Development of Clinical Concept Extraction Applications: A Methodology Review

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1. INTRODUCTION

Electronic health records (EHRs) are widely viewed to have great potentials to advance clinical research and healthcare delivery [1]. To achieve “meaningful use” of EHRs, transforming routinely generated EHR data into actionable knowledge requires systematic approaches [2]. However, a significant portion of clinical information remains locked away in free text [3]. Concept extraction, a subdomain of natural language processing (NLP) which extracts concepts of interest, has been adopted to computationally extract clinical information from text for a wide range of applications ranging from supporting clinical decision making [3] to improving the quality of care [10]. The review done by Meystre et al in 2008 reported an increasing utilization of NLP in the clinical domain and a major challenge faced in advancing clinical NLP due to the unavailability of a large amount of clinical text [14]. A summary of EHR-based clinical concept extraction applications can be found in Wang et al [7].

As an illustrative example, the AHA/ASA has identified silent brain infarcts (SBI), defined as infarcts found by neuroimaging or necropsy without a history of stroke, as a major priority for new studies on stroke prevention. However, the identification of SBI is impeded by the fact that SBI is often considered an incidental finding: there are no ICD codes for SBI, and it is generally not included in a patient’s problem list or structured fields of electronic health records (EHR). Concept extraction can be applied to accurately identify SBI-related findings from neuroimaging reports, a type of EHR data that contains the interpretation and finding from neuroimage such as CT and MRI in unstructured text. The following example shown in Figure 1 presents the process to identify a patient’s potential SBI status using concept extraction techniques.

Figure 1. Example of Concept Extraction for Silent Brain Infarct

Methods for developing clinical NLP applications have been largely translated from the general NLP domain [6], which can be grouped into four categories: rule-based, traditional machine learning, deep learning, or hybrid approaches. For example, an early attempt of concept extraction in the clinical domain, the Medical Language Processing project, was oriented from the Linguistic String Project aiming to extract symptoms, medications, and possible side effects from medical records leveraging a semantic lexicon and a large collection of rules. The rise of statistical NLP in 1990s and recent advances in deep learning technologies [12] have been influencing methods adopted for clinical concept extraction. However, due to the complexity and heterogeneity associated with EHR data and the diverse range of applications, methods for clinical concept extraction are generally buried within the methods sections of the literature. Here, we provide a methodology review of clinical concept extraction, aiming to catalog development processes, available methods and tools, and specific considerations when developing clinical concept extraction applications.

2. METHOD

This review was conducted following a process compliant with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. A literature search was conducted for articles written in English and published from January 2009 through June 2019 from Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Scopus, Web of Science, and the ACM Digital Library. The implementation of search patterns were consistent across different databases. In brief, the high-level patterns are summarized as follows: (clinical OR clinic OR electronic health record OR electronic medical record) AND (information extraction OR named entity extraction OR named entity recognition OR text mining OR natural language processing) AND (NOT information retrieval). The detailed search strategies are provided in the Appendix.

A total of 4,300 articles were retrieved from five libraries, of which 2,306 articles were found to be unique. The articles were then filtered manually based on the title, abstract, and method sections to keep only articles including
EHR-based clinical NLP from English text. After this screening process, 801 articles were considered for subsequent categorization. We then conducted additional manual review to keep full articles with methodology description focusing on clinical concept extraction. Following this screening process, 219 articles were selected and categorized based on the methods used. A comprehensive full-text review of all 219 studies were performed by the study team. A flow chart of this article selection process is shown in Figure 2.

**Figure 2.** Overview of article selection process

| Total 4300 from 2016 September to 2019 June |
|---------------------------------------------|
| 707  Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) |
| 846  Ovid Embase |
| 868  Scopus |
| 486  Web of Science |
| 1393  ACM Digital Library |

| Total 2306 after de-duplication |
|---------------------------------|
| Book section: 9 |
| Series: 31 |
| Journal: 1150 |
| Conference: 1116 |

| Total 801 after Title, Abstract and Method Screening |
|---------------------------------------------------|
| Exclusion criteria: |
| • Non-clinical data (English) |
| • Non-information extraction |

| Total 225 after Full-text Screening |
|------------------------------------|
| Exclusion criteria: |
| • Abstract |
| • No methodology description |
| • Relation extraction |
| • Coreference resolution |

| 102  Rule-based |
|-----------------|
| 51  Hybrid |
| 48  Traditional Machine learning |
| 18  Deep learning |

3. **RESULT**

Figure 3 shows the number of articles and the associated methods used from January 2009 to June 2019 demonstrating an upward trend of clinical concept extraction research. Among 219 articles, the rule-based approach was the most widely used approach for concept extraction (46%), followed by hybrid (23%), traditional machine learning (22%), and deep learning (8%). Despite the lowest utilization rate overall, deep learning has been adopted dramatically for clinical concept extraction since 2017.

**Figure 3.** Trend View of Methodology Utilization from January 2009 to June 2019
The comprehensive mapping of each methodology with its associated application was illustrated in Figure 4 through a sunburst visualization where the applications for concept extraction were categorized into four primary domains (i.e., diseases, drugs, clinical workflows, and social determinants of health) with 20 sub-categories based on ICD-9 classification. An online interactive version accessible at VizReview was created to facilitate in-depth exploration. In the following, we provide a detailed review of methods for development processes, study settings, model development, experiment and evaluation, and practical implementation.

