyper-parameters by random search [1] on development set. Then we merged the training and development sets to retrain the model. The number of training epochs is determined by early stopping strategy [2] according to the training loss. All models were trained and tested on the NVIDIA Tesla V100 GPU.

NER models: We evaluate three state-of-the-art NER models including BiLSTM-CRF, BioBERT-CRF and PubMedBERT-CRF. We used concatenation of word embedding and character-level features generated with a CNN input layer for BiLSTM-CRF. The two BERT-based models used BioBERT-Base-Cased v1.1\(^1\) and PubMedBERT-base-uncased-abstract\(^2\) with default parameter settings to build the encoders via the Hugging Face platform. We optimized BiLSTM-CRF using RMSprop with learning rate of 1e-3. The BERT-based models used Adam with learning rate of 1e-5. The other experimental hyper-parameters are shown in Table S1.

| General Hyper-parameter                  |       |
|-----------------------------------------|-------|
| Batch size                              | 32    |
| Epochs at most                          | 50    |
| Fully connection size                   | 128   |

| BiLSTM-CRF Hyper-parameter              |       |
|-----------------------------------------|-------|
| Character-level CNN hidden size         | 100   |
| Character-level CNN window size         | 3     |
| Word-level LSTM hidden size             | 512   |
| Word-level LSTM dropout rate            | 0.4   |
| Word embedding dimension                | 200   |
| Character embedding dimension           | 50    |

RE models: We applied two state-of-the-art RE models, PubMedBert and BERT-GT for both RE and novelty triage tasks. We first use two tags [SourceEntity] and [TargetEntity] to represent the source entities and target entities. Then, the tagged abstract turns to a text sequence as the input of the models. We use the [CLS]'s hidden layer and a softmax layer in the classification. We applied the source codes provided by BERT-GT to convert the corpus. BERT-GT used the pre-trained language model of BioBERT. The detailed hyper-parameters of both tasks are shown in Table S2.

---

\(^1\) https://huggingface.co/dmis-lab/biobert-base-cased-v1.1

\(^2\) https://huggingface.co/microsoft/BiomedNLP-PubMedBERT-base-uncased-abstract
Table S2. Hyper-parameter settings for RE and Novelty triage.

|             | RE                  | Novelty             |
|-------------|---------------------|---------------------|
|             | PubMedBERT | Bert-GT | PubMedBERT | Bert-GT |
| batch size  | 16        | 8       | 16        | 8       |
| epochs      | 10        | 30      | 10        | 30      |
| learning rate | 1e-5     | 1e-5    | 1e-5     | 1e-5    |
| sequence length | 512     | 512     | 512     | 512     |
| the others  | default   | default | default   | default |

A.2 Performances of different relation types on the test set

Here, we detailed the performances on different relation types of our best model using PubMedBert on the test set. The results are shown in Table S3. We filled "-" in table if the relation type doesn’t exist in the entity pairs.

Table S3. Performance of different relation types on relation extraction (RE) task. All numbers are F-scores. The <G,D> is the concept pair of the gene (G) and the disease (D). G = gene, D = disease, V = variant, and C = chemical.

