Dataset for N-ary Relation Extraction of Drug Combinations

Anonymous ACL submission

Abstract

Combination therapies have become the standard of care for diseases such as cancer, tuberculosis, malaria and HIV. However, the combinatorial set of available multi-drug treatments creates a challenge, particularly in the presence of antagonistic drug combinations that may lead to negative patient outcomes. To assist medical professionals in identifying beneficial drug-combinations, we construct an expert-annotated dataset for extracting information about the efficacy of drug combinations from the scientific literature. Beyond its practical utility, the dataset also presents a unique NLP challenge, as it is the first relation extraction dataset consisting of variable-length relations. Furthermore, the relations in this dataset predominantly require language understanding beyond the sentence level, adding to the challenge of this task. We provide a strong baseline model and identify clear areas for further improvement. We release our dataset and code[1] publicly to encourage the NLP community to participate in this task.

1 Introduction

"*So far, many monotherapies have been tested, but have been shown to have limited efficacy against* ***COVID-19****. By contrast,* ***combinational*** *therapies are emerging as a useful tool to treat SARS-CoV-2 infection.*" (Ianevski et al., 2021).

Indeed, combining two or more drugs together or with non-drug treatments has proven to be useful for treatments of various medical conditions, including cancer (DeVita et al., 1975; Carew et al., 2008; Shuhendler et al., 2010), AIDS (Bartlett et al., 2006), malaria (Eastman and Fidock, 2009), tuberculosis (Bhusal et al., 2005), hypertension (Rochlani et al., 2017) and COVID-19 (Ianevski et al., 2020).

In this work, we examine the clinically significant and challenging NLP task of extracting known drug combinations from the scientific literature. We present an expert-annotated dataset and strong baseline models for this new task. Our dataset contains 1600 manually annotated abstracts, each mentioning between 2 and 15 drugs. 840 of these abstracts describe one or more positive drug combinations, varying in size from 2 to 11 drugs. The remaining 760 abstracts either contain mentions of drugs not used in combination, or discuss combinations of drugs that do not give a combined positive effect.

From a clinical perspective, solving the drug combination identification task will assist researchers in suggesting and validating complex treatment plans. For example, when searching for effective treatments for cancer, knowing which drugs interact synergistically with the first line treatment allows researchers to suggest new treatment plans that can subsequently be validated in-vivo and become a standard protocol (Wasserman et al., 2001; Katzir et al., 2019; Ianevski et al., 2020; Niezni et al., 2021).

From an NLP perspective, the drug combination identification task and dataset pushes the boundaries of relation extraction (RE) research, by introducing a relation extraction task with several challenging characteristics:

Variable-length n-ary relations Most work on relation extraction is centered on *binary relations* (e.g. Li et al. (2016), see full listing in §5), or on *n-ary relations with a fixed* n (e.g. Peng et al. (2017)). In contrast, the drug combination task involves *variable-length n-ary relations*: different passages discuss drug combinations of different sizes, and the model is tasked with predicting, for each subset of drugs mentioned in a passage, if they participate in a drug combination and whether this drug combination is effective.

No type-hints As noted by Rosenman et al. (2020)

[1] Dataset and code can be found at https://anonymous.4open.science/r/drug-synergy-models--C8B7/README.md

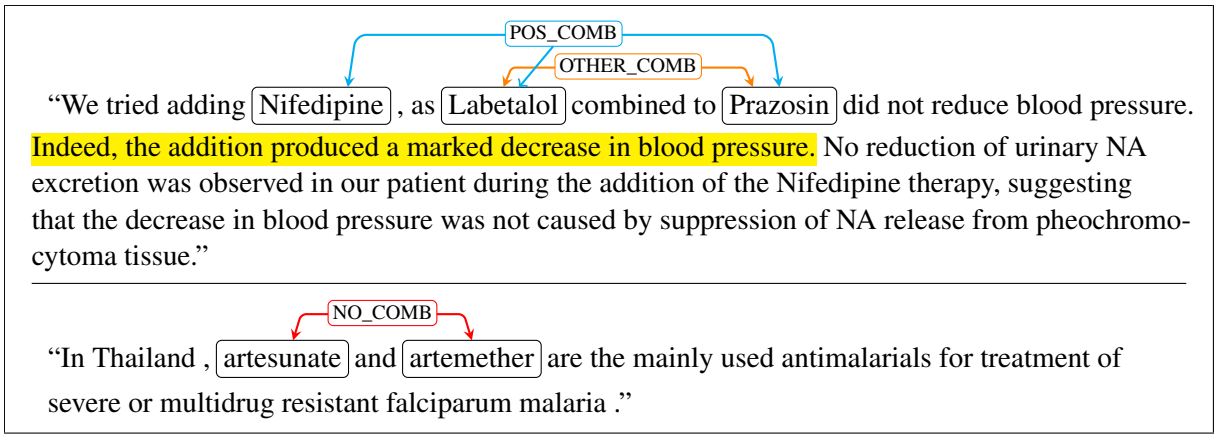

Figure 1: Examples of our label scheme. The top example contains two relations: a binary OTHER_COMB relation and a ternary POS_COMB relation. The evidence required to annotate the latter relation is found in a different sentence (highlighted). In the bottom example, each drug is described as a separate treatment rather than a combination theapy.

and Sabo et al. (2021), in many relation extraction benchmarks (Han et al., 2018; Sabo et al., 2021; Zhang et al., 2017), the argument types serve as an effective heuristic. However, this heuristic does not hold in the drug combination task, in which all possible relation arguments are entities of the same type (drugs) and we need to identify specific subsets of them.