**Figure 4.** Overview of the Utilization of Four Different Approaches
3.1 Concept Extraction Development Process

With consultation of existing guidelines, literature [6, 17], and clinical NLP experts, we defined the process of developing clinical concept extraction solutions into four key components: 1) task formulation, 2) model development, 3) experiment and evaluation, and 4) implementation (Figure 5).

**Figure 5.** Overview of Concept Extraction Development

3.2 Study Setting
All studies were summarized into two experimental settings: shared-task settings and clinical settings. The shared-task setting is defined as participation in a shared-task challenge or subsequent use of the resources provided by the past shared-tasks to conduct concept extraction-related research. The clinical setting involves the direct use of EHRs for concept extraction. Among the total of 219 articles, 61 (28%) were categorized as belonging to a shared task setting and 158 (72%) were categorized as belonging to a clinical application setting. The overall ratios for rule-based, hybrid, traditional machine learning, and deep learning were 34%, 33%, 18%, and 15% in the shared task setting respectively and 51%, 20%, 23%, and 6% in the shared task setting, respectively. The ratio comparison shows a substantial difference between the statistical-based approaches and rule-based approaches in the two settings.

We further used Mesh API to collect the first author affiliations from 156 articles that were indexed in PubMed. Of which, 56% were affiliated with academic institution, 32% with medical center, 6% with research institution, 4% with technology company and the rest 2% were based on healthcare company, medical library and pharmaceutical company.

Shared-task Setting - Shared-tasks have successfully engaged NLP researchers in the advancement, adoption, and dissemination of novel NLP methods. Furthermore, because shared-task corpora are usually made accessible with well-defined evaluation mechanisms, they usually carried forward as standard benchmarks. competition and access to often times large open-source clinical data can drive unique solutions to difficult problems. Furthermore, because the data is often left open source and having stringent evaluation methods, these shared-tasks can carry forward as standardized benchmarks. The tasks focusing on clinical concept extraction include the Informatics for Integrating Biology and the Bedside (i2b2) challenges, the Conference and Labs of the Evaluation Forum (CLEF) eHealth challenges, and the Semantic Evaluation (SemEval) challenges. Besides that, the recent IE-related NLP shared tasks including BioCreative/OHNLP 2018 Family History Extraction, 2018 n2c2 Adverse Drug Events and Medication Extraction in EHRs, 2018 SemEval Clinical TempEval, and 2018 CLEF eHealth.

The winning system in many past shared task typically has a hybrid approach, which combines supervised traditional machine learning for concept extraction and an an abstract representation trained through unsupervised learning algorithms [1-5]. The current state-of-the-art supervised traditional machine learning models use the long short-term memory (LSTM) variant of bidirectional recurrent neural networks (BiRNN) with a subsequent conditional random field (CRF) decoding layer [12, 18-20]. The convolution neural network (CNN)-based network, such as Gate-Relation Network (GRN), also performs well in tasks requiring long-term context information [21].

Recently, the contextual pre-trained language models, such as Bidirectional Encoder Representations from Transformers (BERT) and Elmo leveraged the bidirectional training of transformer, an attention mechanism that learns contextual relations between words, resulting in state-of-the-art results in the NER task [12]. Table 1 summarized the list of past shared tasks with the state-of-the-art methods.

**Table 1.** Benchmark of Clinical Concept Extraction Tasks

| Task                                  | F-measure | Model              |
|---------------------------------------|-----------|--------------------|
| i2b2 2006 IB de-identification        | 94.6      | BioBERT [19]       |
| i2b2 2010/VA                           | 90.25     | BERT – large [20]  |
| i2b2 2012                              | 80.91     | BERT – large [20]  |
| ShARe/CLEFE 2013                      | 77.1      | BERT- Base (P+M) [22] |
| i2b2 2014 7A de-identification challenge | 93.0      | BioBERT [19]       |
| SemEval 2014 Task 7                   | 80.74     | BERT – large [20]  |
| SemEval 2014 Task 14                  | 81.65     | BERT – large [20]  |

Clinical Setting - Unlike the shared task setting, studies conducted for clinical applications may not have pre-defined tasks or fully-annotated corpora for model development and evaluation. Therefore, the study teams are required to prepare task-specific gold corpora as an additional process for concept extraction. The process of clinical
data abstraction and annotation were summarized into the following steps: data abstraction [23], study protocol development [24], cohort screening [25], and corpus annotation [26] (Figure 6).

Figure 6. Data collection and corpus annotation process

There are also studies that directly use clinical registries as gold standard outcome labels. For example, Liao et al leveraged a previously published phenotype algorithm to create cohorts of diabetes mellitus, coronary artery disease, and rheumatoid arthritis [27].

