Distant supervision for treatment relation extraction by leveraging MeSH subheadings

Tung Tran⁷, Ramakanth Kavuluru⁸,⁹,⁎

Department of Computer Science, University of Kentucky, Lexington, KY, United States
Division of Biomedical Informatics, Department of Internal Medicine, University of Kentucky, Lexington, KY, United States

Abstract

The growing body of knowledge in biomedicine is too vast for human consumption. Hence there is a need for automated systems able to navigate and distill the emerging wealth of information. One fundamental task to that end is relation extraction, whereby linguistic expressions of semantic relationships between biomedical entities are recognized and extracted. In this study, we propose a novel distant supervision approach for relation extraction of binary treatment relationships such that high quality positive/negative training examples are generated from PubMed abstracts by leveraging associated MeSH subheadings. The quality of generated examples is assessed based on the quality of supervised models they induce; that is, the mean performance of trained models (derived via bootstrapped ensembling) on a gold standard test set is used as a proxy for data quality. We show that our approach is preferable to traditional distant supervision for treatment relations and is closer to human crowd annotations in terms of annotation quality. For treatment relations, our generated training data performs at 81.38%, compared to traditional distant supervision at 64.33% and crowd-sourced annotations at 90.57% on the model-wide PR-AUC metric. We also demonstrate that examples generated using our method can be used to augment crowd-sourced datasets. Augmented models improve over non-augmented models by more than two absolute points on the more established F1 metric. We lastly demonstrate that performance can be further improved by implementing a classification loss that is resistant to label noise.

1. Introduction

The growing body of knowledge in the biomedical domain, constituting over 27 million articles indexed by PubMed¹ as of 2018, is too vast for human consumption. These articles span academic journals, books, and other resources covering a wide range of topics including medicine, nursing, dentistry, pharmacy, biology, and healthcare. In order to leverage this wealth of information, there has been intense research focus on creating high precision systems for information retrieval and question-answering. These efforts, under the broad theme of knowledge discovery, rely on being able to intelligently recognize and capture semantic relations as conveyed in natural language — hence the importance of relation extraction systems. In this study, we focus on the binary relation extraction of treatment relations. The task of binary relation extraction is simple: given some textual input, extract (subject, predicate, object) triples where subject and object are entities and predicate is a class of semantic relation. For example, (insulin, treats, diabetes type 1) is a triple, or semantic predication, that can be extracted from the sentence “Insulin is prescribed for the treatment of Diabetes Type 1.” The difficult nature of this task becomes obvious when we consider that such relationships can be expressed in a variety of complex yet valid ways.

The treats predicate is an important predicate in the medical domain, alongside causes, and warrants special attention. In this study, we propose a method to generate quality examples for distant-supervised learning of treatment relation extraction. The proposed method builds on the concept of distant supervision originally proposed by Mintz et al. [23] — henceforth referred to as traditional distant supervision (TDS). TDS considers any pair of entities in the same sentence to be a positive example so long as they participate as part of a known semantic predication in an existing knowledgebase. The proposed distant supervision method, referred to as MeSH Subheadings based Distant Supervision (MSDS), relies on MeSH indexing to approximate concept relationships. Specifically, we look for PubMed abstracts for which there exists both the Therapeutic Use and Therapy Medical Subject Headings (MeSH) subheadings; these subheadings (also known as

⁎ Corresponding author.
E-mail addresses: tung.tran@uky.edu (T. Tran), ramakanth.kavuluru@uky.edu (R. Kavuluru).
¹https://www.ncbi.nlm.nih.gov/pubmed/
https://doi.org/10.1016/j.artmed.2019.06.002
Received 16 August 2018; Received in revised form 4 June 2019; Accepted 5 June 2019
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expressions. MSDS is similar to MeTAE in that both are designed to exploit the MeSH indexing of PubMed to pinpoint pairs of entities that are related by a treatment semantic relation; however, there are major differences in terms of both motivation and execution. We highlight the differences between our method and MeTAE as follows.

- MeTAE leverages MeSH subheadings to curate sentences for manual pattern construction; the hand-crafted patterns are later used for rule-based relation extraction. On the other hand, MSDS leverages MeSH subheadings to automatically generate distantly-supervised examples, without human intervention, for the purpose of training supervised relation extraction models.

- MSDS utilizes MeSH subheadings in a more precise manner in that we leverage not only the Drug Therapy subheading but also the Therapeutic Use subheading, the latter of which allows us to better filter for entities representing a treatment or drug. To show why this is advantageous, we offer the following example. Suppose we want to extract positive treatment examples from the sentence “A 15-year-old female adolescent developed drug hypersensitivity syndrome 4 weeks after starting minocycline therapy for acne vulgaris.” Also, suppose the related abstract contains MeSH terms including “Acne Vulgaris/drug therapy”, “Minocycline/therapeutic use”, and “Drug Hypersensitivity/etiology.” If entities are only bounded by the Drug Therapy subheading, the system would thus extract triples (minocycline, treats, acne vulgaris) and (minocycline, treats, drug hypersensitivity syndrome), the latter of which is not only a negative example of treats but in fact an example for the opposing causes relation (as hinted by the “etiology” subheading). Given MSDS is bounded on both the Drug Therapy and Therapeutic Usage subheading, we would correctly ignore (minocycline, treats, drug hypersensitivity syndrome) as a positive example for treats. Consequently, we reduce the possibility of introducing training examples to the supervised model that are not only incorrect but actually contradictory.

