Learning from Negative Samples in Biomedical Generative Entity Linking

Anonymous ACL submission

Abstract

Generative models have become widely used in biomedical entity linking (BioEL) due to their excellent performance and efficient memory usage. However, these models are usually trained only with positive samples—entities that match the input mention's identifier—and do not explicitly learn from hard negative samples, which are entities that look similar but have different meanings. To address this limitation, we introduce ANGEL (Le**a**rning from **N**egative Samples in Biomedical **G**enerative **E**ntity **L**inking), the first framework that trains generative BioEL models using negative samples. Specifically, a generative model is initially trained to generate positive entity names from the knowledge base for given input entities. Subsequently, both correct and incorrect outputs are gathered from the model's top-k predictions. Finally, the model is updated to prioritize the correct predictions through preference optimization. Our models fine-tuned with ANGEL outperform the previous best baseline models by up to an average top-1 accuracy of 1.4% on five benchmarks. When incorporating our framework into pre-training, the performance improvement further increases to 1.7%, demonstrating its effectiveness in both the pre-training and fine-tuning stages. We will make our models and code publicly available upon acceptance.

1 Introduction

Biomedical entity linking (BioEL) involves aligning entity mentions in text with standardized concepts from biomedical knowledge bases (KB) such as UMLS (Bodenreider, 2004) or MeSH (Lipscomb, 2000). BioEL encounters significant challenges due to the diverse and ambiguous nature of biomedical terminology, including synonyms, abbreviations, and terms that look similar but have different meanings. For instance, 'ADHD' (CUI:*C1263846*, where CUI stands for Concept Unique ID) has synonyms such as hyperkinetic disorder and attention deficit hyperactivity disorder. Additionally, 'ADA' can be mapped to either adenosine deaminase (CUI:*C1412179*) or American Diabetes Association (CUI:*C1705019*) depending on the context in which the entity appears.

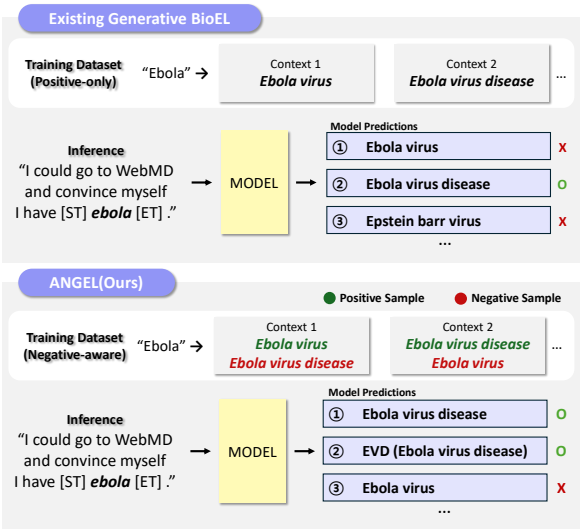

Figure 1: Comparison of training approaches between existing generative BioEL models and our ANGEL method. The main limitation of current generative BioEL methods is that they are trained only on positive samples. This restricts their ability to distinguish between entity names that look similar but different meanings depending on the context. Our ANGEL framework addresses this issue by training the model to prefer positive samples over negative ones.

Recent studies have focused on addressing these challenges, broadly categorized into two approaches: similarity-based and generative BioEL. Similarity-based models (Sung et al., 2020; Liu et al., 2021; Lai et al., 2021; Bhowmik et al., 2021; Agarwal et al., 2022) encode input mentions and entities from KBs into the same vector space using embedding models. They then calculate similarity scores to identify the most similar entities for each input entity. Although these approaches have

achieved remarkable improvements, they require significant space to index and load embedding vectors for all candidate entities (De Cao et al., 2020). Furthermore, representing both the input and candidate entities as single vectors using a bi-encoder can limit the quality of their representations, making it difficult to handle challenging cases.