Long-range dependencies The information describing the efficacy of a combination is often spread-out across multiple sentences. Indeed, our annotators reported that for 67% of the instances, the label could not be determined based on a single sentence, and require reasoning with a larger textual context. Interestingly, our experiments show that our models *are not* helped by the availability of longer context, showing the limitations of current standard modeling approaches. This suggests our dataset can be a test-bed for models that attempt to incorporate longer context.

Challenging inferences As we show in our error analysis (§4.2), instances in this dataset require processing a range of phenomena, including coordination, numerical reasoning, and world knowledge.

We hope that by releasing this dataset we will encourage NLP researchers to engage in this important clinical task, while also pushing the boundaries of relation extraction.

2 The Drug Combinations Dataset

A set of drugs in a biomedical abstract are classified to one of the following labels:

Positive combination (POS_COMB): the sentence indicates the drugs are used in combination, and the text indicates that the combination has additive, synergistic, or otherwise beneficial effects which warrant further research.

Non-positive combination (OTHER_COMB): the sentence indicates the drugs are used in combination, but there is no evidence in the text that the effect is positive (it is either negative or undetermined).[2]

Not a combination (NO_COMB): the sentence does not state that the given drugs are used in combination, even if a combination is indicated somewhere else in the wider context. An example is given in the lower half of Figure 1, where each of the drugs Artesunate and Artemether is given in isolation, and no combination is reported.

Our primary interest is to identify sets of drugs that match the POS_COMB case.

2.1 Relevant Context Size for Classifying Drug Combinations

When formulating the extraction task and designing our data collection methodology, we first established the locality of the phenomenon: whether drug combinations are typically expressed in a single sentence or whether a larger context is needed. We sampled a set of 275 abstracts which included known drug combinations according to DrugCom-

[2]We also experimented with a another label for combinations that are discouraged (antagonisitc, harmful or not effective). The agreement for this label was low, leading us to keep it as a subset of OTHER_COMB.

boDB.[3] Analysis showed that $140/275$ of these abstracts mentioned attempted drug combinations. In $136/140$ of these cases, all participating drugs in the attempted combination could be located within a single sentence in the abstract (for an example, see the OTHER_COMB relation in Figure 1). However, establishing the efficacy of the combination frequently required a larger context (such as the context accompanying the POS_COMB relation in Figure 1).

2.2 Task Definition

We define each instance in the Drug Combination Extraction (DCE) task to consist of a sentence, drug mentions within the sentence, and an enclosing context (e.g. paragraph or abstract).

The output of the task is a set of relations, each consisting of a set of participating drug spans and a relation label (POS_COMB or OTHER_COMB). Each subset of drug mentions not included in the output set is implicitly considered to have relation label NO_COMB.

More formally, DCE is the task of labeling an instance $X = \{C, i, D\}$ with a set of relation instances R, where $C = (S_1, ...S_n)$ is an ordered list of context sentences (e.g. all the sentences in an abstract or paragraph), $1 \leq i \leq n$ is an index of a target sentence $S_i = (w_1, ..., w_{n(i)})$ with $n(i)$ words, and $D = \{(d_{\mathbf{1}start}, d_{\mathbf{1}end}), ..., (d_{\mathbf{m}start}, d_{\mathbf{m}end})\}$ is a set of $m >= 2$ spans of drug mentions in S. The output is a set $R = \{(c_i, y_i)\}$ where $c_i \in \mathcal{P}(D)$ is a drug combination from $\mathcal{P}(D)$, the set of all possible drug combinations, and $y_i \in \{\text{POS\_COMB}, \text{OTHER\_COMB}\}$ is a combination label.

2.3 Evaluation Metric

We consider two settings: "Exact Match", a strict version which considers identifying exact drug combinations, and "Partial Match", a more relaxed version which assigns partial credits to correctly identified subsets.

For both cases, we use standard Precision, Recall and F1 metrics for relation extraction. For the partial-match case, we replace the binary 0 or 1 score for a given combination with a refined score: $shared\_drugs/total\_drugs$ when $shared\_drugs > 1$. If there are multiple partial matches with the gold one, we take the one that maximizes the refined score. We compute **recall** as $identified\_relations/all\_gold\_relations$, and **precision** as $correct\_relations/identified\_relations$.

We consider two metrics, the averaged Positive Combination F1 score which compares POS_COMB to the rest, and the averaged Any Combination F1 score which counts correct predictions for any combination label (POS or OTHER) as opposed to NO_COMB. The latter is an easier task, but still valuable for identifying drug combinations irrespective of their efficacy.

2.4 Collecting Data for Annotation

To collect data for annotation we curated a list of 2411 drugs from DrugBank [4] and sampled from PubMed a set of sentences which mention 2 or more drugs. Analysis of the first 50 sentences from this sample showed that only $8/50$ of the sentences included mentions of drug combinations. This meant that annotating the full sample will be costly, and will result in a dataset that's highly skewed toward relatively trivial NO_COMB instances.