The remainder of this section is organized as follows. Section 2.1 provides a background on the CrowdTruth method and corresponding crowd-sourced dataset. Section 2.2 serves as an overview of deep learning architectures while Section 2.3 discusses relation extraction techniques suited for the biomedical domain. In Section 2.4, we discuss an advanced approach for learning on noisy labels.

2.1. CrowdTruth

Dumitrache et al. [7] showed that, at least in the medical domain, crowd-sourced annotations are of similar or better quality when compared with expert annotations. A method was proposed, referred to as CrowdTruth, to obtain a sentence-relation score in [0, 1] by measuring disagreement between multiple crowd-sourced annotations; this score, when thresholded, can be used to determine whether an example (that is, a subject/object pair and its textual context) is positive or negative with respect to a particular type of relation. The dataset used in experiments consisted of 3,984 sentences from PubMed that were originally collected by Wang and Fan [41] and re-annotated via the CrowdTruth method. Herein, we refer to the aforementioned dataset as the CrowdTruth dataset. Dumitrache et al. [7] demonstrated that, with enough crowd-sourced annotations for a particular example (specifically 15), the quality is on-par or better compared with using a single expert annotator — at least for the treats and causes predicates. This is accomplished by comparing the performance of models trained on different methods of annotation and evaluated on a common held-out adjudicated subset amounting to 975 sentences with “gold standard” annotations.

While the CrowdTruth dataset covers causes and treats, we focus specifically on treats for which there are 606 sentences with adjudicated “gold standard” annotations (simply referred to as GOLD labels) that

qualifiers) inform us respectively that there is an entity corresponding to a drug or physical agent being used and that there is also an entity corresponding to a disease for which a therapy is specified.

Although MeSH indexing does not provide explicit concept linkage, the intuition is that articles with both Therapy and Therapeutic Use subheadings are more likely to convey treatment than articles with only one of them or without any of them. Furthermore, we use the headings (also known as descriptors) associated with these subheadings (also known as qualifiers) as a concept-level filter when considering candidate entity pairs given all mentioned entities identified by NLM’s MetaMap [3] concept identification and mapping tool. MSDS relies on the fact that each MeSH term with a heading and subheading is associated with a descriptor unique identifier (DUI) and a qualifier unique identifier (QUI) respectively. For example, the MeSH term “Type 1 Diabetes Mellitus/drug therapy” is annotated with a DUI of D003922 representing Diabetes Mellitus Type 1 and QUI of Q000188 representing Drug Therapy. DuIs can be mapped to Concept Unique Identifiers (CUIs) by referencing UMLS Metathesaurus and therefore indexed for the same article, it is reasonable to infer that the article discusses the treatment of diabetes type 1 through insulin administration. Therefore, sentences in the article where both entities occur together are considered positive examples for treatment.

An important appeal of distant supervision is the fact that there are no costs in terms of money and labor. Compared to human-annotated datasets, quality is usually compromised for quantity. MSDS is capable of generating an abundance of training data without compromising as much on quality when compared with TDS. In fact, the quality of examples extracted by MSDS is closer to human crowd-sourced annotations than TDS. We demonstrate this by comparing models trained using data generated by MSDS to models trained on TDS; the models are evaluated using an adjudicated “gold standard” dataset curated by Dumitrache et al. [7]. Moreover, we demonstrate that examples obtained using MSDS can be used to augment crowd-sourced data for improved performance at no additional cost in human annotations.

Lastly, we show that using a modified loss function resistant to noisy labels can improve the performance of models trained on data generated by our method. As presented, MSDS is limited to treatment-type relations while TDS is readily generalizable to other relation types; we discuss this limitation and ways of extending MSDS to other major relation types including causes, prevents, and diagnose in Section 5.

2. Background

Abacha and Zweigenbaum [1] introduced the MeTAE (Medical Texts Annotation and Exploration) platform that allows for the extraction and annotation of medical entities and relationships from medical text. The rule-based method begins with seed concept pairs that are linked by the “may treat” relation according to the UMLS Metathesaurus. The pair consists of a “problem” concept and a “treatment” concept. For each concept pair, very focused queries are submitted to the PubMed Central database2; these queries target articles where the problem concept exists as the major-focused heading of a Therapy (TH) subheading and the treatment concept exists as an unbounded MeSH heading. The queries are designed according to the following pattern: “〈problem〉/TH[MAJR]and〈treatment〉/MH”3. The text of the returned articles are sentence-segmented and each constituent sentence is sent to the MetaMap tool [3] for concept identification and mapping. Only sentences containing both concepts of the seed pair are kept for further pattern construction in the form of regular

2https://www.ncbi.nlm.nih.gov/pmc/

3Note that 〈problem〉 and 〈treatment〉 are placeholders for the queried concept pair.
can be used as a basis for direct model comparison. The remaining 3378 sentences are annotated with TDS and CROWD labels; the former refers to labels obtained via TDS while the latter refers to the crowd-sourced annotations obtained via CrowdTruth. The GOLD labels are well-balanced such that there is approximately a 1:1 positive-negative ratio, while TDS and CROWD exhibit more imbalanced ratios of 1:4 and 1:2 respectively. The exact distributions are recorded in Table 1. It is noted that while the same dataset is used, our experimental results are not directly comparable to those in the original study [7] given that the authors conducted experiments using 5-fold cross-validation over the test partition; that is, examples not in a test fold are used for training with the corresponding TDS or CROWD labels. In this study, we reserve the 606 sentences with gold annotations strictly for testing while opting for a bootstrapped model averaging setup (more in Section 4.1) as in a prior work [17] to obtain mean model performance.

