

Extraction of Diagnostic Reasoning Relations for Clinical Knowledge Graphs

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Abstract

Clinical knowledge graphs lack meaningful diagnostic relations (e.g. comorbidities, sign/symptoms), limiting their ability to represent real-world diagnostic processes. Previous methods in biomedical relation extraction have focused on concept relations, such as *gene-disease* and *disease-drug*, and largely ignored clinical processes. In this thesis, we leverage a clinical reasoning ontology and propose methods to extract such relations from a physician-facing point-of-care reference wiki and consumer health resource texts. Given the lack of data labeled with diagnostic relations, we also propose new methods of evaluating the correctness of extracted triples in the zero-shot setting. We describe a process for the intrinsic evaluation of new facts by triple confidence filtering and clinician manual review, as well as extrinsic evaluation in the form of a differential diagnosis prediction task.

1 Introduction

Knowledge graphs (KGs) are increasingly utilized in key knowledge-intensive applications, such as recommendation and question answering. However, their utility in these systems can be limited due to missing facts (triples) among entities (Balazevic et al., 2019). The missing knowledge in KGs largely comes from three main sources: missing unknown entities, missing unknown relations, and missing existing relations between known entities. Significant advances have been made in the general and biomedical domains in recent years to tackle each of these problems, using techniques from the NLP and graph communities such as entity linking (EL) (Thibault Févry, 2020), relation extraction (RE) (Trisedya et al., 2019), and link prediction (Kazemi and Poole, 2018).

In the clinical domain, SNOMED-CT¹ is the most comprehensive and broadly used knowl-

Relation Name	# of Rel. (%)
isa	567356 (19.0)
mapped_to	140394 (4.7)
finding_site_of	95138 (3.2)
same_as	90158 (3.0)
possibly_equivalent_to	80502 (2.7)
associated_morphology_of	70230 (2.4)
method_of	64902 (2.2)
interprets	37094 (1.2)
direct_procedure_site_of	35592 (1.2)
pathological_process_of	21719 (0.7)

Table 1: Names and occurrences of top 10 relations in SNOMED-CT.

edge base, containing over 350,000 medical concepts and 1 million relations organized into a poly-hierarchy. When mapping documentation to SNOMED-CT, Travers and Haas (2006) found high coverage of clinical concepts. However, its taxonomic structure leads to a lack of clinically meaningful relations between concept hierarchies. Therefore, in this work we focus on the problem of missing unknown relations.

As shown in Table 1, SNOMED-CT largely contains hierarchical *is-a/has-a* relations and lacks important diagnostic relations between clinical concept hierarchies. For instance, since SNOMED-CT lacks a *is_contraindicated_by* relation, associations between medications and clinical findings are largely missing. Those existing inter-hierarchy relations are often trivial and would not meaningfully contribute to downstream knowledge representation (e.g. litigation of aneurysm of popliteal artery \rightarrow direct_morphology_of \rightarrow aneurysm). Explicit relations (e.g. comorbidities, sign/symptoms, risk factors) that draw meaningful connections between entities in different hierarchies have the potential to better model clinical reasoning and understand text describing diagnostic processes, such as progress notes and discharge summaries.

¹<https://www.nlm.nih.gov/healthit/snomedct>

In this work, we define a set of missing clinically meaningful diagnostic relations based on an existing clinical reasoning ontology (CRO). We then propose two methods of adding such relations to the SNOMED-CT knowledge graph (KG) using distinct and complementary data sources. We describe a relation extraction task using a semi-structured emergency department (ED)-focused wiki and a zero-shot relation classification (RC) task using a newly gathered corpus of consumer health information derived from MedlinePlus² and Merck Manuals (Bullers, 2016), described in detail in section 3.2. Throughout this work, we will address the following research questions:

RQ1. Can we leverage the semi-structured form of a wiki to extract reasoning relations?

RQ2. Do consumer health resources provide distinct missing relations from those found in RQ1?

RQ3. How do we evaluate the accuracy of new relations in a clinical KG?

In RQ1 and RQ2, we limit ourselves to a predetermined set of relations to minimize hand curation by domain experts, such as would be required with free text relations extracted using an open information extraction system (Juric et al., 2020). However, we still need to determine the accuracy of our new facts to evaluate the model. This leads us to RQ3, in which we determine how to evaluate the accuracy of new relations in a clinical KG, given that such relations don't currently exist. We propose intrinsic and extrinsic methods of evaluation in this zero-shot setting.