We therefore repeated this experiment, this time sampling sentences whose PubMed abstract included a trigger phrase indicative of a drug combination context.[5] This time $24/50$ of the sampled sentences included mentions of drug combinations. Evaluating the coverage of the trigger list against a new sample of abstracts with known drug combinations showed that 90% of these new abstracts included one of the trigger words. This implied that the trigger list is useful in creating a more balanced sample without prohibitively restricting coverage and diversity.

Based on these results, we decided to collect the majority of instances for annotation, 90%, using a basic search for sentences that contain at least two different drugs, and whose abstract contains one of the trigger phrases. To account for the lexical restrictions imposed by our trigger list, we sampled the remaining 10% of instances using distant supervision, curating sentences which include pairs of drugs known to be synergistic according DrugComboDB, but whose abstract does not include one of our trigger phrases. All data collecting queries were performed using the SPIKE Extractive Search

[3] We used `Syner&Antag_voting.csv` taken from http://drugcombdb.denglab.org/download/ and ranked according to the *Voting* metric.

[4] Curation included downloading a premade drug list from DrugBank's website, while removing non pharmacological intervention such as Vitamins and Supplements. The later we got from the FDA orange book.

[5] See the full trigger phrase list in Appendix A.3

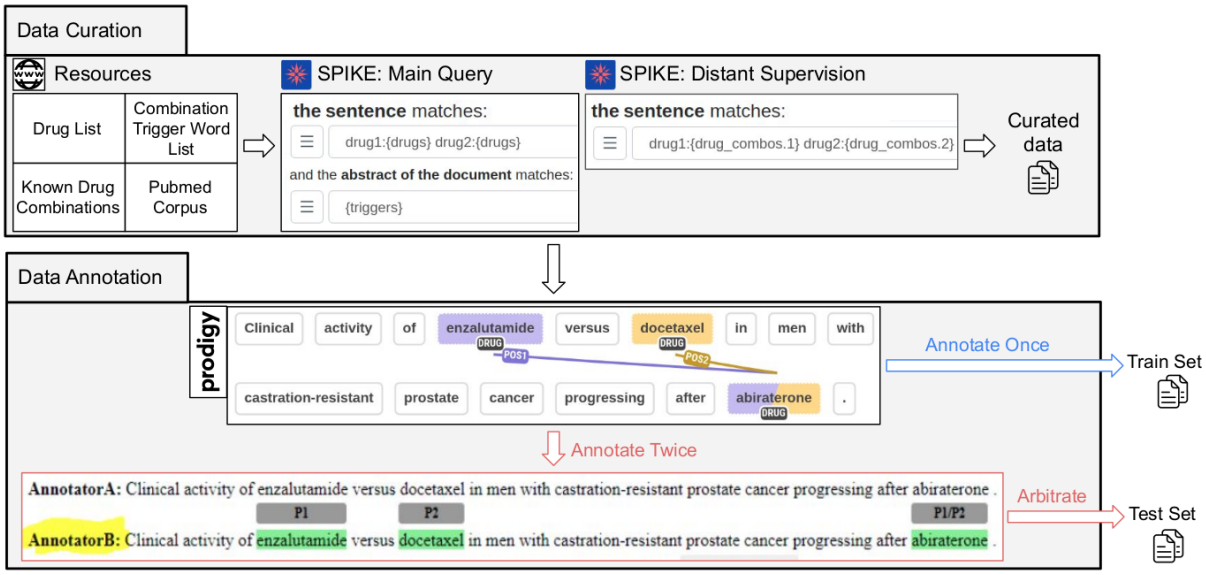

Figure 2: Illustration of the data construction process. First we construct the required knowledge resources. Then, we collect data using SPIKE –an extractive search tool– over the PubMed database. The train and test sets were annotated using Prodigy over the curated data. For test data, we collected two annotations for each sample, and then had a domain expert resolve annotation disagreements.

tool (Shlain et al., 2020; Taub-Tabib et al., 2020). The process is illustrated in the top part of Figure 2.

2.5 The Annotation Process

Seven graduate students in biomedical engineering took part in the annotation task. The students all completed a course in combination therapies for cancer and were supervised by a principled researcher with expertise in this field.

We provided the participants with annotation guidelines which specified how the annotation process should be carried out (see Appendix A.1) and conducted an initial meeting where we reviewed the guidelines with the group and discussed some of the examples together.

Each of the participants had access to a separate instance of the Prodigy annotation tool (Montani and Honnibal, 2018), pre-loaded with the candidate annotation instances. Once a session starts, the instances (containing of a sentence with marked drug entities, and its context) appear in a sequential manner, with no time limit. For each instance we instructed the annotators to mark all subsets of drugs that participated in a combination, and for each subset to indicate its label (POS_COMB or OTHER_COMB). Moreover, we instructed them to indicate whether the context was needed in order to determine the positive efficacy of the relation.

Out of a total of 1634 instances, 272 were assigned to at least two annotators. After further arbitration by the lead researcher, these were used to construct the test set. The process is illustrated in the bottom part of Figure 2.

Metric	Partial Match	Exact Match
Avg. Any Combination F1	88.9	86.1
Avg. Positive Combination F1	83.4	79.6

Table 1: Agreement scores using our adaptation of F1 score to allow for partial-match.

2.6 Inter-annotator Agreement

During the course of the task we calculated Inter-annotator agreement multiple times. Each time, a set of 25 instances were randomly selected and assigned to all annotators. Agreement was calculated based on a pairwise F1 measure (with some modifications as described in §2.3) and averaged over all pairs of annotators (see discussion of alternative metrics in Appendix A.2). The results were used to identify cases of disagreement, provide feedback to annotators and prompt refinement of the annotation guidelines.