### 2.2. Deep learning and bi-directional LSTMs

The recent state-of-the-art performance in natural language tasks such as text classification, relation extraction, named entity recognition, and machine translation are typically achieved with deep learning approaches such as convolutional neural networks (CNNs) or recurrent neural networks (RNNs) [4,5,15,17,38]. These deep learning models are neural networks designed with many hidden layers that compose meaningful intermediate representations. High performance is additionally owed to use of neural word embeddings [19,38,40]. RNNs are particularly adept at modeling sequences which makes them suitable for natural language tasks. Long Short-Term Memory (LSTM) [11,14] networks in particular are a type of RNN that feature a complex mechanism for memory management such that it is able to overcome issues such as the vanishing gradients [33] problem. We encourage readers to refer to Graves [13,Chapter 4] and Goldberg [12,Section 11] for thorough details of LSTMs and the corresponding derivations of gradients. Regular LSTMs model sequence accumulating at the last element, while bi-directional LSTMs (BiLSTMs) model a sequence jointly from both directions. The latter architecture has been shown to perform competitively especially for relation extraction tasks. With this model, words are fed as input to the network in the form of word embedding vectors. These word vectors are processed by a bi-directional LSTM, the output of which is max-pooled over the time-step dimension to produce a final feature vector. The feature vector is fully-connected to a softmax output layer with two units corresponding to a binary Yes/No output indicating whether or not there is a treats relation being conveyed. The additional use of position vectors may further enhance the performance of relation extraction models in our experience. These learnable embedding vectors that represent the offset of a word to either entity.

### 2.3. Relation extraction in the biomedical domain

Relation extraction approaches in the biomedical domain typically operate by exploiting the shortest dependency path between candidate entities according to a preprocessed dependency parse tree [2,10,20,21,37]. The concept of network centrality has also been explored [32] while other studies, including Frunza et al. [9], rely on more traditional linear methods that focus on syntactic and lexical features. More recent studies on relation extraction approaches are based on exploring meaningful deep learning architectures [17,21,36], including Segment-CNNs [22] and Graph-LSTMs [35]. Meanwhile, there is ongoing research effort to explore end-to-end relation extraction by jointly modeling entity recognition and relation detection to exploit inter-task correlations [16,24,42].

### 2.4. Dealing with noisy labels

A short-coming of utilizing annotations from distant supervision is noise arising from erroneously including examples as positive cases even when there is no relationship conveyed. Conversely, there will be examples that are included as negative cases even when there is evidence to the contrary. These sources of noise are a primary contributing factor to the quality of the training data and derived models. Supervised learning on data with noisy labels has been studied extensively [8]. One popular technique is to modify the loss function such that it is more robust to noisy labels [25,34]. Natarajan et al. [25] established that it is possible to modify the original loss $\ell$ to a noise-resistant loss $\ell'$ such that training with $\ell'$ on noisy data is equivalent to training with $\ell$ on clean data — provided the noise rates are known a priori. Alternatively, it is possible to directly correct test predictions [39] without changing the architecture. Generally, the former is known as backward correction while the latter is known as forward correction. Patrini et al. [34] applied these ideas to the deep neural network setting and formalized an end-to-end, architecture-independent procedure to effectively train on data with noisy labels. Moreover, they propose a method for approximating the noise rates in case it is not known a priori. We discuss the modification of the loss function to deal with noisy labels (referred to as noisy-label loss) in our experiments in Section 4.1.

### 3. Methodology

In this section, we formalize MSDS as a method for generating distantly-supervised examples for treatment relation extraction. Section 3.1 describes the article pruning process; not unlike document triage, the goal is to identify articles that contain expressions of treatment relationships and prune articles that do not. In Sections 3.2 and 3.3, we describe the formal process for generating positive and negative examples respectively.

#### 3.1. Article pruning

MSDS processes articles according to a list of PubMed Identifiers (PMIDs) and generates examples in the sequential order that they appear. We specifically extract examples from the title and the abstract (in that order) of the articles associated with each PMID. Clearly, it is prudent to avoid processing the entire PubMed database as this would be very time consuming with little return because the vast majority of articles do not pertain to medical treatment. It is ideal to target only the subset of articles that are very likely discussing illnesses and related therapeutic agents or procedures. To that end, a list of candidate PMIDs is generated by performing a Boolean search on PubMed with the following query: “therapy[sh] AND (therapeutic use[sh:noxexp] OR administration and dosage[sh])”. This query returns a list of approximately 2.18 million articles that contain both the Therapy and Therapeutic Use subheadings. As an aside, MeSH subheadings take upon a tree structure such that a parent subheading is only applied if the article does not fit into one of the more specific child subheadings. Searching for a particular subheading by default also includes articles with its child subheadings. In the case of the Therapy subheading, by excluding the noexp (no expansion) option, we consequently allow for all articles with child subheadings to be included; specifically, we allow for Diet Therapy, Drug Therapy, Nursing, Prevention & Control, Radiotherapy, Rehabilitation, Surgery, and Transplantation. In the case of Therapeutic Use, there are three child subheadings to consider: Administration & Dosage, Adverse Effects, and Poisoning. Here, we allow

<table>
<thead>
<tr>
<th>Annotation</th>
<th>Positives</th>
<th>Negatives</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDS</td>
<td>683</td>
<td>2695</td>
<td>3378</td>
</tr>
<tr>
<td>CROWD</td>
<td>1127</td>
<td>2251</td>
<td>3378</td>
</tr>
<tr>
<td>GOLD</td>
<td>291</td>
<td>315</td>
<td>606</td>
</tr>
</tbody>
</table>

**Table 1** Counts of positive/negative examples for each set of annotations for treats.
for Administration & Dosage while disallowing Adverse Effects and Poisoning which would otherwise be counterproductive with respect to the original objective. Henceforth, when mentioning Therapy or Therapeutic Use, we implicitly refer to the subheading itself and all child subheadings except the ones deemed “counterproductive.”