The rest of this proposal will be structured as follows. In section 2, we will describe the existing biomedical and clinical relation extraction datasets and methods, as well as the CRO we define our relation label set on. In section 3, we describe our methodology for RQ1 and RQ2. Finally, in section 4, we discuss two strategies to address RQ3: manual evaluation by clinician review after pruning low confidence triples and prediction on a proxy clinical diagnostic reasoning task.

2 Related Work

2.1 Biomedical Relation Extraction

Considerable progress has been made in biomedical relation extraction, with large language models achieving state of the art results on a variety of tasks (Lee et al., 2020). Biomedical relation extraction datasets largely concentrate on relations

between a few entity types such as chemicals and diseases (Li et al., 2016) or chemicals and proteins (Krallinger et al., 2017). A number of these tasks have been consolidated as part of a large biomedical language understanding benchmark known as BLURB (Tinn et al., 2021). The authors also pre-trained a BERT model, PubMedBERT, on PubMed abstracts, achieving over 80% micro F1, averaged over three RE tasks. In the autoregressive setting, SciFive (Phan et al., 2021) further improved on these results, achieving an average of 84% micro F1, averaged over two RE datasets.

However, biomedical RE tasks do not capture clinical relationships. Due to the cost of anonymization, clinical RE datasets tend to be smaller and more limited. Many are focused on particular tasks such as adverse event and medication treatment relations. For instance, the 2010 i2b2/VA challenge (Uzuner et al., 2011) requires assigning relation types between conditions, tests, and treatments. Similarly, Henry et al. (2020) propose a RE task in which adverse events and signatures are related to medications. Outside of the pharmaceutical relation space, we only found one task with available data, involving temporal relation extraction (Sun et al., 2013).

Despite considerable progress, most clinical datasets don't effectively model real world settings in which the class of relations can be large, include both existing and missing relation types, and few training examples for a particular relation may exist. Our task of identifying and extracting new diagnostic relations falls within this category. The models developed in this project may help us better understand the real world challenges of extracting new meaningful relation types for KG construction.

2.2 Clinical Reasoning Ontologies

Clinical decision tools often need to model diagnostic axioms employed by clinicians to derive decision rules and provide users with relevant alerts and recommendations. Many of these tools use existing ontologies (Mohammed and Benlamri, 2014) or domain experts (Abidi et al., 2007) to develop a controlled set of reasoning terms. In order to standardize the vocabulary used to model the clinical reasoning process, Dissanayake et al. (2020) identified a set of preexisting ontologies through literature review. They then propose a consolidated ontology, normalizing reasoning concepts and relations. In this work, we model our reasoning relation extrac-

²<https://medlineplus.gov>

tion task as a classification task among a relevant subset of relationships [Dissanayake et al. \(2020\)](#) propose, including important inter-hierarchical relations such as *complication_of* and *comorbidity_of*. We describe a subset of relevant relations, along with the SNOMED-CT hierarchies they involve, in [Table 2](#).

The full list of relations that define our label set can be found in [Appendix B](#).

3 Research Plan

3.1 Wiki-Based Relation Extraction

In order to extract relations relevant to diagnostic reasoning, we select WikEM ([Donaldson et al., 2016](#)), a domain-specific point-of-care reference wiki under active development by ED residents at Harbor-UCLA Medical Center for clinical use during diagnostic processes. It has over 7000 pages and is based on Mediawiki³, the same wiki engine underlying Wikipedia. Unlike Wikipedia’s Wikidata project ([Vrandečić and Krötzsch, 2014](#)), smaller domain-specific wikis rarely have an accompanying structured knowledge base. Therefore, in the first part of this work we plan to automatically extract an open KG based on the existing structure within WikEM. Then, we will link these entities and relations to SNOMED-CT and the CRO, leveraging recent advances in medical EL methods. An overview of the system is shown in [Figure 1](#).

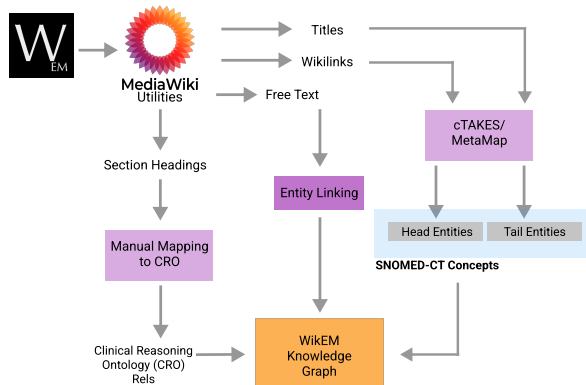


Figure 1: System overview for extraction of knowledge triples from WikEM

We first employ a wikicode parser to extract open text entities that serve as nodes. The link label will act as the head entity and the title of the link destination will become the tail entity. We also extract