Results of the final agreement round are reported in Table 1 and are overall satisfactory (Aroyo and Welty, 2013; Araki et al., 2018).

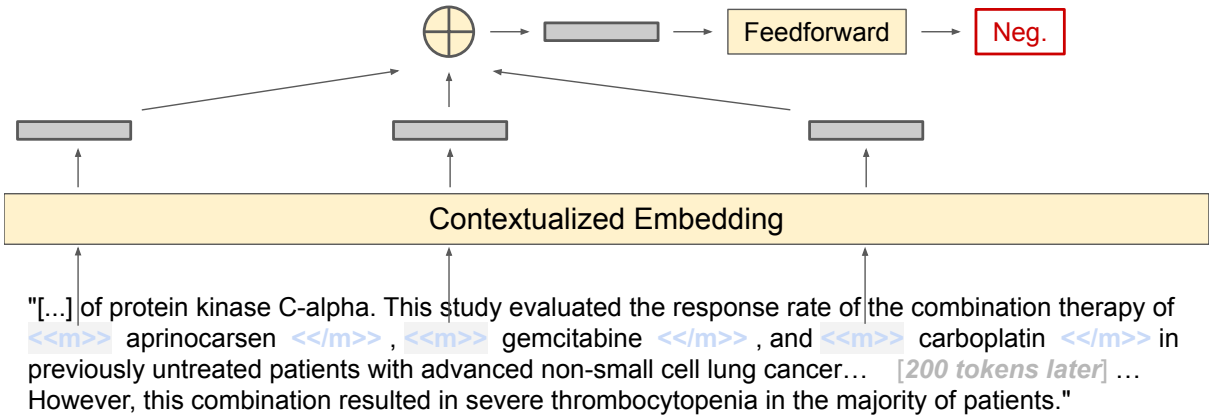

Figure 3: Our baseline architecture, adapted from the PURE model (Zhong and Chen, 2021)

2.7 Resulting Dataset

The dataset consists of 1634 annotated instances (sentences with drug mentions and abstract context). The final split of train and test is 1362 train instances, and 272 test instances. These include 1248 relations, 835 are POS_COMB and 374 are OTHER_COMB, while keeping this label ratio in the train and test sets. 591 sentences contain no drug combination, the majority (877) contain one relation (either POS_COMB or OTHER_COMB), and 166 contain two or more different combinations. Of the relations, 900 are binary, 226 are 3-ary, 69 are 4-ary, and 53 are 5-ary or more.

For each instance in the resulting dataset we include the context-required indication provided by the annotators. In 835 out of 1248 relations the annotator marked the context as needed which is 67% of the time, showing the importance of the context in the DCE task.

3 Experiments

3.1 Baseline Model Architecture

We establish a baseline model to measure the difficulty of our dataset and reveal areas for improvement. For our underlying baseline model architecture, we adopt the PURE architecture from Zhong and Chen (2021), which is state-of-the-art on several relation classification benchmarks, including the SciERC binary scientific RE dataset (Luan et al., 2018). The PURE architecture, designed for 2-ary and 3-ary relation extraction, consists of three components. First, special "entity marker" tokens are inserted around all entities in a candidate relation. Next, these marker tokens are encoded with a contextualized embedding model. Finally, the entity marker embeddings are concatenated and fed to a feedforward layer for prediction.

Unlike the original PURE architecture, we consider the more challenging case of extracting relations of variable arity. To support this setting, we *average* the entity marker tokens in a relation rather than concatenate. The final baseline model architecture is shown in Figure 3. For the contextual embedding component of this architecture, we experiment with four different pretrained scientific language understanding models (SciBERT (Beltagy et al., 2019), BlueBERT (Peng et al., 2019), PubmedBERT (Gu et al., 2020), and BioBERT (Lee et al., 2020)). During training, we only finetune the final *BERT layer. We train each model architecture for 10 epochs on a single NVIDIA Tesla T4 GPU with 15GB of GPU memory, which takes roughly 7 hours to train for each model.

To our knowledge, there are no other models designed for variable-length N-ary relation extraction, so we consider no other baselines.

3.2 Domain-Adaptive Pretraining

Our baseline model architecture relies heavily on a pretrained contextual embedding model to provide discriminative features to the relation classifier. Gururangan et al. (2020) showed that continued domain-adaptive pretraining almost always leads to significantly improved downstream task performance. Following this paradigm, we performed continued domain-adaptive pretraining ("DAPT") on our contextual embedding models.

We acquired in-domain pretraining data using the same procedure used to collect data for annotation: running a SPIKE query against PubMed to find all abstracts containing multiple drug names and a "trigger phrase" (from the list in Appendix A.3). This query resulted in