3.2. Positive examples

Before processing each article, we randomly shuffle the list of PMID’s according to a seed value. This allows us to extract examples uniformly such that the distribution of the resulting data is not biased toward any subheadings or publication period. We re-use the same seed value to naturally generate negative examples via the procedure described later in Section 3.3. In order to generate positive examples, we apply the following procedure to each article in the shuffled list denoted as a sequence $x^1, ..., x^n$.

Allowable subject and object entities for $x^i$ are identified by gleaming the document’s MeSH terms. Recall from Section 1 that a heading/descriptor is associated with a UDI and a subheading/qualifier is associated with a UCI. Generally, the former identifies a concept and the latter describes a qualifier with respect to the concept. Let $\chi^i$ be the set of concepts (UDIs mapped to CUIs via the UMLS [29] database) associated with the Therapeutic Use (Q000627) and Administration & Dosage (Q000008) subheadings; $\chi^i$ intuitively serves as the set of allowable subject concepts for the treatment relation. For candidate object concepts, we denote $\phi^i$ as the set of all concepts (mapped to CUIs) associated with the following subheadings: Therapy (Q000628), Diet Therapy (Q000178), Drug Therapy (Q000188), Nursing (Q000451), Radiotherapy (Q000532), Rehabilitation (Q000534), Surgery (Q000601), and Transplantation (Q000637). Prevention & Control are excluded as they would be more appropriate for the prevents predicate despite the potential for overlap.

Next, we perform sentence splitting on $x^i$ to obtain a list of $m^i$ sentences $s^i_1, ..., s^i_m$. This step is important as we are only concerned with intra-sentence relations. Let $C$ be the set of all possible CUIs. We apply the following procedure for each sentence $s^i_j$:

1. The MetaMap tool is used to annotate $s^i_j$ with a set of concepts $M^i_j$; here, each concept is defined as a triple $(\alpha, \beta, c)$ where $\alpha \in \Xi$ is the beginning character offset, $\beta \in \Xi$ is the ending character offset, and $c \in C$ is the CUI of the concept. When utilizing MetaMap, we disable the Word Sense Disambiguation (WSD) option$^1$ and we ignore concepts with mentions that are non-contiguous.$^5$

2. The set of candidate subject concepts $X^i_j$ for sentence $s^i_j$ is obtained by computing the intersection of concepts identified by MetaMap and allowable subject concepts as informed by the MeSH indexing for document $i$. Formally, we define this set as

$$X^i_j = [(\alpha, \beta, c) : (\alpha, \beta, c) \in M^i_j \land c \in \Xi^i].$$

Similarly, $\phi^i_j$ is the list of candidate object concepts, defined as

$$\phi^i_j = [(\alpha, \beta, c) : (\alpha, \beta, c) \in M^i_j \land c \in \phi^i].$$

3. The set of positive examples $\{X^i_j, \phi^i_j\}$ to be extracted from sentence $j$ of article $i$ is obtained by considering all pairs of candidate subject and object concepts with non-overlapping mentions. Concretely,

$$|X^i_j| = \{((\alpha, \beta, c), (\alpha', \beta', c')) : (\alpha, \beta, c) \in X^i_j \land (\alpha', \beta', c') \in \phi^i_j \land ((\alpha < \beta < \alpha' < \beta') \lor (\alpha > \beta > \alpha' > \beta'))\}.$$

Here, each extracted example is a pair of concepts along with their mention offsets.

The sentence and character offsets of each entity mention are necessarily recorded if they are to serve as training examples. Since it is possible for a single CUI to map to multiple mentions (corresponding to multiple start/end offset pairs), we consider each mention to be a distinct entity so that the examples are consistent with respect to linguistic considerations. Retaining this nuance allows more flexibility in future work which may involve identifying and purging “positive” examples that are not semantically sound. For example, consider the sentence, “Blood sugar levels are regulated by the hormone insulin1; man-made insulin2 is used to treat diabetes.” Here, both (insulin1,diabetes) and (insulin2,diabetes) will be extracted as positive examples, but we only consider (insulin2,diabetes) to be semantically sound given the linguistic context. Once each sentence is processed and all predications are extracted from the article abstract, we proceed to the next article in the sequence. An example illustrating the procedure is shown in Fig. 1.