³<https://www.mediawiki.org/wiki/MediaWiki>

section titles (e.g. *Differential Diagnosis*, *Evaluation*, *Management*) that serve as open text edges. In order to use this open KG in downstream tasks and integrate new triples back into SNOMED-CT, we need to link all three components of the knowledge triple. To determine the range of relations in WikEM, we visualized meaningful extracted section titles, shown in [Figure 2](#). The relations found in WikEM encompass a subset of our full relation set which we can manually map to the predetermined CRO labels. Exploratory testing has also shown that existing named entity recognition and linking methods like cTAKES ([Savova et al., 2010](#)) are effective in mapping named entity lists, like those that appear in WikEM sections (example in [Appendix A](#)). However, we will also test BERT-based models such as SapBERT ([Liu et al., 2021](#)). These two approaches allow us to map the head, relation, and tail entities of new reasoning fact triples.

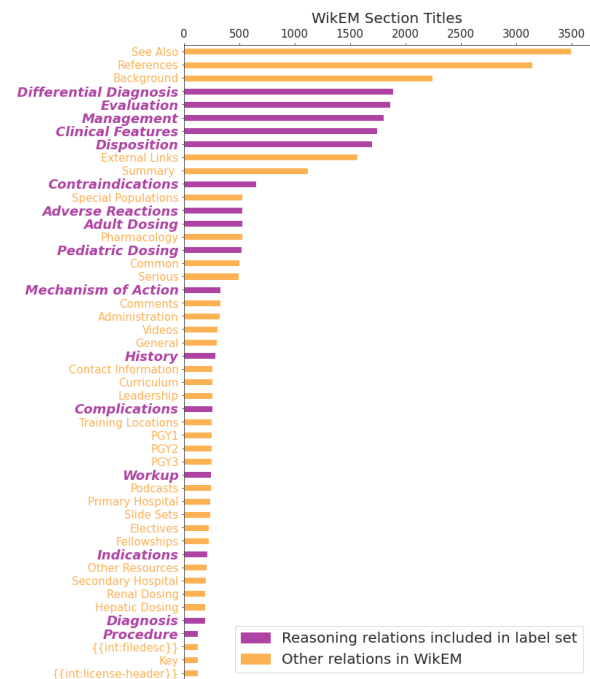


Figure 2: Most common relations extracted from WikEM section titles (relations highlighted in purple correspond to relations in our CRO label set)

3.2 Zero-Shot Relation Classification from Consumer Education Resources

While we can take advantage of the wiki structure to identify high quality triples in WikEM, relation types that aren’t captured by section titles may be missed. Therefore, we also perform RC using consumer education resources. By employing these

SNOMED-CT Head	CRO Relation	SNOMED-CT Tail
clinical finding	cause_by	clinical finding, procedure
clinical finding	is_symptom_of	clinical finding
clinical finding	hasSyndrome	clinical finding
clinical finding	has_treatment	procedure, substance
substance	Can_be_combined_with	substance
substance	has_effect_on_disease	clinical finding
substance	may_prevent	clinical finding

Table 2: Sample of relation label set for RQ1 and RQ2, including domain of SNOMED-CT top level hierarchy concepts for head and tail entities

two data sources, we may also gain some insight into different relation frequencies common to either physician- or patient-facing resources.

Similar to (Juric et al., 2020), we plan to use MedlinePlus, a curated consumer health resource developed by the National Library of Medicine. We combine this with the consumer edition of the Merck Manuals, medical references published by Merck geared towards patient education. These two sources constitute a new consumer health corpus from which we extract new clinical reasoning triples. We develop this corpus, as opposed to using a preexisting resource such as PubMed because these texts describe primary care and contain relevant reasoning relations, like side effects and comorbidities, unlike the research articles in PubMed. Unlike in RQ1, we must extract and link both entities and relations from free text in this setting.

Similar to Riedel et al. (2010)’s distantly supervised NYT corpus, we first detect and link named entities in our corpus using an end-to-end entity linker. Namely, we will fine-tune SciFive, a new T5 model (Raffel et al.) pretrained on PubMed articles, on the newly proposed autoregressive entity retrieval task (De Cao et al., 2021). Having identified a set of entities, we can take advantage of recent zero-shot relation classification methods. Many of these models use auxiliary information, like relation descriptions (Chen and Li, 2021), to reason about unseen relations. However, they don’t take advantage of semantic types. For instance, the relation *contradict_with* can only have a pharmaceutical product as its head entity and a disease as its tail entity. We propose training a BERT model to embed relations and descriptions, while restricting the search space to relevant semantic types, hopefully improving zero-shot RC results.