Model	Positive Combination F1		Any Combination F1	
	Exact Match	Partial Match	Exact Match	Partial Match
Human-Level	79.6	83.4	86.1	88.9
SciBERT	44.6 (± 4.6)	55.0 (± 5.9)	50.2 (± 1.9)	63.6 (± 2.7)
w/ DAPT	54.8 (± 3.2)	63.6 (± 2.0)	61.8 (± 2.7)	72.8 (± 2.1)
BlueBERT	41.2 (± 4.8)	51.7 (± 6.0)	47.3 (± 4.2)	59.9 (± 6.2)
w/ DAPT	56.6 (± 2.3)	63.5 (± 3.1)	64.2 (± 2.6)	74.7 (± 2.7)
PubmedBERT	50.7 (± 5.5)	59.6 (± 5.8)	55.9 (± 3.2)	66.7 (± 3.8)
w/ DAPT	**61.8** (± 5.1)	**67.7** (± 4.8)	**69.4** (± 1.7)	**77.5** (± 2.2)
BioBERT	45.4 (± 3.7)	55.8 (± 2.2)	46.7 (± 3.6)	58.3 (± 5.1)
w/ DAPT	56.0 (± 6.5)	63.5 (± 7.5)	65.6 (± 1.8)	75.7 (± 2.2)

Table 2: Comparing different foundation models (with and without continued domain-adaptive pretraining) on Exact-Match and Partial-Match relation extraction metrics. Mean score from 4 different random seeds is reported, and standard deviation is computed across seeds.

190K unique abstracts. We performed domain-adaptive training against this dataset using the `Huggingface Transformers` library. We trained for 10 epochs using a learning rate of 5e-4, finetuning all *BERT layers and using the same optimization parameters specified by Gururangan et al. (2020). This pretraining took roughly 8 hours per model using four NVIDIA Tesla T4 GPUs, each with 15GB of GPU memory.

3.3 Relation Prediction

To apply the model to drug combination extraction, we reduce the RE task to an RC task by considering all subsets of drug combinations in a sentence, treating each one as a separate classification input, and combining the predictions. This poses two challenges: there may be a large number of predicted candidate relations for a given document, and each relation is classified independently despite the combinatorial structure. To handle these issues, we add a filtering step based on a greedy heuristic to choose the smallest set of disjoint relations that collectively cover as many drug entities as possible in the sentence. We do this iteratively: at each step, we simply choose the largest predicted candidate relation (i.e. the N-ary relation with largest N) that has no overlap with relations chosen at previous steps. In case of a tie we take the first occurring drug spans. One downside of this greedy heuristic is that it favors large relations (i.e. N-ary relations with larger n). Nonetheless, we empirically find it is critical to extracting high-precision drug combination relations in our architecture.

4 Results

4.1 Effect of Pretrained LMs and Domain-Adaptive Pretraining

We show results of our baseline model architecture in Table 2. For each model, we report the mean and standard deviation of each metric over four identical models trained with different seeds.[6] Among the four base scientific language understanding models in our experiments, we observe PubmedBERT to be the strongest on every metric. We additionally find that domain-adaptive pretraining provides significantly improvements for every base model, consistently giving 5-10 points of improvement on Positive Combination F1 score. The value of domain-adaptive pretraining supports our observation that encoding domain knowledge is critical to solving this new task.

4.2 Qualitative Error Analysis

We identify classes of challenges that make this task difficult, both in terms of humam annotation and machine prediction.

Coordination Ambiguity: A known linguistic challenge is the ambiguity that stems from vague coordination. In cases where explicit combination words (e.g. combination, plus, together with, etc) are not used, it may be unclear whether two drugs are being used together or separately. For example in *"These findings may help clinicians identify patients for whom acamprosate **and** naltrexone may be most beneficial"* it is unclear if *acamprosate* and *naltrexone* are being described in combination or as independent treatments, leading to either a POS label for the former or NO_COMB for the latter.

[6] Seeds used are 2021, 2022, 2023, and 2024

Model	Positive Combination F1		Any Combination F1	
	Exact Match	Partial Match	Exact Match	Partial Match
PubmedBERT (DAPT) with context	61.8 (± 5.1)	67.7 (± 4.8)	69.4 (± 1.7)	77.5 (± 2.2)
PubmedBERT (DAPT) without context	63.4 (± 0.6)	68.5 (± 1.1)	69.7 (± 1.3)	76.8 (± 1.7)
PubmedBERT (no DAPT) with context	50.7 (± 5.5)	59.6 (± 5.8)	55.9 (± 3.2)	66.7 (± 3.8)
PubmedBERT (no DAPT) without context	64.9 (± 1.8)	70.2 (± 2.8)	70.8 (± 1.7)	78.7 (± 1.2)

Table 3: The effect of extra-sentential context on model performance. Mean and standard deviation of each metric are reported over 4 different random seeds. Models without domain-adaptive pretraining are surprisingly much more effective *without* exposure to paragraph-level context.

Numerical and Relative Reasoning: In some cases, the effect of a treatment is described in relative or numerical terms, rather than an absolute claim. Consider the example, *"The infection rate in the control group was 3.5% and in the treated group 0.5%."*. Here, the reader must compare the control vs experimental groups and deduce that the experimental outcome is positive, because the treatment yields a lower infection rate.

Domain Knowledge: Similarly, classifying relations in this dataset may require an understanding of domain knowledge. In *"Growth inhibition and apoptosis were significantly higher in BxPC-3, HPAC, and PANC-1 cells treated with **celecoxib and erlotinib** than cells treated with either **celecoxib** or **erlotinib**"*, one must understand that having higher values of *Growth inhibition and apoptosis* in specific cells is a positive outcome, in order to classify this combination as positive.

Context related Complications: The following are kinds of complications found when the evidence lies in the wider part of the context.

Coreference Resolution: Sometimes anaphoric or complex coreference reasoning is needed to solve the efficacy of the relation e.g. *"it was demonstrated that **they** could be combined with acceptable toxicity."*.