3.3. Negative examples

Discriminative models require negative examples in addition to positive examples. Herein, we describe a complementary method to generate negative examples. The process is similar to positive example generation; however, external knowledge is leveraged to ensure that we only extract non-trivial examples and that we only extract examples likely to be negative. That is, we wish to avoid extracting an excessive number of false negatives while retaining the more nuanced or borderline cases. The proposed method heavily relies on the UMLS Semantic Network [26] (SemNet) which categorizes concepts and relationships in a hierarchical taxonomy. SemNet assigns broad categories to concepts (that is, CUIs) in the form of Semantic Types [28] (SemTypes). Moreover, the so-called Semantic Relations [27] (such as affects, causes, uses, and treats) are associated with a set of SemType pairs serving as plausible entity types for that particular relationship. Intuitively, the SemNet constraints for treats provides a basis for choosing negative examples that are likewise plausible and therefore more nuanced. A training example in which a drug “treats” another drug is clearly a negative case, but its utility is limited if the goal is to train a robust classifier. Hence, as a rule, only negative examples with subject/object concepts that are consistent with SemNet constraints for the treats relation in SemNet are extracted. Let $T$ denote the set of all SemTypes defined by UMLS. As a preliminary step, we compute $S \subseteq T \times T$ as the set of subject-object SemType pairs valid for the treats relation according to SemNet.

SemMedDB [18,31], a repository of semantic predications extracted by the rule-based relation extraction tool SemRep [30], serves as another knowledge source that is used to filter out potential false negatives. Specifically, if a semantic predications appears in SemMedDB with the treats relation, then it is disregarded as it doesn’t treat a negative example. Essentially, recall is sacrificed in order to limit the introduction of false negatives (and therefore noise). With that in mind, we define $S \subseteq C \times C$ as the set of subject-object CUI pairs that appears in SemMedDB at least once for the treats relation.

A feature of this approach is that it is capable of naturally generating negative examples alongside positive examples from the same list of abstracts. Consequently, the positive-negative imbalance naturally reflects the imbalance observed in a real-world setting. Here, positive examples are generated first via the method in Section 3.2 and then used as a filter when generating negative examples. Intuitively, a
A simple example illustrating how a positive instance for the relation "treats" is extracted from a sentence appearing in the PubMed abstract with PMID 21148442.

Fig. 1. A simple example illustrating how a positive instance for the relation "treats" is extracted from a sentence appearing in the PubMed abstract with PMID 21148442.

unique predication that has already been extracted as a positive example should not be extracted again as a negative example.

Using the same notations established in Section 3.2, the following procedure is proposed for the extraction of negative examples from sentence $s_i$:

1. As in generating positive examples, $s_i$ is annotated with a set of concepts $\mathcal{A}_i^j$ using the MetaMap tool. However, WSD is enabled such that each mention is mapped to only one of potentially many concepts. This is necessary as it is no longer possible to rely on MeSH subheadings to inform us of allowable subject and object concepts.

2. Next, we compute the set of predications based on the following filtering criteria. Each subject-object pair must follow the SemType constraints for "treats", must not exist as a previously-extracted positive example. Moreover, as when extracting positive examples, the entity mentions should likewise not overlap. Formally, the set of negative examples $\mathcal{Z}_i^j$ extracted from article $i$, sentence $j$ is defined as

$$\mathcal{Z}_i^j = \{((\alpha, \beta, c), (\alpha', \beta', c')) : (\alpha, \beta, c) \in \mathcal{A}_i^j \land (\alpha', \beta', c') \in \mathcal{A}_i^j \land (c, c') \not\in \mathcal{S} \land ((\alpha < \beta < \alpha' < \beta') \lor (\alpha > \beta > \alpha' > \beta')) \}$$

where type(c) is the SemType of concept c according to UMLS.

4. Experiments and results

In order to evaluate the quality of our dataset, we trained supervised models using TDS and CROWD labels as well as data generated by our distant supervision method (simply referred to as MSDS). We observe the performance of trained models as a proxy for data quality as in past work [7]. Of the 3984 examples in the CrowdTruth dataset, 606 held-out sentences with GOLD labels are used exclusively for testing. The remaining 3378 examples with TDS and CROWD labels are used to train models that are evaluated to assess data quality. We provide more detail about our experimental design in Section 4.1 and discuss the corresponding results in Section 4.2.

4.1. Experimental setup

As deep neural networks are not guaranteed to outperform traditional linear models for this particular task, we consider both traditional and deep neural models in our experiments; hence, we include both a traditional machine learning model (namely, logistic regression) and a deep learning model (namely, the BiLSTM as described in Section 2.2). The BiLSTM model is implemented as described in Kavuluru et al. [17, Section 5B]; however, the number of labels is fixed to 2 as the target task is strictly binary classification. This particular model is suitable as it is designed specifically for the task of relation extraction; with this in mind, the hyper-parameters are mirrored from [17] and fixed across all experiments to ensure a fair comparison. We additionally include a variant of the BiLSTM model with a modified noise-resistant loss function as described in Section 2.4, referred to as BiLSTM-NLL. The implementation of the noisy-label loss is based on the backward correction procedure described in Patrini et al. [34, Section 4.1]. The matrix representing the approximated noise rates used in the cited method is computed by following the procedure for noise rate estimation [34, Section 4.3], where the set of “testing” instances for noise approximation is a sample of MSDS-generated data with 3000 examples. Note that regardless of the model, we perform an entity-binding step, wherein mentions of the subjects and objects are replaced with generic SUBJECT and OBJECT tokens respectively, as in prior work [17]. This implies that we are effectively evaluating models based entirely on their ability to learn the linguistic context without regard for subject-object pair correlations.