3.3 Model Development

This section provides an overview of the specific approaches for processing clinical records. Based on our review, we summarized the five model architectures provide readers a high level overview of each method (Table 2). Examples were also provided based on the relevancy of the architecture. The more indepth discussion of each architecture were provided the following two sections. §3.3.1 provides an overview of commonly used features for concept extraction. §3.3.2 discusses generic pre-processing techniques.

Table 2. Comparision of model architecture

| Methodology         | Architecture                                                                 | Example |
|---------------------|------------------------------------------------------------------------------|---------|
| Rule-based          | A. Rule-based System                                                         | [56-65] |
|                     | Raw Clinical Texts                                                           |         |
|                     | Rule-based NLP pipeline (sentence detection, tokenization)                    |         |
|                     | Manual Chart Review                                                          |         |
|                     | Results                                                                      |         |
| Traditional machine learning | B. Machine Learning System                                                 | [66-70] |
|                     | Raw Clinical Texts                                                           |         |
|                     | Feature extraction and representation Bag-of-words, Graph-of-words           |         |
|                     | Machine Learning Off, MaxEnt, HMM, SVM, Logics, Bayesian, Random forest      |         |
|                     | Results                                                                      |         |
| Deep learning       | C. Deep Learning System                                                     | [71-75] |
|                     | Raw Clinical Texts                                                           |         |
|                     | Word Representation Word embedding, Character embedding, Word2vec, CBOW     |         |
|                     | Deep Learning LSTM, BLSTM, CNN, Temporal Convolutional Neural Network         |         |
| Hybrid              |                                                                              | [28-39] |
3.3.1 Text Representation

Designing computer systems to process text requires preparing the text in such a way that a computer can understand and perform operations on it. For example, the simplest method is a naïve 1-hot encoding of the entire dictionary of words. Such a data representation presents several problems. First, the represented space is both high dimensional and highly sparse, leading to inefficient and noise. There are over 150,000 words in the English dictionary, not including domain specific vocabulary. Trying to learn from such a dataset would break almost all learning algorithms. Second, such a representation completely removes any semantic and synthetic features which may guide IE tasks. For example, “cardiac” and “heart” would have two very different representations, and therefore any IE system could not easily learn their similarities. Therefore, we often engineer data representations which either explicitly or implicitly encode semantic and syntactic similarities.

We broadly break these features down into linguistic features, domain knowledge features, statistical features, and general document features, as summarized in Table 2. Features such as part of speech tagging, bag-of-words, and language models are used to give models more information on how to complete its task. Different approaches also tend to use different features. For example, the top three frequently used features for traditional machine learning (non-deep learning) and hybrid approaches are lexicon features (24%), syntactic features (20%), and ontologies (13%). Many rule-based systems are dependent on explicitly created features which tend to be more interpretable to humans. Alternatively, the latest techniques in deep learning create features which are often abstract (e.g. word embeddings or language models) and implicitly encode the semantic or synthetic features. Such features are very difficult to use by rule-based systems, but can greatly improve deep learning systems.

Table 3. Features for Concept Extraction

| Feature Categories | Feature Types | Description | Approaches | Examples |
|--------------------|---------------|-------------|------------|----------|
| Linguistic features | Lexicon feature | A dictionary or the vocabulary of a language | Bag-of-words (BoW); “periarticular joint infection” |
| Orthographic features | A set of conventions for writing a language | Spelling; capitalization; hyphenation; punctuation; special characters | “igA”; “Pauci-immune vasculitis”; “BRCA1/2” |
| Morphologic feature | Structure and formation of words | Prefix; suffix | “Omnipaque” is the prefix of “Omnipaque” |
| Syntactic feature | Syntactic patterns presented in the text | Part-of-Speech, constituency parsing, dependency parsing | “Communicating [verb] by [preposition] sinus tract [noun]” |
### 3.3.2 Rule-based approach

Symbolic rule-based extraction uses a comprehensive set of rules and keyword-based features to identify predefined patterns in text [49, 50]. The rule-based approach has been adopted in many clinical applications due to their simplicity and effectiveness of implementing domain-specific knowledge. One particular advantage of using rule-based approach is that the solution provides reliable results in a timely, accurate, and low-cost manner, with the benefit of not needing manually annotated a large amount of training examples [6]. Based on specific tasks, the combination of rules and well-curated dictionaries can result in excellent performance. Many tasks have used rule-based matching methods to varying levels of success [51-53]. For example, in the 2014 i2b2/UTHealth De-identification challenge, the top four performing teams (including the winning team) used a rule-based approach [54]. In previous i2b2 challenges, the 2009 medication challenge [55] reported 10 rule-based systems in the top 20 systems. In the i2b2/UTHealth Cardiac risk factors challenge, Cormack et al demonstrated that a pattern matching system can achieve competitive performance with diverse lexical resources [56].