4 Evaluation

From RQ1 and RQ2, we have a set of new clinical reasoning triples, grounded in SNOMED-CT entities and the CRO relation set. However, without existing labeled reasoning relations, we have no way to use conventional confusion matrix-based evaluation measures. Therefore, to tackle **RQ3**, we propose two evaluation approaches.

Filtering and Evaluation By Clinicians As a first step, we plan to evaluate our zero-shot RE system on BioRel (Xing et al., 2020), a large distantly-supervised RE dataset for the biomedical domain, carefully selecting train/test splits to model the zero-shot setting. While this provides a comparison to baselines, the noisy nature of distant supervision and lack of external validation of the training data by the authors may obscure the accuracy of the model. Furthermore, this evaluation scheme doesn’t measure our final goal of contributing new facts to SNOMED-CT.

To that end, we will first calibrate our extraction model and filter out any low confidence triples. This reduces potentially noisy triples and allocates clinical resources to the most promising triples. Then, we randomly sample triples from the model and have several clinicians determine the proportion of accurate predicted relations, measuring inter-rater reliability.

Evaluation Using Proxy Discharge Diagnoses Prediction Task To investigate whether extracted diagnostic reasoning relations improve downstream clinical prediction tasks, we choose a relevant auxiliary task: differential diagnosis prediction of ED patients presenting with abdominal pain. Given a patient’s ED triage information and their past medical history, the goal is to rank the list of relevant differential diagnoses that a physician may assign the patient upon discharge in order of likelihood.

To accomplish this task, we augment patient representations with a clinical KG that includes relations derived in RQ1 and RQ2. Bisk et al. (2020) discuss the importance of augmenting language with other modalities in representation learning, and so we include other clinical variables (e.g. demographics, lab measurements, vitals) in our patient representations. To combine a drug-drug interaction network with an external knowledge base, Yu et al. (2021) extracted KG subgraphs and attended on relevant relations. Similarly, we compute a patient similarity graph and extract subsets of our 3 versions of SNOMED-CT with the goal of comparing predictive performance on a set of differential diagnoses for each ED patient. Using the attention maps, we also plan to investigate the importance of clinical reasoning relations in prediction, as compared to pre-existing relations in SNOMED-CT.

5 Societal Impact

Extraction of triples using the relation set described in this proposal and their alignment with an existing clinical KG has the potential to significantly improve automated diagnostic reasoning. For instance, a KG-augmented system may be able to remind the physician to order labs based on probable diagnoses or extract disease-specific, relevant past medical history from patient records in real-time. We can also expect improvement in conventional NLP tasks such as reading comprehension of progress notes and reports (e.g. radiology summaries) and clinical knowledge question answering (QA) involving multi-hop reasoning. Benchmarks to evaluate such tasks exist, like MMLU-Professional Medicine (Hendrycks et al., 2021) and MedQA (Jin et al., 2021), both of which draw QA pairs from medical licensure exams.

However, such benchmarks are abstractions that do not fully align with complex real-world use cases. To better model the challenges of clinical reasoning, we suggested the particular task of differential diagnosis prediction, which involves incorporating additional clinical data modalities. However, additional considerations may be necessary for evaluating KG use in real-world applications, such as modeling temporality. A task involving prediction of changing disease states over time may focus on the longitudinal nature of diagnostic reasoning. A portion of this work will involve continuing to define tasks that consider the challenges of

real-world clinical reasoning use cases.

6 Summary

In this thesis proposal, we suggest methods to address the problem of missing reasoning relations in clinical knowledge graphs. We select a subset of relations from a clinical reasoning ontology and extract relations from two data sources: a point-of-care reference for ED physicians and a newly created consumer health resource corpus. We plan to train a T5-based EL model to link entities and develop a zero-shot RE method to extract relations. Finally, we discuss methods of evaluation in the real world context of zero-shot relation extraction using filtered expert review and a proxy diagnostic reasoning prediction task. Our work should provide a case study for the complex task of introducing new types of knowledge into an existing structured knowledge base.

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A WikEM Sample Page with Entities

In Figure 3, we show the head, relation, and tail entities as they appear in an example WikEM page. In this case, if another wikilink linked to *Peritonitis*, it would act as the tail entity, and the section headings (i.e. Background, Clinical Features, Differential Diagnosis) act as relations. Finally, the link texts act as open text head entities.