Bootstrapped Ensembling. The performance of each variant is measured based on the bootstrapped model averaging [17] technique wherein average behavior is studied through building and evaluating large numbers of ensembles. This is motivated by the fact that deep neural networks are trained using stochastic gradient descent; the result is that we will often find parameters corresponding to some “good enough” local minimum as opposed to an optimal global minimum. Different random parameter initializations of the network will converge to different solutions corresponding to these local minima. In order to arrive at a more stable model, it is typical to train a number of such models (each with a different parameter initialization) as part of an ensemble in an effort to improve both stability and accuracy. In a prior work [17], we proposed an experimental setup in which 20 deep neural models were trained for each architecture as part of a sampling pool. 10000 ensembles are assembled and evaluated by randomly sampling 10 models from the pool for each ensemble. With this setup, it is possible to assess mean performance and corresponding confidence intervals such that conclusions are drawn based on statistical significance. We apply the same methodology to assess the average behavior of each variant in this study. Although intended for deep neural networks, we apply bootstrapped model averaging to all models uniformly, including logistic regression, to ensure a fair comparison.
We measure performance as a proxy for label quality using the Precision-Recall Area Under the Curve (PR-AUC) metric instead of F1. Our rationale for this decision is as follows. The difference in label distribution (even when binary) can serve as a misleading factor when comparing the quality of datasets. A model trained on a training dataset having a similar label distribution to that of the test set is at a significant advantage regardless of the quality of individual examples; this is especially the case when the F1 metric is considered given performance is dependent on predictions made at individual examples; this is especially the case when the F1 metric is rated examples are incapable of competing against human annotations with respect to raw quality. However, we argue that there is value in being able to achieve approximately 80% in mean PR-AUC with MSDS when crowd-curated annotations achieve approximately 90% mean PR-AUC. This is especially the case when we consider that CROWD sentences and the test set sentences used to evaluate both CROWD and MSDS examples are collectively obtained via the same curation method (using the same seed articles and relations). Therefore, CROWD examples have a natural distributional advantage over MSDS examples within our evaluation framework. MSDS is therefore closer to CROWD in terms of performance compared with TDS. These results show that MSDS-generated examples are higher in quality compared to those obtained via traditional distant supervision examples and are actually closer in quality to crowd-sourced annotations.

4.2. Results and discussion

Table 2 displays results from our experiments to assess the quality of examples. Here, we observe that CROWD and TDS achieve roughly 90% and 65% PR-AUC respectively, while MSDS achieves a “middle-ground” of 80% PR-AUC across the three methods. Clearly, automatically-curated examples are incapable of competing against human annotations with respect to raw quality. However, we argue that there is value in being able to achieve approximately 80% in mean PR-AUC with MSDS when crowd-curated annotations achieve approximately 90% mean PR-AUC. This is especially the case when we consider that CROWD sentences and the test set sentences used to evaluate both CROWD and MSDS examples are collectively obtained via the same curation method (using the same seed articles and relations). Therefore, CROWD examples have a natural distributional advantage over MSDS examples within our evaluation framework. MSDS is therefore closer to CROWD in terms of performance compared with TDS. These results show that MSDS-generated examples are higher in quality compared to those obtained via traditional distant supervision examples and are actually closer in quality to crowd-sourced annotations.

Next, we examine the potential for using MSDS to augment crowd-sourced labels. As observed in Table 3, logistic regression achieves 78.47% mean F1 compared to 80.84% mean F1 by BiLSTM on CROWD at N = 3000. As the 95% confidence intervals do not overlap, the improvements are statistically significant. This indicates that deep learning may be more suitable than logistic regression for this particular task. We note that the deep neural model with noisy-label loss also exhibits better performance than without in most cases when MSDS labels are added. More importantly, we observe that regardless of method – but more so for deep learning models – there is an advantage in augmenting CROWD examples with instances generated by MSDS. And we can also observe that more data is not necessarily better, as performance peaks at certain proportions and tend to decrease when more noisy data is added. With BiLSTM, there is an approximate gain of one F1 point arriving at 81.79% when augmenting the 3000 CROWD examples with an additional 3000 MSDS examples. We see a slightly higher increase at 82.02% for the BiLSTM-NLL model. These improvements are statistically significant at the 95% level based on comparing confidence intervals.

Based on results from Table 3, augmenting crowd-based examples with high quantities of MSDS is not necessarily better. As such, we perform an auxiliary experiment to determine an optimal balance between CROWD and MSDS examples, focusing on the case where there are fewer MSDS examples than CROWD examples. We find that by augmenting 3000 CROWD examples with only an additional 1500 (+50%) MSDS examples, the resulting model achieves 81.92% mean F1 with BiLSTM-NLL. The result is as high as 83.22% mean F1 when evaluating on 3000 CROWD examples augmented with 750 (+25%) MSDS examples. Based on these results, we can see that there is an optimal ratio of 4:1 between CROWD and MSDS examples where peak performance is observed. This trend is visualized in Fig. 2; we note that the shaded area in this case represents standard deviation.