| Semantic feature | Semantic patterns presented in the text (whether a word is semantically related to the target words) | Synonym; hyponym/hypernym (etc), frame semantics | “Loosing” is semantically related to “subsidence”, “lucency”, and “radiolucent lines” |
|------------------|---------------------------------------------------------------------------------|-------------------------------------------------|------------------------------------------------------------------|
| Sequential feature | Sequence order to each word (label assigned to previous words) | Concept position: Inside–outside–beginning (IOB), B-beginning, L-intermediate, E-end, S-single word entity and O-outside (BIESO) | “Patient [O] has [O] an [O] acute [B] infarct [I] in [I] the [I] right [I] frontal [I] lobe [E]” |
| Domain knowledge features | Conceptual feature | Semantic categories and relationships of words | Classifications and taxonomies, thesauri, ontologies: | ICD9/10, NCI Thesaurus, UMLS, UMLS Semantic Network, usecase-specific code systems or controlled terminology |
| Statistical features | Graphic feature | Node and edge for each word in a document | Graph-of-Words (GOW) [48] | Bi-directional representation: “grade” - 3; 3’; “grade” |
| Statistical corpus features | Features generated through basic statistical methods | Word length, TF-IDF, semantic similarity, distributional semantics, co-occurrence | |
| Vector-based representation of text | One-hot encoding Word embedding Sentence encoding Paragraph encoding Document encoding | Word2vec/doc2vec, Bert, one-hot character-level encoding. | Embedding feature |
| General document features | Pattern and rule-based feature | A label for a note if certain rules satisfied | Logic (if-then) rules and expert systems | If “Metal” and “Polyethylene” then “Metal-on-Polyethylene bearing surfaces” |
| Contextual feature | Context information | Negated; status; hypothetical; experienced by someone other than the patient | “Patient [experiencer] does not [negation] have history of [status] infection” |
| Document structural feature | Structural and organizational patterns presented in the text and document | Section information; indentation; semi-structured information | “Family History [section]: CVD Diabetes Hypertension” |
The development of rules is an iterative process that requires manual effort to hand craft features based on clinical criteria, domain knowledge or expert opinions. The following steps were summarized based on the reported utilization and importance: (1) rule-based system adoption, (2) assessment of existing knowledge resources, (3) development of features and logic rules, and (4) iterative rule refinement. The top performed rule-based applications often utilize existing NLP systems (frameworks). There are many different NLP systems developed at different institutions and utilized to convert clinical narratives into structured data that may be used for other clinical applications and studies, including MedLEE[57], MetaMap[58], KnowledgeMap[59], cTAKES[60], HiTEX[61], and MedTagger[62]. A comprehensive summary of NLP systems can be found [7]. Adopting of existing resources such as clinical criteria, guideline, and clinical corpus can substantially reduce development effort. The most common case is to leverage well curated clinical dictionary. The dictionary acts as the domain or task specific knowledge base, which can be easily modified, updated, and combined [63]. It works best in tasks and situations where modifier detection and the recognition of complex dependencies in the document is not necessary[64, 65], such as de-identification. Since the common features being exploited are morphologic, lexical and syntactic, the dictionary-based methods are highly interpretable, adoptable and customizable. Well-established medical terminologies and ontologies such as Unified Medical Language System (UMLS) metathesaurus, Medical Subject Headings (MeSH), and MEDLINE, have been used as the basis for clinical information extraction tasks as it already contains well-defined concepts associated with multiple terms [66]. In 2014 i2b2/UTHealth challenge, Khalifa and Meystre leverage UMLS dictionary lookup to identify cardiovascular risk factors and achieved a F-measure of 87.5% [51]. Table 3 provides the summary of the list of dictionaries used in our review papers.

**Table 4. Summary of dictionary for clinical concept extraction**

| Name                                      | Description                                                                 | Link                                                                 | Number of Articles |
|-------------------------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------|--------------------|
| Unified Medical Language System (UMLS) - Metathesaurus | Biomedical thesaurus organized by concept and it links similar names for the same concept | https://www.nlm.nih.gov/research/umls/knowledge_sources/metathesaurus/   | 14                 |
| Wikipedia                                  |                                                                              | https://en.wikipedia.org/wiki/                                        | 3                  |
| MEDLINE plus                               | Bibliographic database of life sciences and biomedical information         | https://www.nlm.nih.gov/bsd/medline.html                              | 2                  |
| MeSH (Medical Subject Headings)           | MeSH is the NLM controlled vocabulary thesaurus used for indexing articles for PubMed. | https://www.ncbi.nlm.nih.gov/mesh                                   | 1                  |
| RadLex                                     | Radiology lexicon                                                          | http://www.radlex.org/                                                | 1                  |
| BodyParts3D                                | Anatomical concepts                                                        | https://dbarchive.biosciencedbc.jp/en/bodyparts3d/download.html       | 1                  |
| NCI Database                               | Cancer related information                                                  | https://cactus.nci.nih.gov/download/nci/                              | 1                  |
| PredMED                                    | Drug related                                                               |                                                                     | 1                  |
| Berman taxonomy                            | Tumor taxonomy                                                             |                                                                     | 1                  |
| CTCAE                                      | Common Terminology Criteria for Adverse Events                              | https://ctep.cancer.gov/protocolDevelopment/electronic_applications/etc.htm | 1                 |
In many situations, solely relying on dictionary cannot fully capture all the patterns, and custom rules are created to address complex patterns. The creation of custom rules is an iterative process involving multiple subject matter experts. At each iteration, the rules are applied to a reference standard corpus, and its results are evaluated. The algorithm was applied to the training data. False classified reports were manually reviewed by domain experts. This pattern repeats until all issues were resolved. For example, Cormack et al leveraged data-driven rule-based approachology - start with high recall rules and refine them to increase precision while maintaining recall with contextual patterns based on observations [56]. Kelahan et al extract impression text and assign positive and negative labels to sentences based on manual rules. The final label of the radiology report is determined based on greater frequency of sentence labels [67].