On the other hand, generative models (De Cao et al., 2020; Yuan et al., 2022b), built upon an encoder-decoder structure (Lewis et al., 2020; Raffel et al., 2020), directly generate the most likely entity name from the KB for the input entity. The output space is dynamically controlled through a constrained decoding strategy, ensuring that only entities from the target KB are generated. Generative models offer several advantages over similarity-based models, including greater memory efficiency and higher performance. They eliminate the need to index large external embedding vectors, and their auto-regressive formulation effectively cross-encodes the input document and candidate entities.

However, existing generative models are trained solely on positive samples and do not explicitly learn from negative samples. Despite their high performance, they encounter limitations when distinguishing between biomedical entities with similar surface forms but different meanings. Although similarity-based models address this issue by incorporating negative samples through synonym marginalization (Sung et al., 2020) or contrastive learning (Liu et al., 2021), applying these approaches to generative models is not straightforward. Consequently, generative models may overfit to surface-level features, reducing the models' ability to generalize effectively across varied contexts, as illustrated in Figure 1.

To harness the benefits of generative approaches while overcoming their limitation of not using negative samples, we introduce a novel training framework, ANGEL. Our framework operates in two stages: positive-only training and negative-aware training. In the first stage, a generative model is trained to generate biomedical terms from the KB that share the same identifier as the given input entity. In the second stage, we gather both correct and incorrect outputs from the model's top-k predictions. The model is then updated to prioritize the correct predictions using the direct preference optimization (DPO) algorithm (Rafailov et al., 2024). Models trained on our ANGEL framework significantly outperform the previous best similarity-based and generative BioEL models, achieving an average accuracy improvement of 1.7% across five datasets. Our contributions are as follows:

- We introduce ANGEL, the first-of-its-kind training framework that utilizes negative samples in generative entity linking. ANGEL overcomes the limitations of existing generative approaches by effectively employing negative samples during training.
- ANGEL is a versatile framework, demonstrating its applicability in both the pre-training and fine-tuning phases, leading to performance improvements at each stage. Additionally, our method is model-agnostic, consistently improving results across various backbone language models, with gains ranging from 0.9% to 1.7%.
- Our best model, pre-trained and fine-tuned with our framework, outperforms the previous best baseline model by 1.7% across five benchmark datasets.

2 Related Work

2.1 Biomedical Entity Linking

Biomedical entity linking (BioEL), also known as biomedical entity normalization, is a crucial task because of its application in several downstream tasks in the biomedical domain, such as literature search (Lee et al., 2016), knowledge extraction (Li et al., 2016a; Xiang et al., 2021; Zhang et al., 2023), knowledge graph alignment (Cohen and Hersh, 2005; Lin et al., 2022), and automatic diagnosis (Shi et al., 2021; Yuan and Yu, 2024). Typically, it is assumed that the target mention is already provided, and the task is solely to link this mention to the appropriate entity name from the KB. End-to-end BioEL (Zhou et al., 2021; Ujiie et al., 2021), which also involves identifying mentions within a sentence, is being actively researched, but this is not our focus and will not be discussed in detail.

Traditional classification-based approaches (Limsopatham and Collier, 2016a; Miftahutdinov et al., 2019) employed a softmax layer for classification, treating concepts as categorical variables and thereby losing the detailed information of concept names. Similarity-based (Sung et al., 2020; Liu et al., 2021; Lai et al., 2021; Zhang et al., 2022) models have significantly improved BioEL performance, which encodes mentions and candidate entity names in the same vector

space. They are characterized by high memory consumption due to the need to encode entities into pre-computed embeddings, posing scalability challenges with large datasets (De Cao et al., 2020). Several studies have integrated the concept of clustering into BioEL (Angell et al., 2021; Agarwal et al., 2022).