4.3. Error analysis

In this section, we perform error analysis by assessing performance

<table>
<thead>
<tr>
<th>Method</th>
<th>TDS</th>
<th>MSDS</th>
<th>CROWD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logistic Regression</td>
<td>64.57 ± 0.00646</td>
<td>82.86 ± 0.00889</td>
<td>90.46 ± 0.00187</td>
</tr>
<tr>
<td>BiLSTM</td>
<td>63.59 ± 0.02015</td>
<td>81.18 ± 0.01334</td>
<td>90.82 ± 0.00504</td>
</tr>
<tr>
<td>BiLSTM-NLL</td>
<td>64.33 ± 0.01708</td>
<td>81.38 ± 0.00137</td>
<td>90.57 ± 0.00441</td>
</tr>
</tbody>
</table>

Each example in the dataset constitutes a pair of concepts, the sentence in which the pair is observed, and a Yes/No label indicating whether or not the pair is positive for the treats relation.
based on pairs of subject/object semantic types to identify cases that are difficult for a model trained on MSDS generated examples. In Table 4, we examine evaluation results on the test set by BiLSTM-NLL trained on MSDS at $N = 3000$ partitioned by pairs of subject/object SemTypes. We only include results for cases where there are at least 10 examples. An interesting aspect of the test set (with GOLD labels) is that there are many SemType pairs for which there are no positive examples; these pairs can be identified by rows where both true positives (TPs) and false negatives (FNs) rates are zero. Of course, this leads to an F1 of 0 which can be misleading at first glance; accuracy is more informative in this case.

An example of this phenomenon exists when “Disease or Syndrome” occur as the SemType for both the subject and object — there are 50 such examples in the test set. These are all negative cases for the MSDS-based models are not trained on trivially negative examples (e.g., a disease treating another disease) and may have difficulties dealing with trivially negative cases at test time. It is possible to overcome this issue by introducing a filtering step in which we predict as negative all test examples that fail to adhere to SemNet constraints. However, this may adversely impact recall given there exists examples of treatment relations (in the wild) where the subject/object do not necessarily adhere to SemNet constraints.

One interesting case stems from the SemType pair “Neoplastic Process” (subject) and “Disease or Syndrome” (object) in which there is exactly one positive case in the groundtruth corresponding to a single example. In this case, the subject refers to chronic lymphocytic leukaemia. From inspection, the linguistic phrasing in this case is understandably difficult for a machine learning system; the connecting word here is “consider”, which is consistent with reality given it is atypical for a disease to treat another disease. This phenomenon is problematic for models trained on MSDS as the corresponding examples are bounded by SemNet constraints; hence, there are no MSDS examples generated where both the subject and object are diseases. In other words, MSDS-based models are not trained on trivially negative examples (e.g., disease treating another disease) and may have difficulties dealing with trivially negative cases at test time. It is possible to overcome this issue by introducing a filtering step in which we predict as negative all test examples that fail to adhere to SemNet constraints. However, this may adversely impact recall given there exists examples of treatment relations (in the wild) where the subject/object do not necessarily adhere to SemNet constraints.

Table 3
Results showing change in mean F1 with respect to varying training set size and proportion of CROWD to MSDS examples. We report the 95% confidence interval around mean F1 over 10,000 ensembles across linear and deep neural methods.

<table>
<thead>
<tr>
<th>N</th>
<th>CROWD</th>
<th>1:1 CROWD/MSDS</th>
<th>1:2 CROWD/MSDS</th>
<th>1:3 CROWD/MSDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logistic Regression</td>
<td>3000</td>
<td>78.47 ± 0.00779</td>
<td>73.33 ± 0.010306</td>
<td>70.25 ± 0.01469</td>
</tr>
<tr>
<td></td>
<td>6000</td>
<td>-</td>
<td>77.81 ± 0.00971</td>
<td>75.99 ± 0.01256</td>
</tr>
<tr>
<td></td>
<td>9000</td>
<td>-</td>
<td>-</td>
<td>78.60 ± 0.00781</td>
</tr>
<tr>
<td></td>
<td>12000</td>
<td>-</td>
<td>-</td>
<td>77.32 ± 0.00570</td>
</tr>
<tr>
<td>BiLSTM</td>
<td>3000</td>
<td>80.84 ± 0.01499</td>
<td>79.22 ± 0.01917</td>
<td>78.08 ± 0.01681</td>
</tr>
<tr>
<td></td>
<td>6000</td>
<td>-</td>
<td>81.79 ± 0.01361</td>
<td>80.12 ± 0.01269</td>
</tr>
<tr>
<td></td>
<td>9000</td>
<td>-</td>
<td>-</td>
<td>80.56 ± 0.01117</td>
</tr>
<tr>
<td></td>
<td>12000</td>
<td>-</td>
<td>-</td>
<td>79.34 ± 0.01263</td>
</tr>
<tr>
<td>BiLSTM-NLL</td>
<td>3000</td>
<td>80.86 ± 0.01324</td>
<td>80.82 ± 0.01808</td>
<td>78.64 ± 0.01798</td>
</tr>
<tr>
<td></td>
<td>6000</td>
<td>-</td>
<td>82.02 ± 0.01572</td>
<td>80.11 ± 0.01109</td>
</tr>
<tr>
<td></td>
<td>9000</td>
<td>-</td>
<td>-</td>
<td>80.83 ± 0.01188</td>
</tr>
<tr>
<td></td>
<td>12000</td>
<td>-</td>
<td>-</td>
<td>79.17 ± 0.01181</td>
</tr>
</tbody>
</table>

Fig. 2. Change in mean F1 w.r.t. amount of examples added from MSDS to CROWD, indicated as a proportion of CROWD dataset size, for the BiLSTM-NLL model.

Table 4
Results at N = 3000 for BiLSTM-NLL partitioned by subject/object semantic type.