3.3.3 Supervised traditional machine learning approach – feature engineering

Advances in methods and computational power have shepherded in a traditional machine learning era of NLP. Although the rule-based approaches can be developed on a small number of documents, traditional machine learning can learn from the patterns without explicit programming through learning the association of input data and labeled outputs [11, 68-70]. The learning function is inferred from the data, with the form of the function limited only by the assumptions made by the learning algorithm. As machine learning algorithms can learn from raw text data, it is typical to provide these algorithms with human developed features (e.g. part-of-speech, etc.). Although feature engineering can be complex, the ability to process and learn from large document corpora’ greatly reduces the need to manually review documents and also has the possibility of developing more accurate models. For example, Esuli leveraged supervised traditional machine learning methods over rule-based approach due to the human effort required for annotating the texts needed for training the system is smaller [71].

The processes of developing traditional machine learning methods were summarized into the following steps: data pre-processing, feature extraction, modeling, optimization, and evaluation. Raw text is difficult for today’s computers to understand. In particularly, non-deep learning methods were developed to learn from categorical or numerical data. Therefore, it is common to pre-process the text into a format that is readily computable. There are a wide variety of different pre-processing methods which have been proposed, however they are outside the scope of this manuscript. Standard pre-processing techniques include sentence segmentation that splits text into sentences, tokenization that divides a text or set of text into its individual words, stemming that reducing a word to its word stem, POS tagging that marking up a word in a text (corpus) as corresponding to a particular part of speech, and dependency parsing. NLTK and Stanford parser were the two most popular toolkits for performing data pre-processing [72-75].

The majority of traditional machine learning approach leverages bag-of-words for the word representation [73, 76-80]. Bag-of-words often tokenize words in sparse, high dimensional one-hot space. Although simple, this approach introduces sparsity, greatly increases the size of data, and also removes any sense of semantic similarity between words. Building on top of an existing bag of words feature, Yoon et al proposed graph-of-words, a new text representation approach based on graph analytics which overcomes the limitations by modeling word co-occurrence [48]. Chen et al proposed a clustering method using Latent Dirichlet Allocation (LDA) to summarize sentences for feature representation [81]. Another approach to text representation is to leverage deep learning to automatically learn abstract, low-dimensional representation of the words. Common ones are word2vec [82-85] or CBOW [86, 87]. Recently, advanced embedding and language representations have further improved the state-of-the-art in clinical concept extraction. Conventional word embeddings capture latent syntactic and semantic similarities, but cannot incorporate context dependent semantics present at sentence or even more abstract levels. Peter et al addressed this issue through training a neural language model which was able to capture the semantic roles of words in context. They found that the addition of the neural language model embeddings to traditional word embeddings yielded state-of-the-art results for NER and chunking [18]. In a step more abstract, Akbik et al proposed character-level LM to capture not only the the latent syntactic and semantic similarities between words, but also capture linguistic concepts such as sentences, subclauses and sentiment[88]. Many these embeddings can be used in conjunction with others. For example, Liu et al used both token-level and character-level word representations as the input layer [82]. Choosing the appropriate embedding for the task can have large effects on the end model performance [82, 86].

The labeling for concept extraction is typically more complex compared to the standard classification or regression task. This is because entities in text are varying in length, location in text, and context. Commonly reported labeling for traditional machine learning include boundary detection-based classification and sequential labeling. Boundary
detection aimed at detecting the boundaries of the target type of information. For example, the BIO tags use B for beginning, I for inside, and O for outside of a concept [89]. Sequential labeling based extraction methods represent each sentence into a sequence of tokens with a corresponding property or label. One particular advantage of sequential labeling is the consideration of the dependencies of the target information. Despite that, the classification-based extraction is more commonly used than the sequential labeling based extraction.

Table 5. Summary of Traditional machine learning (non-deep learning) Approaches

| Learning Task                  | Tag Examples                      | Word Representation                                      | Model Examples                                      | Number of Articles |
|-------------------------------|-----------------------------------|---------------------------------------------------------|-----------------------------------------------------|--------------------|
| Boundary detection-based classification | Word position tag (i.e. BIO, BIESO); Binary outcome tag (i.e. 0, 1) | Flat or naive representation; clustering-based word representation; distributional word representation | SVM; SSVM, Naïve Bayes; Decision Trees; AdaBoost; RandomForests; MIRA[90] | 15                 |
| Sequential learning           | Word level tag (i.e. POS)         | Sequential representation                               | CRF; Hidden Markov Model (HHM); Maximum Entropy Markov Models (MEMMs) | 10                 |

Frequently used traditional machine learning models for clinical concept extraction includes conditional random fields (CRF)[91], Support Vector Machine (SVM)[92], Structural Support Vector Machines (SSVMs), Logistic Regression (LR)[92], Bayesian model, and random forest[93]. Among above mentioned, CRF and SVM are the two most popular models for clinical concept extraction[94]. CRFs can be thought of as a generalization of LR for sequential data. SVMs use various different kernels to transform data into a more easily discriminative hyperspace. SSVMs is an algorithm that combines the advantages of both CRFs and SVMs [94]. Tang et al compared SSVMs and CRF using the data sets from 2010 i2b2 NLP challenge, the SSVMs achieved better performance than the CRFs using the same features.