2.2 Generative Entity Linking

Generative models have become a powerful method for entity linking by overcoming the limitations of similarity-based models. The GENRE framework (De Cao et al., 2020) was the first to demonstrate this approach. To enhance precision and reduce memory usage, GENRE introduced a constrained decoding method (Hokamp and Liu, 2017) using a prefix tree (trie), which restricts the output space to valid entity names. This technique also facilitates easy updates to the set of entities, making the system highly adaptable to changes in the KB. In the biomedical field, notable examples of generative models include GenBioEL (Yuan et al., 2022b) and BioBART (Yuan et al., 2022a). GenBioEL, in particular, is the first model to apply a generative model BART (Lewis et al., 2020) to BioEL, after pre-training it using UMLS. Additionally, several hybrid approaches, known as retrieve-and-generate methods, have been proposed (Xu et al., 2023; Lin et al., 2024). In these methods, a similarity-based model first retrieves the top-k candidates, which are then reranked using a generative model. Although generative approaches have shown high performance, their training has typically been limited to positive samples, as discussed in the introduction section. In this study, we introduce the use of negative samples during training and demonstrate that this approach can significantly enhance the performance of generative models.

3 Method

3.1 Task Formulation

Let $\mathcal{D} = \{(\mathbf{x}_n, y_n)\}_{n=1}^{N}$ be a human-labeled dataset, where $\mathbf{x}_n$ represents an input text and y_n is the gold identifier defined in a KB denoted by $\mathcal{E}$. Each $\mathbf{x}_n$ contains a target entity mention $\mathbf{m}_n$ along with its surrounding contextual information $\mathbf{c}_n^-$ and $\mathbf{c}_n^+$, which represents the tokens before and after the entity mention $\mathbf{x}_n$, respectively. For simplicity, we will omit the subscript n. Our goal is to map each mention $\mathbf{x}$ to its corresponding identifier y^* from the set of entity names $\mathcal{E}$ as follows:

$$y^* = \mathcal{F}(\text{argmax}_{\mathbf{e}\in\mathcal{E}}\ p_\theta(\mathbf{e}|\mathbf{x})), \quad (1)$$

where $\mathcal{F}$ is a mapping function that converts entities to their identifiers, and θ represents the model parameters.

Previous generative BioEL approaches train the model to generate a synonym $\mathbf{s} \in S$ for the given mention in an autoregressive manner as follows:

$$p_\theta(\mathbf{s} \mid \mathbf{x}, \mathbf{v}) = \prod_{t=1}^{T} p_\theta(s_t \mid s_{<t}, \mathbf{x}, \mathbf{v}), \quad (2)$$

where $\mathcal{S} \subset \mathcal{E}$ is the set of entity names (i.e., synonyms) corresponding to the identifier y^*, and T is the number of tokens of the synonym $\mathbf{s}$ and s_t indicates the t-th token of the synonym. The prefix prompt $\mathbf{v}$ to the decoder, represented as '`[BOS]` $\mathbf{m}$ `is`', is designed to make the decoder's output resemble a natural language sentence, which helps to minimize discrepancies between language modeling and fine-tuning on the BioEL task. The target mention in the input is surrounded by the special tokens, `[ST]` and `[ET]`, as follows:

$$\texttt{[BOS]}\ \mathbf{c}^-\ \texttt{[ST]}\ \mathbf{m}\ \texttt{[ET]}\ \mathbf{c}^+\ \texttt{[EOS]},$$

where the special tokens `[BOS]` and `[EOS]` represent the 'Begin Of Sentence' and 'End Of Sentence,' respectively.

As shown in Equation 2, existing models are trained only to output synonyms corresponding to the given mention (i.e., positive samples), without learning from negative samples. In contrast, we introduce a new method called negative-aware training, which allows the model to learn by comparing both positive and negative samples, enhancing the model's generalizability. We will describe our framework in detail in the following sections.

3.2 ANGEL Framework

Our framework consists of two main stages: positive-only training, which warms up the model on target datasets, and negative-aware training, which continuously improves the model by learning from negative samples (see Figure 2).