<table>
<thead>
<tr>
<th>Subject SemType</th>
<th>Object SemType</th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
<th>Total</th>
<th>P (%)</th>
<th>R (%)</th>
<th>F (%)</th>
<th>Acc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic Chemical</td>
<td>Disease or Syndrome</td>
<td>74</td>
<td>11</td>
<td>10</td>
<td>25</td>
<td>120</td>
<td>88.10</td>
<td>74.75</td>
<td>80.87</td>
<td>70.83</td>
</tr>
<tr>
<td>Disease or Syndrome</td>
<td>Disease or Syndrome</td>
<td>0</td>
<td>40</td>
<td>10</td>
<td>0</td>
<td>50</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>78.43</td>
</tr>
<tr>
<td>Amino Acid, Peptide, or Protein</td>
<td>Disease or Syndrome</td>
<td>20</td>
<td>11</td>
<td>2</td>
<td>6</td>
<td>39</td>
<td>90.91</td>
<td>76.92</td>
<td>83.33</td>
<td>79.49</td>
</tr>
<tr>
<td>Organic Chemical</td>
<td>Sign or Symptom</td>
<td>9</td>
<td>4</td>
<td>0</td>
<td>9</td>
<td>22</td>
<td>100.00</td>
<td>50.00</td>
<td>66.67</td>
<td>59.09</td>
</tr>
<tr>
<td>Neoplastic Process</td>
<td>Finding</td>
<td>0</td>
<td>18</td>
<td>3</td>
<td>0</td>
<td>21</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>85.71</td>
</tr>
<tr>
<td>Neoplastic Process</td>
<td>Disease or Syndrome</td>
<td>0</td>
<td>14</td>
<td>4</td>
<td>1</td>
<td>19</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>73.68</td>
</tr>
<tr>
<td>Organic Chemical</td>
<td>Mental or Behavioral Dysfunction</td>
<td>13</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>17</td>
<td>100.00</td>
<td>81.25</td>
<td>89.66</td>
<td>82.35</td>
</tr>
<tr>
<td>Organic Chemical</td>
<td>Pathologic Function</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>8</td>
<td>16</td>
<td>100.00</td>
<td>38.46</td>
<td>55.56</td>
<td>50.00</td>
</tr>
<tr>
<td>Organic Chemical</td>
<td>Neoplastic Process</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>14</td>
<td>100.00</td>
<td>78.57</td>
<td>88.00</td>
<td>78.57</td>
</tr>
<tr>
<td>Neoplastic Process</td>
<td>Pathologic Function</td>
<td>0</td>
<td>8</td>
<td>4</td>
<td>0</td>
<td>12</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>66.67</td>
</tr>
<tr>
<td>Neoplastic Process</td>
<td>Sign or Symptom</td>
<td>0</td>
<td>10</td>
<td>2</td>
<td>0</td>
<td>12</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>83.33</td>
</tr>
<tr>
<td>Bacterium</td>
<td>Disease or Syndrome</td>
<td>0</td>
<td>6</td>
<td>5</td>
<td>0</td>
<td>11</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>54.55</td>
</tr>
<tr>
<td>Pharmacologic Substance</td>
<td>Disease or Syndrome</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>6</td>
<td>10</td>
<td>100.00</td>
<td>25.00</td>
<td>40.00</td>
<td>40.00</td>
</tr>
</tbody>
</table>
makes this example particularly difficult.

Another issue that leads to false negatives is the way in which entities are annotated when there are multiple mentions of a unique concept entity in the same sentence. First, we note that relation classification is performed between mentions of entities wherein the subject and object entities are bound to generic SUBJECT/OBJECT tokens. Hence, predictions are highly dependent on context. Consider the following sentence as an example, “In the trial based analysis, fondaparinux was estimated to prevent 15.1 thromboembolic events per 1000 lowing sentence as an example, ‘In the trial based analysis, fondaparinux was estimated to prevent 15.1 thromboembolic events per 1000 lowing sentence as an example, ‘In the trial based analysis, fondaparinux was estimated to prevent 15.1 thromboembolic events per 1000 lowing sentence as an example, ‘In the trial based analysis, fondaparinux was estimated to prevent 15.1 thromboembolic events per 1000 lowing sentence as an example, ‘In the trial based analysis, fondaparinux was estimated to prevent 15.1 thromboembolic events per 1000

resistant loss. In future efforts, we anticipate using the proposed distant supervision method to facilitate production of a large, high-quality human-annotated dataset solely for medical treatment relations.

Acknowledgment

We are grateful to the U.S. National Library of Medicine for offering the primary support for this work through grant R21LM012274. We are also thankful for additional support by the National Center for Advancing Translational Sciences through grant UL1TR001998. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. We gratefully acknowledge the support of NVIDIA Corporation with the donation of the Titan X Pascal GPU used for this research.

References


6. Conclusion

In this study, we introduced a distant supervision approach for relation extraction of medical treatment predications by exploiting MeSH subheadings. We demonstrated that our distant supervision method is a desirable compromise between traditional distant supervision and crowd-sourced annotations with the advantage that it is of reasonable quality and can be obtained without the costs associated with human involvement. We also showed that it is possible to use data obtained via our proposed method to augment existing crowd-sourced data for performance gains and this can be further improved by using a noise-resistant loss. In future efforts, we anticipate using the proposed distant supervision method to facilitate production of a large, high-quality human-annotated dataset solely for medical treatment relations.