| Relation Type       | <G,D> | <G,G> | <G,C> | <D,V> | <C,D> | <C,V> | <C,C> | <V,V> |
|---------------------|-------|-------|-------|-------|-------|-------|-------|-------|
| Association         | 60.0  | 61.9  | 45.6  | 51.5  | 25.5  | 32.6  | 25.5  | 0.0   |
| Positive_Correlation| 7.7   | 79.1  | 61.9  | 50.0  | 76.6  | 0.0   | 47.8  | -     |
| Negative_Correlation| 30.8  | 54.1  | 79.1  | 0.0   | 61.9  | 0.0   | 76.1  | -     |
| Cotreatment         | -     | -     | 66.7  | -     | -     | -     | 60.0  | -     |
| Drug_Interaction    | -     | -     | 0.0   | -     | -     | -     | 66.7  | -     |
| Bind                | -     | 57.1  | 54.5  | -     | -     | -     | -     | -     |
| Comparison          | -     | -     | -     | -     | -     | -     | 50.0  | -     |
| Conversion          | -     | -     | -     | -     | -     | -     | 0.0   | -     |
| Overall             | 56.6  | 66.4  | 59.9  | 50.8  | 65.8  | 25.8  | 54.4  | 0.0   |
| Dataset        | # Doc./Sent. | # Entity | # Relation | SEN/DOC Level | Description                                                                                                                                                                                                 |
|---------------|-------------|----------|------------|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Protein-protein interaction**                                                                                                                                   |
| Aimed [3]     | 230 abstracts | 4,141 genes | 1,101 relations | Sentence | The Aimed dataset aims to develop and evaluate protein name recognition and protein-protein interaction (PPI) extraction. It contains 750 Medline abstracts, which contain the “human” word, and has 5,206 names. Two hundred abstracts previously known to contain protein interactions for PPI extraction were obtained from the Database of Interacting Proteins (DIP) [4] and tagged for both 1,101 protein interactions and 4,141 protein names. Because negative examples for protein interactions were rare in the 200 abstracts, they manually selected 30 additional abstracts with more than one gene but did not have any gene interactions. |
| HPRD50 [5]    | 50 abstracts  | -        | 138 relations | Sentence  | They randomly selected 50 abstracts (called hprd50) from the Human Protein Reference Database (HPRD) [6] and manually annotated PPI, involving direct physical interactions, regulatory relations, and modifications (e.g., phosphorylation). There are 138 gene/protein relation pairs and 92 distinct pairs in abstracts. |
| Biolinfer [7] | 1100 sentences | 4,573 proteins | 2,662 relations | Sentence | A PPI dataset uses ontologies defining the fine-grained types of entities (like “protein family or group” and “protein complex”) and their relationships (like “CONTAIN” and “CAUSE”). They developed a corpus of 1,100 sentences containing full dependency annotation, dependency types, and comprehensive annotation of bio-entities and their relationships. |
| IEPA [8]      | 300 abstracts  | -        | -           | Document  | The Interaction Extraction Performance Assessment (IEPA) corpus consists of ~300 abstracts retrieved from MEDLINE using ten queries. Each query was the AND of two biochemical nouns which domain experts suggested. The studied set included approximately forty abstracts describing interaction(s) between the biochemicals in the query, plus those that contained the biochemicals but did not describe interactions between them that were also encountered. Thus the ten queries yielded ten sets of abstracts, with each abstract in a set containing both terms in the query corresponding to that set. |
| LLL [9]       | 167 sentences  | -        | 377 relations | Sentence  | The LLL05 challenge task aims to learn rules to extract protein/gene interactions in the form of relations from biology abstracts from the Medline bibliography database. The challenge aims to test the ability of ML systems to learn rules for identifying the gene/proteins that interact and their roles, agent or target. |
| BioCreative II PPI IPS [10] | 1,098 full-texts | -        | -           | Document  | The BioCreative II PPI protein interaction pairs subtask (IPS) provides 750 and 356 full texts for training and test sets, respectively. The full-text includes corresponding gene mention symbols and PPI pairs. |
| BioCreative II.5 IPT [11] | 122 full-texts | -        | -           | Document  | The BioCreative II.5 interaction pair task (IPT) provide 595 full-texts for both training (FEBS Letters articles from 2008) and test (FEBS Letters articles from 2007) sets. The full-texts include both with and without curatable protein interactions, and only 122 full-texts contain PPI annotations. |
| BioCreative VI PM[12] | 5,509 abstracts | -        | 1,232 relations | Document  | BC6PM contains PubMed abstracts (from IntAct/Mint [13]) annotated with those interacting PPI pairs affected by mutations. The relation annotation is represented in Entrez Gene ID pair. |

| Chemical-protein interaction                                                                                                                                     |
| ChemProt [14]  | 2,482 abstracts | 32,514 chemicals, 30,912 genes | 10,270 relations | Sentence | The ChemProt dataset consists of manually annotated chemical compound/drug and gene/protein mentions and 22 different chemical-protein relation types. Five relation types are used for evaluation, including agonist, antagonist, inhibitor, activator, and substrate/product relations. |
| DrugProt [15]  | 5,000 abstracts | 65,561 chemicals; 61,775 | 24,526 relations | Sentence | The DrugProt dataset aims to promote the development of chemical-gene RE systems, an extension of the ChemProt dataset. The addressed 13 different chemical-gene relations, |

**Table S4.** Overview of biomedical RE and event extraction datasets. The value of "-" means that we could not find the number in their papers or websites. The SEN/DOC Level means that whether the relation annotation is annotated in “Sentence,” “Document,” or “Cross-sentence.” “Document” includes abstract, full-text, or discharge record. “Cross-sentence” allows two entities within a relation appear in three surrounding sentences.
## BioRED: A Comprehensive Biomedical Relation Extraction Dataset