Positive-only Training In this initial stage, the goal is to learn the morphological similarities among synonyms. To achieve this, we train the model to generate synonyms (i.e., positive samples) that are predefined in the KB, similar to

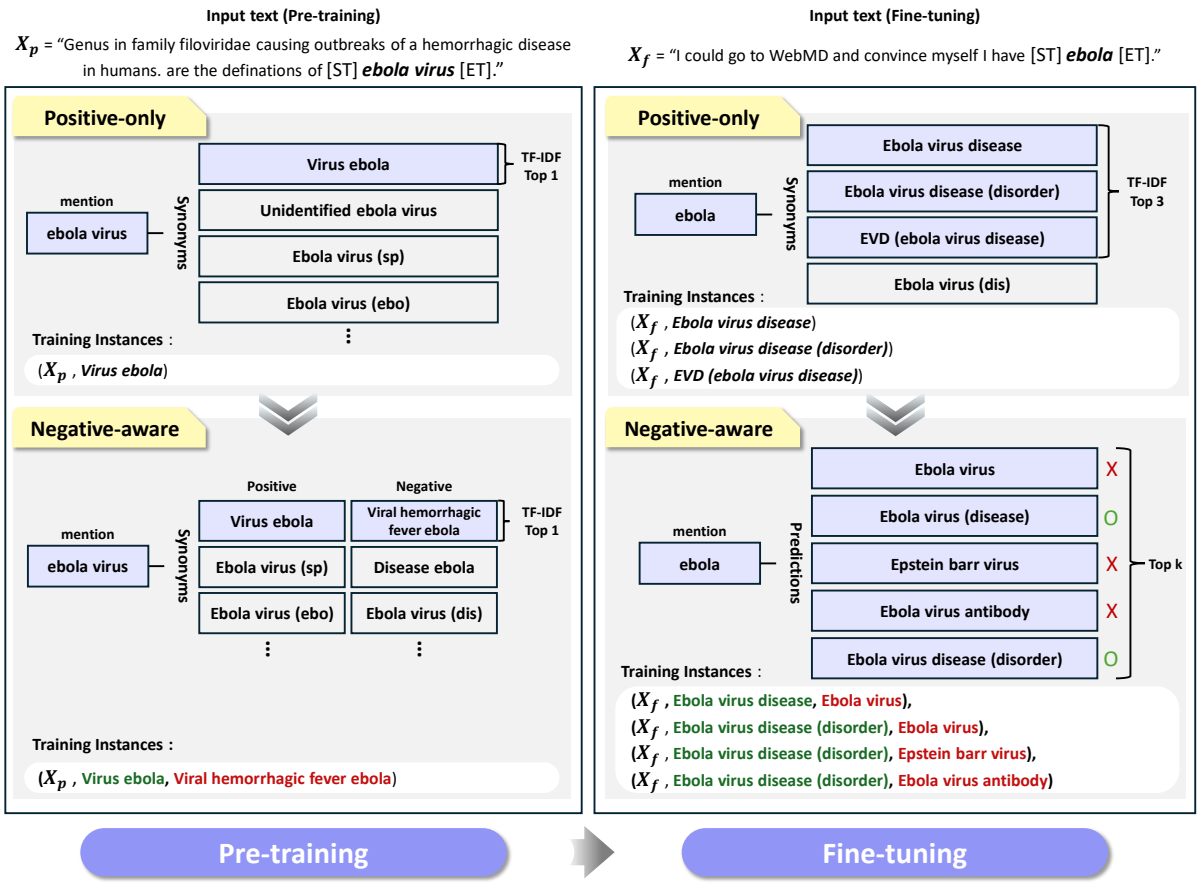

Figure 2: Overview of our method ANGEL (Learning from Negative Samples in Biomedical Generative Entity Linking). The core idea of ANGEL is to enhance both pre-training and fine-tuning by incorporating negative samples, which are obtained either through TF-IDF similarity or the model's top-k predictions. This approach helps the model distinguish subtle differences between correct and incorrect entities.

traditional generative methods (see Equation 2). Our preliminary study indicated that using all synonyms, $\mathbf{s} \in \mathcal{S}$, was not effective. Also, relying solely on the top-1 synonym, as done in a previous study (Yuan et al., 2022b), may limit generalizability. Therefore, we select several of the most similar synonyms to the mention based on their TF-IDF similarity, which is calculated as follows:

$$\hat{\mathcal{S}} = \text{argsort}_{\mathbf{s}\in\mathcal{S}}(\text{TFIDF}(\mathbf{m}, \mathbf{s})), \qquad (3)$$

where $\text{TFIDF}(\cdot)$ returns similarity scores. We use the top-k subset $\hat{\mathcal{S}}_\text{k} = \hat{\mathcal{S}}[:\text{k}] = \{\hat{\mathbf{s}}_1, \ldots, \hat{\mathbf{s}}_\text{k}\}$ as training instances for each mention.