Contradicting Evidence: the reader often must infer a conclusion given opposing claims within a given abstract. This can happen as combinations can be referred as e.g. *toxic but effective*.

Long Distance: The target sentence can be as far as the entire context—in our case up to 41 sentences apart— from the evidence sentence. Which makes it harder for a reader let alone a machine to solve.

4.3 Quantitative Error Analysis

To probe the nature of this task, we analyze the performance of our strongest model—the one using a PubmedBERT base model tuned with domain-adaptive pretraining—along different partitions of test data. We trained our model for four different seeds, and perform each comparison using a paired multi-bootstrap hypothesis test where bootstrap samples are generated by sampling hierarchically over the available model seeds and subsets of the test set (Sellam et al., 2021). We use 1000 bootstrap samples for each tests.

4.3.1 Do models leverage context effectively?

Each relation in our dataset consists of entities contained within a single sentence, but labeling the relation frequently requires extra-sentential context to make a decision. In our dataset, annotators record whether or not each relation actually requires paragraph-level context to label, and reported that 67% of drug combinations required such context to annotate their relation label.

To understand the extent to which models can leverage and benefit from paragraph-level context, we experiment with using our PubmedBERT-based model with extra-sentential context concealed - i.e., the model only sees a single sentence containing drug entities at both training and evaluation time. In the results in Table 3, we first observe that our strongest model (the PubmedBERT-DAPT model) shows almost identical performance with or without paragraph-level context. Second, we observe that a weaker version of this model without additional domain-adaptive pretraining performs *significantly worse* when equipped with paragraph-level context.

These results suggest there is ample room for improvement in effectively extracting evidence from other sentences in this document-level RE task. We believe this can make our dataset a useful benchmark for document-level language understanding.

4.3.2 Binary vs. higher-arity relations

Given that our dataset is the first relation extraction dataset where the relation *arity* is variable, do

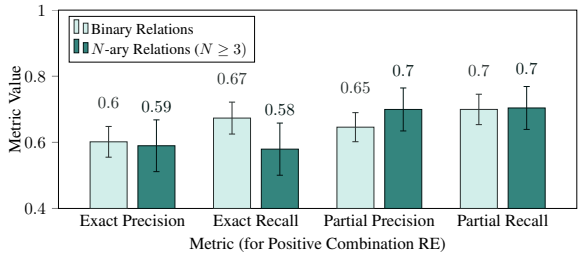

Figure 4: Comparing models performance on binary vs higher-order N-ary relations, averaged over 4 seeds of the PubmedBERT-DAPT model. No consistent significant differences were observed; p-values for these comparisons are 0.456, 0.149, 0.240, and 0.276.

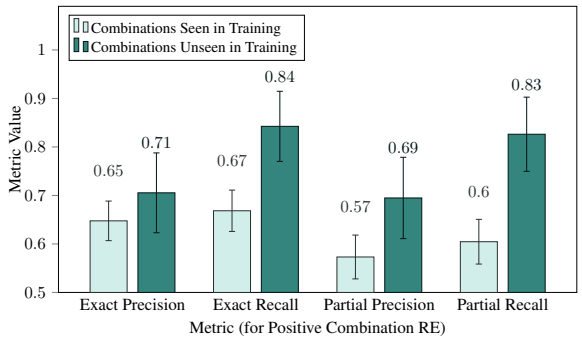

Figure 5: Comparing relation extraction on test set drug combinations that are observed in the training set or not, using the PubmedBERT-DAPT model. Paired multi-bootstrap test p-values for these four comparisons are 0.262, 0.025, 0.103, and 0.009, respectively.

higher-order relations pose a particular challenge for current models? To answer this question, we partition all predicted and ground truth relations for the test set into two categories: binary relations, and higher-arity relations. We then report precision among each subset of predicted relations, and recall among each subset of ground truth relations. We perform this experiment across four different model seeds, and report results in aggregate using a paired multi-bootstrap procedure. In the results in Figure 4, we see no consistent significant differences between models of different arities, suggesting that our technique of computing relation representations by averaging entity representations scales well to higher-order relations.

4.3.3 Generalizing to new drug combinations

How well can relation extraction models classify drug combinations not seen during training? Similar to the setup in §4.3.2, we divide all predicted and ground truth relations for the test set into the set of drug combinations which are also annotated in our training set, and the set that have not been. In our dataset, over 80% of annotated test set relations are not found in the training set.

In Figure 5, performance is consistently better for relations observed in the training set than for unseen relations, by a margin of 10-15 points. Recall, in particular, is significantly worse for relations unseen during training (at 95% confidence), and precision is potentially also worse. Considering that unseen drug combinations are practically more valuable than already-known combinations, improving generalization to new combinations is a critical area of improvement for this task.

5 Related Work

The DDI dataset (Herrero-Zazo et al., 2013) is the only work to our knowledge that annotates drug interactions for text mining. However, it fundamentally differs from our dataset in the type of annotations provided: the DDI annotates the type of discourse context in which a drug combination is mentioned, without providing explicit information about combination efficacy. In contrast, our dataset is focused on semantically classifying the efficacy of drug combinations as stated in text.