The image shows a screenshot of a WikEM page for "Peritonitis". The page is annotated with red arrows and labels to identify entities and relations. The "Peritonitis" title is labeled as a "Tail Entity". The "Background" section heading is labeled as a "Relation". The "Clinical Features" section heading is also labeled as a "Relation". The "Differential Diagnosis" section heading is labeled as a "Relation". The "Diffuse Abdominal pain" section heading is labeled as a "Head Entity". The "Abdominal aortic aneurysm" link text is labeled as a "Head Entity". The "Aortocaval fistula" link text is labeled as a "Head Entity". The "Acute gastroenteritis" link text is labeled as a "Head Entity". The "Valvulus" link text is labeled as a "Head Entity". The "Contents" table of contents is also visible on the right side of the page.

Peritonitis ← **Tail Entity**

Background [edit]

- Inflammation of serosal membrane lining abdominal cavity and intraabdominal organ
- May be infectious (bacterial, viral, fungal) or sterile (mechanical, chemical)
- Etiology
 - Primary: Hematogenous, [spontaneous bacterial peritonitis](#) (SBP)
 - Secondary: Perforation or trauma, most common
 - Tertiary: Persistent/recurrent infection, [peritoneal dialysis-associated peritonitis](#)

Clinical Features [edit]

- [Abdominal pain](#) or discomfort
- Abdominal distention, tenderness
- Rebound, guarding, or rigidity on exam
- Anorexia and [nausea](#)
- Guarding or rebound
- Sepsis
- Signs of liver failure
- [Spontaneous bacterial peritonitis](#)
 - Fever and chills
 - [Abdominal pain](#) or discomfort

Differential Diagnosis [edit]

Diffuse Abdominal pain [edit]

- [Abdominal aortic aneurysm](#)
- [Aortocaval fistula](#)
- [Acute gastroenteritis](#)
- [Valvulus](#)

Evaluation [edit]

Work-up [edit]

- Imaging = CT Abd/pelvis (preferred) or 3-view abdomen XR
 - Ultrasound may reveal certain etiologies
- Other work-up based on clinical suspicion, and may include:
 - CBC, metabolic panel, coags, lipase, UA, stool studies
 - Diagnostic [paracentesis](#) to evaluate for SBP (PMN ≥ 250 cells/mm³)

Evaluation [edit]

- Generally a clinical diagnosis

Contents [hide]

- 1 Background
- 2 Clinical Features
- 3 Differential Diagnosis
 - 3.1 Diffuse Abdominal pain
- 4 Evaluation
 - 4.1 Work-up
 - 4.2 Evaluation
- 5 Management
 - 5.1 Antibiotics
 - 5.2 Intra-Abdominal Sepsis/Peritonitis
- 6 Disposition
- 7 See Also
- 8 External Links
- 9 References

Figure 3: Example of a WikEM page with Links. Each entry in the table of contents can act as a relation.

B Full Clinical Reasoning Relation Set

In Table 3, we show the full set of labels we selected from the clinical reasoning ontology developed by (Dissanayake et al., 2020), along with the domain and semantic types that the relation accepts.

Domain	Relation Name	Range
Diagnostic process	observationMethod	observation method
	Assessment_Reason	reason
	has_device	medical device
	has_Assessment	assessment
Signs & Symptoms	has_Recommendation	recommendation
	Is_assessed_by	assessment name
	is_not_caused_by	factors
	cause_by	causing factor
Diagnosis & Disease	is_symptom_of	disease
	hasSyndrome	syndrome name
	has_severity	severity level
	has_treatment	treatment
	has_Contraindication	contraindication
	has_causing_factors	causing factor
	hasRisk	risk factor
	affected_Body_Site	body part
	hasLabTest	lab test name
	has_Sign_and_Symptom	sign and symptoms
	is_transmitted_by	vector
	has_complication	complication list
	occurs_with	disease, symptom, risk factor
hasExperimentalData	experimental data related to disease	
Treatment	has_ part	order list
	part_of	treatment plan
	has_intervention_goal	intervention goal
	has_pharmacological_plan	medication list
	hasSurgicalProcedure	surgery type
	is_recommended_for_illness	recommendation
Medication	Can_be_combined_with	medication
	Contradict_with	drug ingredient
	has_treatment_target	treatment target
	has_active_ingredient	active ingredient
	has_administrationProcess	medication administration process
	has_cost	medication cost
	has_dose	dose
	dosage_Measurement_Unit	measurement unit
	has_cumulative_dose	accumulative dose
	has_drug_Form	dosage form
	has_maximum_dose	medication dosage
	has_treatment_duration	time
	has_frequency	drug Frequency
	has_effect_on_disease	medication effect on disease
	has_application_route	medication application route
	has_explanation	explanation
	has_toxicity	toxicity
component_interact_with	drug, ingredient	
may_prevent	disease	

Table 3: Full set of clinical reasoning labels selected from the CRO