Negative-aware Training Although surface similarities are a useful feature for BioEL, over-relying on them can limit the model's generalization ability. To address this issue, we update the model using negative-aware training. First, we obtain the top-k predictions of the model for mentions in the training dataset. We then automatically construct a training dataset consisting of triplets: a mention with context (if it exists), a correct prediction, and an incorrect prediction. Among all pairs of correct and incorrect predictions, we select only those pairs where the incorrect prediction's rank is higher than the correct prediction's rank. Particularly, when the highest ranked entity is the correct one, we pair this entity with the highest ranked incorrect entity to preserve the model's prior learning. Finally, using this dataset $\mathcal{D}'$, we then optimize the model with the DPO algorithm. This maximizes the likelihood of generating the correct prediction, $\mathbf{e}_w$, over the incorrect prediction, $\mathbf{e}_l$, defined as follows:

$$\mathcal{L}(p_\theta; p_\text{ref}) = -\mathbb{E}_{(\mathbf{x},\mathbf{e}_w,\mathbf{e}_l)\sim\mathcal{D}'}\Bigg[\log\sigma\left(\beta\log\frac{p_\theta(\mathbf{e}_w|\mathbf{x})}{p_\text{ref}(\mathbf{e}_w|\mathbf{x})} - \beta\log\frac{p_\theta(\mathbf{e}_l|\mathbf{x})}{p_\text{ref}(\mathbf{e}_l|\mathbf{x})}\right)\Bigg], \qquad (4)$$

where p_θ is the generative model to be trained, p_ref is the generative model that was trained in the pre-

vious stage using positive-only training, σ is a sigmoid function, and β is a hyperparameter.

Applying ANGEL in Pre-training Our framework is versatile, supporting not only fine-tuning with labeled datasets but also pre-training with the KB itself. Initially, we conduct positive-only training using synonym lists defined in UMLS, the most extensive KB in the biomedical field. We generate its surrounding contextual information automatically for each entity, using clause templates or definitions, as outlined in GenBioEL (Yuan et al., 2022b).[1] We then use the TF-IDF similarity to identify the top synonym and set it as the target (Equation 3). For negative-aware training, using the model's top-k predictions is impractical due to UMLS's vastness, which includes over 3 million entities. Instead, we use entities with the highest TF-IDF similarity but different identifiers from the input mentions as negative samples. This approach significantly reduces computation, enabling effective training across the entire UMLS.

4 Experiments

4.1 Datasets

We utilized five popular BioEL benchmark datasets: NCBI-disease (Doğan et al., 2014), BC5CDR (Li et al., 2016b), COMETA (Basaldella et al., 2020), AskAPatient (Limsopatham and Collier, 2016b), and MedMentions (Mohan and Li, 2019), with the ST21pv subset used for MedMentions. Due to the lack of a test set in the AskAPatient dataset, we adhere to the 10-fold evaluation protocol outlined by Limsopatham and Collier (2016b). Also, this dataset does not include context for the mentions. In the following tables, NCBI-disease, AskAPatient, and MedMentions are denoted as NCBI, AAP, and MM-ST21pv, respectively. Please refer to Appendix B for detailed dataset descriptions and statistics.

4.2 Baseline Models

We use top-performing similarity-based models (Sung et al., 2020; Liu et al., 2021; Lai et al., 2021; Zhang et al., 2022) and generative models (Lewis et al., 2020; Yuan et al., 2022a,b) as our baselines. To ensure a fair comparison with our model under identical experimental conditions, we replicate the following generative models and then apply our ANGEL framework to them: (1) BART-large (Lewis et al., 2020) is an encoder-decoder language model pre-trained on a general-domain corpus. (2) BioBART-large (Yuan et al., 2022a) is the BART-large model continuously pre-trained on a biomedical-domain corpus. (3) GenBioEL (Yuan et al., 2022b) is initialized with the weights of the BART-large model and then pre-trained specifically for BioEL using UMLS.