3.3.4 Supervised traditional machine learning approach - deep learning

Deep learning is a subfield of traditional machine learning that focuses on automatic learning of features in multiple levels of abstract representations [95]. The algorithms are largely focused around neural networks such as recurrent neural networks (RNN) and CNNs, although there are a few other niche approaches. Deep learning led to revolutionary developments in many fields including computer vision[96, 97], robotics[98, 99], and of course NLP. In contrast to standard traditional machine learning paradigm, deep learning minimizes the need to engineer specific data representations such as bag-of-words or n-grams. These learned representations have can improve performance in many applications, as they can capture latent syntactics and semantics in ways that are more interpretable by the machine compared to human engineered representations.

Much of deep learning in concept extraction have used either variants of RNNs or CNNs. CNNs are aptly named as they rely on convolutional filters to capture spatial relationships in the inputs and pooling layers to minimize computational complexity. Although these have been found to be exceptionally useful for computer vision tasks, CNNs tend to have a difficult time capturing long distance relationships that are common in text. RNNs are neural networks which explicitly models connections along a sequence, making RNNs uniquely suited for dynamic tasks. Conventional RNNs are limited in length of text (and therefore limit in the maximum distance between words) which they can model due to problems with vanishing gradients. Variants such as LSTM and gated recurrent unit (GRU) have been developed to address this issue by explicitly updating the gradient between words. However these only diminish the issue rather than completely solve it, being still limited to sequence lengths on the order of 10s-100s of words long. Furthermore, training these models are very computationally intensive and difficult to parallelize as the weights need to be trained in series. Recently, transformer architecture has been proposed to solve many of these problems. The transformer architecture circumvents the need to sequentially process text by processing the entire sequence at once through a set of matrix multiplications, allowing the network to memorize what element in the sequence is important. Obviously if the sequences are long, the memory requirements for training explodes. Therefore, adding breaking up the sequence to smaller pieces and adding subsequent layers allow the model to accommodate long sequences of text without crippling memory constraints. Thereby, transformers can
effectively model relationships which are 1,000s or even 10,000s of words apart and are much more computationally efficient compared to RNN variants. Models based on this architecture such as BERT [12] and GPT [Radford] have yielded significant improvements for state-of-the-art performance in many NLP tasks [peng]. Many of these architectures can support different applications and tasks with minimal modifications. For example, Also, using a deep learning model does not preclude using a conventional traditional machine learning model. Although deep learning models are extremely powerful feature extractors, other models may have specific attributes which suit particular needs of the problem. This is evident as many of the researchers combined conditional random field (CRF) with various deep neural networks (word embeddings input) to improve the performance on NER, such as Bi-LSTM-CRF (44%), Bi-LSTM-Attention-CRF (22%), and CNN-CRF (22%). This is to take advantage of their relative strengths: long distance modeling of RNNs and CRF’s ability to jointly connect output tags.

Despite the power, generalizability, and ease of use, deep learning approaches still represent only a fraction of published data. The utilization of deep learning approaches in the share task setting is 11.8%, which is higher than the clinical setting (2.7%). Most deep learning approaches fell into two applications: data privacy and disease. The relative lack of representation can be attributed to the computational expense of deep learning and the need for large amounts of annotated data. Deep learning methods are very computational expensive to train, requiring large numbers of GPUs. This may not be feasible for many research settings, as the infrastructure can be expensive. Second, most deep learning architectures have a huge number of parameters, thereby requiring large amounts of annotated data to properly train. Conventional traditional machine learning methods are much simpler, and easier and faster to train [100]. Choosing the correct algorithm that is appropriate for both the research setting and dataset is key to produce a successful model.

3.3.5 Hybrid approach

Hybrid approaches combine both rule- and traditional machine learning-based approaches into one IE system, potentially offering the advantages of both and minimizes their weaknesses. Rule-based approaches in the hybrid approaches mostly aim to extract NLP features using rules as described in Section 3.2.2 due to the weaknesses of pure rule-based systems. One such weakness of rule-based systems is the need to explicitly define entities. When the number of entities is large or hard to define, creating a dictionary becomes extremely labor intensive. Yim et al. solved this by combining regular expressions with a binary logistic regression classification algorithm to extract organisms and specimen entities to avoid explicitly defining the large and diverse organism abbreviations [Yim, Evans [40]. Rule-based systems can also be used to improve traditional machine learning results. Yang and Garibaldi leveraged a dictionary-based method to supply a CRF model for medication concept recognition. The hybrid model achieved desired performance on 2014 i2b2 challenge [43]. In a study to automatically extract heart failure treatment performance metrics, hybrid system outperform both rule- and traditional machine learning-based approaches (ID:50). Traditional machine learning systems tend to do best when the task dataset has well-balanced outcomes. However, many IE tasks’ datasets are highly imbalanced, therefore making learning difficult. Farkas and Szarvas-[ref5] added specific “trigger words” as rules to improve their traditional machine learning de-identification system. Explicitly crafting the rules for these “trigger words” effectively created a “balanced” outcome, improving the algorithm’s ability to correctly learn patterns.