Other RE datasets exist in the biomedical field (Peng et al., 2017; Li et al., 2016; Wu et al., 2019; Krallinger et al., 2017), but do not focus on drug combinations. Similarly, several RE datasets tackle the N-arity problem in the scientific domain (Peng et al., 2017; Jain et al., 2020; Kardas et al., 2020; Hou et al., 2019), and in the non-scientific domain (Akimoto et al., 2019; Nguyen et al., 2016), however, **all of them consider a fixed choice of** N.

6 Conclusions

We present a new resource for drug combination and efficacy identification. We establish strong baseline models that achieve promising results but reveal clear areas for improvement. Beyond the immediate, application-ready value of this task, this task poses unique relation extraction challenges as the first dataset containing variable-arity relations. We also highlight challenges with document-level representation learning and incorporating domain knowledge. We encourage others to participate in this task, and our dataset and modeling code are all available to the public at `https://anonymous.4open.science/r/drug-synergy-models--C8B7`.

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A Appendices

A.1 Annotation Guidelines

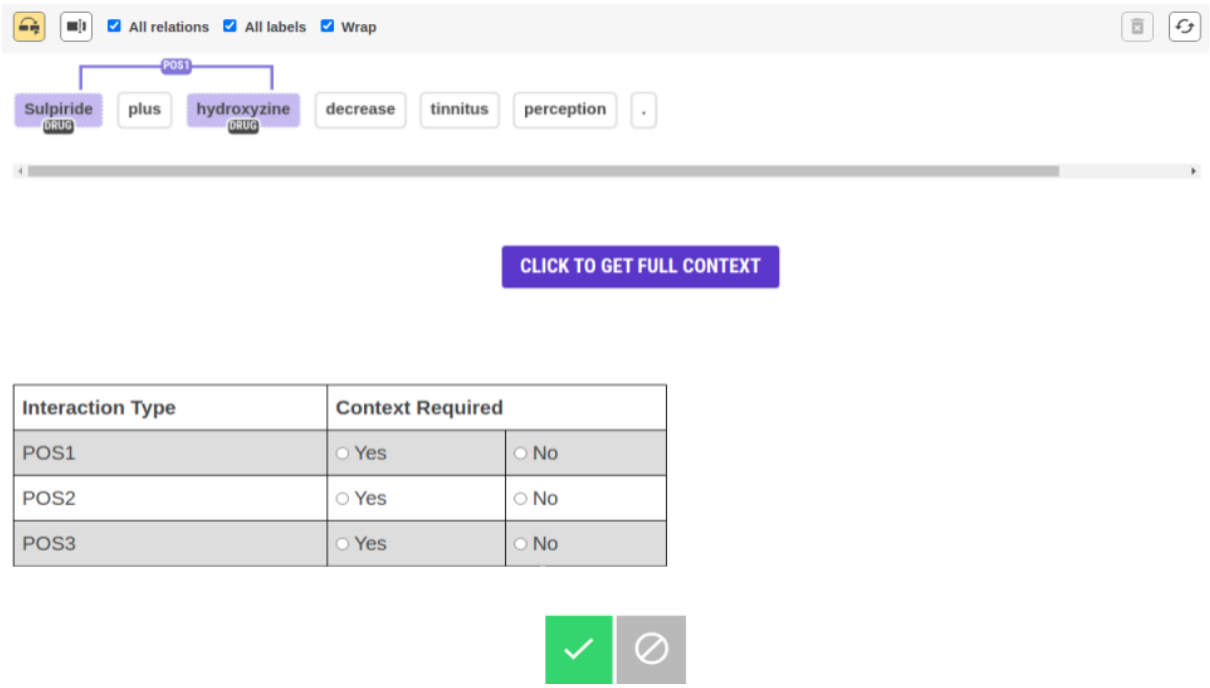

Figure 6: Annotation instance in the Prodigy environment. The screen is constructed of the sentence where they should mark relations, a button to show the full context and a selection per relation to indicate the necessity of the context.

All participating annotators were provided with annotation guidelines. The guidelines specified how the annotation process should be carried out and provided definitions and examples for the different labels used. As the task progressed, the guidelines were also expanded to include discussion of frequently encountered issues.

For a given instance, such as presented in the top of Figure 6 the annotator needs to first recognize any missing drugs and mark them, and then label any interactions they find among the drugs. In case they need to consult a wider context they can press on a 'show more context' button and a text box with the wider context will appear. This context can be again hidden by clicking the same button if needed. Lastly, in the bottom of the sample page, we present a table with questions regarding the necessity of using the context.

Then the annotator should decide if they need to ignore the current sample or to complete the current instance and accept it, by pressing the accept and ignore buttons.

The annotators are instructed as follows. They should read the sentence carefully, and try to answer a two phase question to themselves. first, if the drugs are mentioned in any form of combination or they should be given separately. Second, if indeed the annotator recognized the drugs as a combination can they determine the efficacy of the combination by the sole sentence.

In case they can not determine the efficacy they are instructed to press on the 'get more context' button and read the entire context in order to determine what is the correct efficacy. If after reading the context they can still not determine the efficacy then the label of the interaction should be OTHER_COMB (aside from negative label experimentation mentioned in Footnote 2). Otherwise it should be POS_COMB. In case that they recognized that there is no combination between the drugs in the sentence then they should not use any label and simply accept the current instance. Then they should answer the context related questions for the POS_COMB label in order to signal if the context was needed.

While reading the sentence if the annotators find unmarked drugs they can mark them before continuing to the interaction-labeling phase and treat them the same as the other drugs, but, it is not required to mark a word as drug in order to use it in an interaction. If a drug is marked in a wrong manner they should try

and fix it, e.g. the span of the drug is incorrect.