| Relation Type                          | Genes | Include Regulatory, Specific, Metabolic Relations |
|----------------------------------------|-------|-----------------------------------------------|
| Chemical-disease interaction           |       |                                               |
| CDR [16]                               | 1500  | 15,935 chemicals; 12,850 diseases             |
|                                        |       |                                               |
| Drug-drug interaction and Drug-ADE interaction |       |                                               |
| SemEval 2013 DDIExtraction [17]        | 905   | 13,107 drugs                                  |
|                                        |       |                                               |
| n2c2 2018 ADE [18]                     | 505 summaries | 83,869 entities |
|                                        |       |                                               |
| Variant/gene-disease interaction       |       |                                               |
| EMU [19]                               | 110 abstracts | -   relations |
|                                        |       |                                               |
| RENET2 [21]                            | 1,000 abstracts; 500 full text | -   - |
|                                        |       |                                               |
| N-ary dataset [23]                     |       | 3,462 triples; 137,469 drug-gene relations; 3,192 drug-mutation relations |
|                                        |       |                                               |
| Event extraction                       |       |                                               |
| BioNLP ST 2013 CG [24]                 | 600 abstracts | 21,683 entities | 17,248 events; 917 relations |
|                                        |       |                                               |
| BioNLP ST 2013 PC [24]                 | 525 abstracts | 15,901 entities | 12,125 events; 913 relations |
|                                        |       |                                               |
| BioNLP ST 2013 BB [25]                 | 131 abstracts | 5183 entities | 2312 events |
|                                        |       |                                               |
| BioNLP ST 2013 GRN [25]                | 201 sentences | 917 entities | 819 events |

CDR consists of 1,500 abstracts that chemical and disease mention annotations and their IDs. It annotates chemical-induced disease relation ID pair. There are 1,400 abstracts selected from a CTD-Pfizer collaboration-related dataset, and the remaining 100 articles are new curation and are used in the test set.

It consists of 792 texts selected from the DrugBank database and 233 Medline abstracts. The corpus is annotated with 18,502 pharmacological substances and 5,028 DDIs, including both pharmacokinetic (PK) and pharmacodynamic (PD) interactions.

The discharge summaries are from the clinical care database of the MIMIC-III (Medical Information Mart for Intensive Care-III). The summaries are manually selected to contain at least 1 ADE and annotated with nine concepts and eight relation pairs. The data are split into 303 and 202 for training and test sets, respectively.

The EMU dataset focuses on finding relationships between mutations and their corresponding disease phenotypes. They use ‘MeSH = mutation’ to select abstracts and use MetaMap [20] to annotate the abstracts that are divided into containing mutations related to prostate cancer (PCa) and breast cancer (BCa). They then use rules and patterns to select subsets of PCa and BCa for annotating.

It contains both 1000 abstracts (from RENET [22]) and 500 full-texts from PMC open-access subset. For a better quality, 500 abstracts of the dataset were refined. Authors used the 500 abstracts to train the RENET2 model and conduct their training data expansion using the other 500 abstracts. They further used the model trained on 1,000 abstracts to construct 500 full-text articles.

Authors use distant supervision to construct a cross-sentence drug-gene-mutation RE dataset. They use 59 distinct drug-gene-mutation triples from the knowledge bases to extract 3,462 ternary positive relation triples. The negative instances are generated by randomly sampling the entity pairs/triples without interaction.

The Cancer Genetics (CG) corpus contains annotations of over 17,000 events in 600 documents. The task addresses entities and events at all levels of biological organization, from the molecular to the whole organism, and involves pathological and physiological processes.

The pathway curation (PC) task aims to develop, evaluate and maintain molecular pathway models using representations such as SBML and BioPAX. The PC task stands out in particular in defining the structure of its extraction targets explicitly regarding major pathway model representations and their types based on the Systems Biology Ontology, thus aligning the extraction task closely with the needs of pathway curation efforts. The PC corpus over 12,000 events in 525 documents.

The Bacteria Track tasks aim to demonstrate that the BioNLP community is well-grounded to accompany the progress of Microbiology research. BB targets ecological information for a large spectrum of bacteria species.

The GRN task targets biological processes and whole cell models. The GRN task’s goal is to extract a regulation network from the text. They defined six interaction types for the GRN regulation network representing the whole range of effect and
The Gene Regulation Ontology (GRO) task aims to evaluate systems for extracting complex semantic representation in the gene regulation domain.

The ID task focuses on the functions of a class of ubiquitous signaling systems in bacteria, and includes the molecular mechanisms of infection, virulence, and resistance. They extended the BioNLP'09 Shared Task (ST'09) event representation for the ID dataset, which consists of 30 full-text publications on infectious diseases.

The EPI task aims to extract the events regarding chemical modifications of DNA and proteins related to the epigenetic control of gene expression.

In contrast to these two application-oriented main tasks, the REL task generally seeks to support extraction by separating challenges relating to part-of-relation extraction into a subproblem that independent systems can address. Data for the supporting task REL was created by extending previously introduced GENIA corpus annotations.

As the first BioNLP shared task, it aimed to define a bounded, well-defined bio event extraction task, considering both the actual needs and the state of the art in bio-TM technology and to pursue it as a community-wide effort.

Acknowledgements

This research is supported by the Intramural Research Programs of the National Institutes of Health, National Library of Medicine and partially supported by the NIH grant 2U24HG007822-08 to CNA.