There are two major hybrid approach architectures, as shown in Table 2. According to how traditional machine learning approaches were leveraged, we named these two architectures as either terminal hybrid approach or supplemental hybrid approach. In the terminal hybrid approach, NLP approaches are used as feature extraction, the NLP outputs became the ML system feature inputs, and finally, the ML system was a terminal step to select optimal features. We found that the hybrid approaches used in 12 out of 20 studies were in this category. For example, Wang and Akella [33] used NLP features, such as semantic, syntactic, and sequential features, as input to a supervised traditional machine learning to extract disorder mentions from clinical notes. Other applications of hybrid systems include automatic de-identification of psychiatric notes (ID:572, 570) and detection of clinical note sections (ID:303). Table 3 lists the available NLP features used in the included studies. In the supplemental hybrid approach, the ML system was performed as a supplement to the rule-based NLP system to extract entities that were unable or of low accuracy to be extracted by the NLP system. In one study, such supplemental hybrid system was incorporated with a user interface for interactive IE process (ID:545). For example, Meystr et al. [47] leveraged traditional machine learning classifier to extract congestive heart failure medications as a supplement to the rule-based NLP system that extracted mentions and values of the left ventricular ejection fraction, etc. for treatment performance measures assessment.
3.4 Experiment and Evaluation

Rigorously evaluating the performance of the models is a crucial process for developing valid and reliable models. Evaluation is usually performed at a patient level, document level, or concept level. The level of which to perform the evaluation should be made according to the specific task/application. For example, patient level detection may be sufficient if the task is to detect patients with a disease or a disease phenotype. However, identification of the time of presentation likely requires more fine-grain evaluation. The determination of evaluation, as with any data science task, should be made in consultation with clinical subject matter experts and in the context of application.

The evaluation can be performed by the construction of confusion matrix or contingency table to derive the error ratios. Commonly used ratios measure the number of true positives (predicted label occurs in the gold-standard label), false positives (the predicted label does not occur in the gold-standard label), false negatives (label occurs in the gold-standard label but not as a predicted label), and true negatives (the total number of occurrences that are not predicted to be a given label minus the fps of that label). From these measures, the standardized evaluation metrics, including sensitivity or recall, specificity, precision or positive predictive value (PPV), negative predictive value (NPV), and f-measure, can then be created based on the error ratios. Because traditional machine learning and deep learning models also provide probability logics, for the performance can also be evaluated using area under the ROC curve (AUC) and the area under the precision-recall curve (PRAUC).

A majority of IE methods are evaluated using the hold-out method, where the model is trained on training (and possible validation) sets and evaluated on the held-out test set. Cross validation (CV) can also be used to estimate the prediction error of a model by iteratively training using part of the data and leaving the rest for testing. However, applying CV for error estimation on tuned models using CV may yield biased result. The nested-cross-validation that uses two independent loops of CV for parameters tuning and error estimation can significantly reduce the bias of the true error estimation.

For multiclass prediction or classification, micro-average and macro-average are two methods of weight prioritization. The micro-average calculates the score by aggregating the individual rates (i.e. true positive, false positive and false negative). The macro-average calculates the metrics score (i.e. precision and recall) by each class (i.e. positive and negative) first and then average by the number of class. In addition, mean squared error was also used for evaluating multiclass prediction or classification tasks.

Another important aspect of evaluation Cohen's kappa coefficient is used to measure the inter- or intra-annotator agreement. Human annotators are imperfect, and therefore various problems may be more or less difficult to annotate. This can be due to fatigue, variation in interpretability, or annotator skill. This measure can be important to giving context on the performance of the model, as well as difficulty of the concept extraction task.

3.5 Practical Implementation

When the models are carefully evaluated, they will be implemented for clinical and research use. The implementation process is highly depended on the institutional infrastructure, system requirements, data usage agreements, and research and practice objectives. The majority of the articles implemented the models into different standalone tools with the advantage of flexibility, low development cost, and low maintenance effort. For example, Fernandes et al implemented a suicide ideation model by developing an additional platform to host the traditional machine learning component. Others have implemented the model into their institutional IT infrastructure, which includes an ETL process for document or HL7 messages retrieval, a parser document pre-processing, an engine to host and run rule-based or traditional machine learning models, and database to store extracted results. A more detailed description of the infrastructure, techniques, and challenges is out of the scope of this manuscript. However, interested readers can read.