In order to achieve more consistent and accurate annotations, they are also instructed to annotate all the interactions that they can find in a given sentence. They should always use the *accept* button even if there are no interactions in the sentence. Only in cases where they want to skip a sentence (e.g. when there is an inherent problem with it) or leave it for a future discussion they should use the *ignore* button. An interaction can occur between more than two drugs, if so they should notice that they don't need each pair from this group to have a marked interaction, as long as they all connect to the same graph. e.g. "Drugs A, B and C are synergistic." connecting A to B and B to C is sufficient, no need to connect drug A to drug C. Each interaction should be marked with a different tag (POS_COMB1, POS_COMB2..., OTHER_COMB1, OTHER_COMB2...).

A.2 Evaluation Metric Discussion

For measuring the agreement, we chose to use our adaptation of F1 score and not other common metrics such as Cohen's Kappa (Cohen, 1960) or one of its variations (e.g. Feliss's Kappa (Fleiss, 1971) and Krippendorf's Alpha (Hayes and Krippendorff, 2007)). These metrics expect a setup where the *relation* candidates are already marked and the task is only to label them – a labeling task and not an extraction task. This causes two problems, one is that they inherently do not need to handle partial match. So if for example there are three drugs in a sentence, the first annotator annotated a relation between drugs A and B, while a second annotator annotated the same relation between drugs A, B and C. So we will either underestimate or overestimate their agreement score if we considered this a mismatch or a match respectively. Moreover, their calculations depends on the *hypothetical agreement by chance* normalization factor, but this will not reflect the difficulty of random choosing in our setup as they ignore the size of the combinatorial set of relation candidates we can possibly have.

A.3 Trigger List

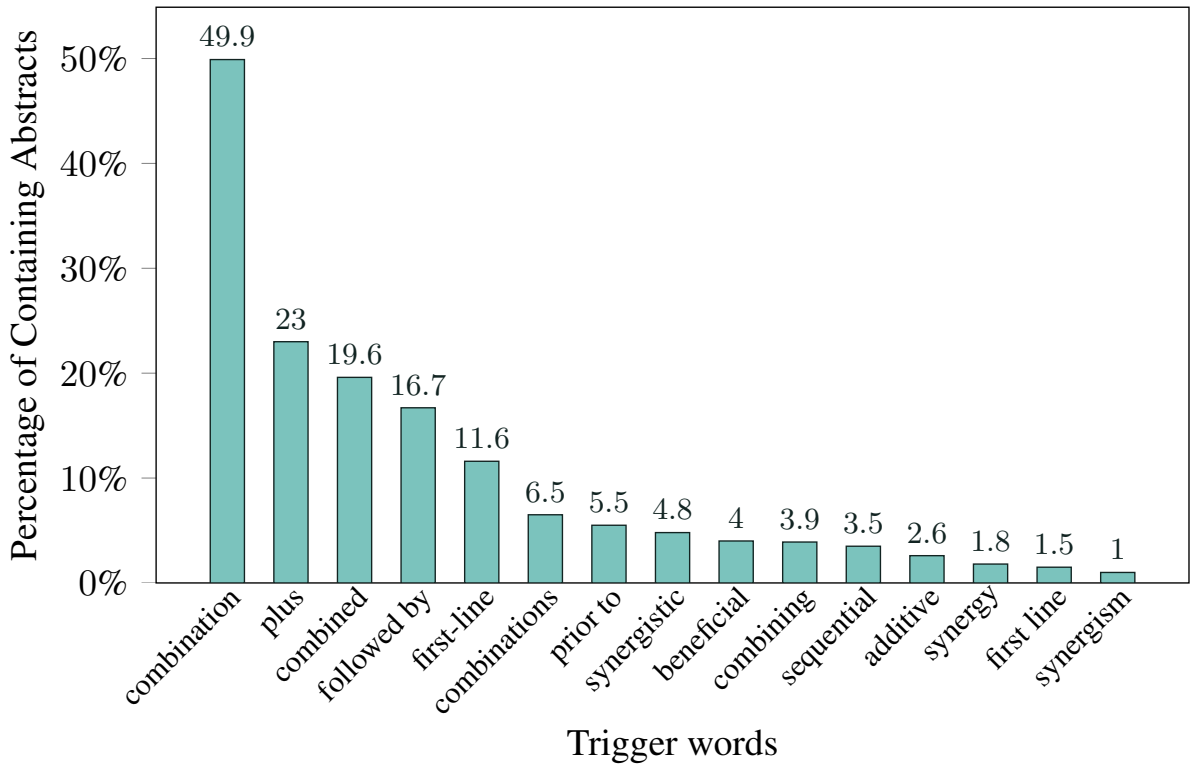

Figure 7: Abstracts percentage including each trigger word (1634 abstracts included; 43 words in the full word list; Words <1% were neglected from the figure.

In Figure 7 we show the triggers that we used in the Spike queries. We show the percentage of abstracts

that included each trigger (others under 1%: *conjunction, two-drug, first choice, additivity, combinational, synergetic, simultaneously with, supra-additive, five-drug, combinatory, over-additive, timed-sequential, co-blister, super-additive, synergisms, synergic, synergistical, less-than-additive, greater-than-additive, 2-drug, sub-additive, more-than-additive, 3-drug*).