Conflict of Interest: none declared.

Reference

1. Bergstra, J. and Y. Bengio, *Random search for hyper-parameter optimization*. The Journal of Machine Learning Research, 2012. 13(1): p. 281-305.
2. Prechelt, L., *Automatic early stopping using cross validation: quantifying the criteria*. Neural Networks, 1998. 11(4): p. 761-767.
3. Bunescu, R., et al., *Comparative experiments on learning information extractors for proteins and their interactions*. Artificial intelligence in medicine, 2005. 33(2): p. 139-155.
4. Xenarios, I., et al., *DIP: the database of interacting proteins: 2001 update*. Nucleic acids research, 2001. 29(suppl_1): p. D497-D501.
5. Pyysalo, S., et al., *BioInfer: a corpus for information extraction in the biomedical domain*. BMC bioinformatics, 2007. 8(1): p. 1-24.
6. Ding, J., et al., *Mining MEDLINE: abstracts, sentences, or phrases?*, in Biocomputing 2002. 2001, World Scientific. p. 326-337.
7. Nédellec, C. *Learning language in logic-genic interaction extraction challenge*. in 4. Learning language in logic workshop (LLL05). 2005. ACM-Association for Computing Machinery.
8. Krallinger, M., et al., *Overview of the protein-protein interaction annotation extraction task of BioCreative II*. Genome biology, 2008. 9(2): p. 1-19.
BioRED: A Comprehensive Biomedical Relation Extraction Dataset

11. Leitner, F., et al., An Overview of BioCreative II.5. IEEE/ACM Transactions on Computational Biology and Bioinformatics, 2010. 7(3): p. 385-399.
12. Islamaj Doğan, R., et al., Overview of the BioCreative VI Precision Medicine Track: mining protein interactions and mutations for precision medicine. Database: The Journal of Biological Databases and Curation, 2019. 2019.
13. Kerrien, S., et al., The IntAct molecular interaction database in 2012. Nucleic acids research, 2012. 40(D1): p. D841-D846.
14. Krallinger, M., et al. Overview of the BioCreative VI chemical-protein interaction Track. in Proceedings of the sixth BioCreative challenge evaluation workshop. 2017.
15. Miranda, A., et al. Overview of DrugProt BioCreative VII track: quality evaluation and large scale text mining of drug-gene/protein relations. in Proceedings of the seventh BioCreative challenge evaluation workshop. 2021.
16. Wei, C.-H., et al., Assessing the state of the art in biomedical relation extraction: overview of the BioCreative V chemical-disease relation (CDR) task. Database: The Journal of Biological Databases and Curation, 2016. 2016.
17. Herrero-Zazo, M., et al., The DDI corpus: An annotated corpus with pharmacological substances and drug–drug interactions. Journal of biomedical informatics, 2013. 46(5): p. 914-920.
18. Henry, S., et al., 2018 n2c2 shared task on adverse drug events and medication extraction in electronic health records. Journal of the American Medical Informatics Association, 2019. 27(1): p. 3-12.
19. Doughty, E., et al., Toward an automatic method for extracting cancer- and other disease-related point mutations from the biomedical literature. Bioinformatics, 2010. 27(3): p. 408-415.
20. Aronson, A.R. Effective mapping of biomedical text to the UMLS Metathesaurus: the MetaMap program. in Proceedings of the AMIA Symposium. 2001. American Medical Informatics Association.
21. Su, J., et al., RENET2: high-performance full-text gene–disease relation extraction with iterative training data expansion. NAR Genomics Bioinformatics, 2021. 3(3): p. lqab062.
22. Wu, Y., et al. Renet: A deep learning approach for extracting gene-disease associations from literature. in International Conference on Research in Computational Molecular Biology. 2019. Springer.
23. Peng, N., et al., Cross-sentence n-ary relation extraction with graph lstms. Transactions of the Association for Computational Linguistics, 2017. 5: p. 101-115.
24. Pyysalo, S., et al., Overview of the cancer genetics and pathway curation tasks of bionlp shared task 2013. BMC bioinformatics, 2015. 16(10): p. 1-19.
25. Bossy, R., et al., Overview of the gene regulation network and the bacteria biotope tasks in BioNLP’13 shared task. BMC bioinformatics, 2015. 16(10): p. 1-16.
26. Pyysalo, S., et al. Overview of the ID, EPI and REL tasks of BioNLP Shared Task 2011. in BMC bioinformatics. 2012. Springer.
27. Kim, J.-D., et al. Overview of genia event task in bionlp shared task 2011. in Proceedings of BioNLP shared task 2011 workshop. 2011.
28. Kim, J.-D., et al. Overview of BioNLP’09 shared task on event extraction. in Proceedings of the BioNLP 2009 workshop companion volume for shared task. 2009.