4. DISCUSSION

From task formulation to practical implementation, we provided a systematic review of the methodology development for clinical concept extraction. We hope, through the studying of different approaches with variant clinical context, can practically enhance the decision making for the development of clinical concept extraction. Our review summarized the current practice of four different approaches to perform the task based on a total of 226 studies from January 2009 to June 2019. However, the specific use of the approach may depend on the context. The following sections discussed the specific use case based on four different context: data, interpretability, customizability, and external resources.
First, due to the differences of study settings, clinical objectives, and team background, the decision to implement the type of approaches can be complicated. In the context of clinical setting, one key challenge to have well-curated and voluminous clinical corpus. Unlike web data such as Wikipedia or Rottentomatos, it is very difficult to crowdsource annotation of EHR data due to privacy laws and requirement of medical expertise. The availability of data becomes a key consideration for determining the type of methods. For example, the amount of data used to train traditional machine learning, specifically deep learning methods may impact the reliability and robustness of the model. On the other hand, rule-based systems have less demand of training data and can be more appropriate when the data set is relatively small. Alternatively, when large amounts of labeled data is available and the task has a significant degree of ambiguity to it, traditional machine learning approach can be considered. This pattern was confirmed by Figure 4 that traditional machine learning had a high utilization than rule-based approach in shared-task setting and vice versa.

Second, considering many models will eventually be implemented for clinical use, the evaluation of a successful model may not solely rely on the performance accuracy, but interpretability, which refers to the capabilities of the model to explain why the decision made and is usually referred to as a key factor of “user trust” [101, 102]. In general, the higher complexity in the training process, the less interpretability that model has. Most of the traditional machine learning models, especially for deep neural networks, are considered as black boxes, and there has been a surge of interest in interpreting these models to explain the statistical inference from output results. In clinical setting, these explanations may serve as important criteria for safety and bias evaluation. Therefore, interpretable traditional machine learning models (e.g., logistic regression, decision tree, support vector machine) are still widely used in clinical domain compared to the state-of-the-art deep learning approaches, due to their explanatory capabilities, transparency of model components, and interpretability of model parameters and hyperparameters [103]. On the other hand, the rule or pattern-based features are highly interpretable. For example, Mowery et al. used regular expressions along with different semantic modifiers to conduct NER of carotid stenosis findings. Based on the clinical definition of carotid disease, semantic patterns were organized into laterality (i.e. right, left), severity (i.e. critical or non-critical), and neurovascular anatomy (i.e. internal carotid artery) [104]. The semantic pattern successfully captured important findings with high interpretability.

Customizability measures how each model can be easily modifiable when the concept definition has changed or there is an update of clinical guideline. Among the previous method presented, the rule-based approach has the highest customizability and allow the model to be easily modified and refined. For example, Sohn et al. applied a rule-refinement process when deploying an existing pattern matching algorithm to a different site to achieve high portability [105]. Davis et al. adopted four previously published algorithms for the identification of patients with multiple sclerosis using the rules combine multiple features including ICD-9 codes, text keywords, and medications lists [106]. The final updated algorithm was shared on PheKB, a publicly available phenotype knowledgebase for building and validating phenotype algorithms [107]. Xu et al. leveraged existing algorithms from the eMERGE (electronic Medical Records and Genomics) network to identify patients with type 2 diabetes mellitus[108]. Regarding traditional machine learning and deep learning models, it is difficult to make customization explicitly due to their data-driven nature. In order to accommodate the models to specific clinical problems, incorporating knowledge-driven perspectives (e.g., sublanguage analysis and biomedical ontology) with the models are commonly adopted to customize the models implicitly. For example, Shen et al., combined surgical site infection features generated by sublanguage analysis with decision tree, random forest, and support vector machine to mine postsurgical complication patients automatically from unstructured clinical notes [109]. Castelheiro et al., combined the word2vec model with knowledge formalized in the cardiovascular disease ontology (CVDO) to provide a customized solution to extract more pertinent CV-related terms from biomedical literatures [110]. The HPO2Vec+ framework provides a way to generate customized node embeddings for the Human Phenotype Ontology (HPO) based on different selections of knowledge repositories, in order to accelerate rare disease differential diagnosis by analyzing patient phenotypic characterization from clinical narratives [111].

**Figure 7.** Data and usability perspective of different concept extraction approaches
Another consideration is the availability of clinical resources. For the rule-based approach, developing rules may require substantial manual efforts such as iterative chart review and manual feature crafting. It may be challenging to involve clinicians to help with case validation and shared-decision making. However, large amounts of a priori knowledge about the domain and clinical problem (i.e. clear concept definition, well-documented abstraction protocol) and availability of clinical expenses are favorable indicators for success of rules-based approach. Liu et al performed a sublanguage analysis of the training data suggesting that excellent textual biomarkers exist with strong associations with the target concept [112]. Transfer learning, an approach to reuse a model trained over an old task as the pre-trained model for a new task, has been widely used in deep learning and NLP specifically. One of such famous pre-trained models is BERT (Bidirectional Encoder Representations from Transformers) [12], which applied the transformers model [113] over huge narratives to generate a robust language representation model. Following the same strategy, some clinical NLP researchers investigated on generating clinical language models as well as clinical embeddings leveraging BERT [20]. The aforementioned models and embeddings are considered as valuable resources for clinical NLP research.

**Citation**

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