In BioEL, several studies utilize retrieve-and-generate methods (Xu et al., 2023; Lin et al., 2024). This involves a similarity-based model retrieving the top-k candidates from the KB, followed by a generative model reranking these candidates. We exclude these methods from our experiments to focus on introducing a novel training method that uses negative samples for generative entity linking and demonstrating its effectiveness in a single generative model. Future research could apply our methodology to enhance the reranking process of generative models.

4.3 Implementation Details

Our framework is applied to each of these models during fine-tuning, referred to as ANGEL_{FT}, and during both pre-training and fine-tuning, referred to as $\text{ANGEL}_{\text{PT+FT}}$. For pre-training, we utilized the 2020AA version of the UMLS database,[2] which comprises 3.09M entities, of which 199K concepts contain definitions. In the pre-training phase, the model was trained for 5 epochs, with checkpoints created every 500 steps. We selected the best checkpoints based on the validation sets. During fine-tuning on MM-ST21pv, we also used the 2020AA version of UMLS because the 2017AA version was not directly accessible. Please note that the reported scores of baseline models were measured based on the 2017AA version of UMLS. For determining the best hyperparameters in positive-only training, we searched for the optimal learning rate within the range of 1e-5 to 3e-7 and adjusted the batch size between 8 and 16, following the approach of Yuan et al. (2022b). For the negative-aware training, we searched for the optimal learning rate from 2e-5 to 1e-6 and experimented with batch sizes ranging from 16 to 64. In pre-processing, following Yuan et al. (2022b), we expanded abbreviations using AB3P (Sohn et al., 2008), lowercase texts, mark mention boundaries with special tokens `[ST]` and `[ET]`, and discard

[1] Detailed descriptions of data generation during the pre-training stage are provided in Appendix A.

[2] https://www.nlm.nih.gov/research/umls/licensedcontent/umlsarchives04.html

Model	NCBI	BC5CDR	COMETA	AAP	MM-ST21pv	Average
Similarity-based BioEL						
BioSYN (Sung et al., 2020)	91.1	-	71.3	82.6	-	-
SapBERT (Liu et al., 2021)	92.3	-	75.1	89.0	-	-
ResCNN (Lai et al., 2021)	92.4	-	80.1	-	55.0	-
KRISSBERT (Zhang et al., 2022)	91.3	-	-	-	72.2	-
Generative BioEL (reported)						
BART (Lewis et al., 2020)	90.2	92.5	80.7	88.8	71.5	84.7
BioBART (Yuan et al., 2022a)	89.9	93.3	81.8	89.4	71.8	85.2
GenBioEL (Yuan et al., 2022b)	91.9	93.3	81.4	89.3	-	-
Generative BioEL (reproduced)						
BART† (Lewis et al., 2020)	90.3	93.0	80.4	88.7	70.1	84.5
+ ANGEL$_{FT}$ (**Ours**)	91.4 (+1.1)	93.6 (+0.6)	81.3 (+0.9)	89.5 (+0.8)	71.2 (+1.1)	85.4 (+0.9)
BioBART† (Yuan et al., 2022a)	89.4	93.5	81.3	89.3	71.3	85.0
+ ANGEL$_{FT}$ (**Ours**)	91.9 (+2.5)	**94.7** (+1.2)	82.2 (+0.9)	89.9 (+0.6)	**73.4** (+2.1)	86.4 (+1.4)
GenBioEL† (Yuan et al., 2022b)	91.0	93.1	80.9	89.3	70.7	85.0
+ ANGEL$_{FT}$ (**Ours**)	92.5 (+1.5)	94.4 (+1.3)	82.4 (+1.5)	89.9 (+0.6)	71.9 (+1.2)	86.2 (+1.2)
+ ANGEL$_{PT+FT}$ (**Ours**)	**92.8** (+1.8)	94.5 (+1.4)	**82.8** (+1.9)	**90.2** (+0.9)	73.3 (+2.6)	**86.7** (+1.7)

Table 1: The top-1 accuracy of the models across the five BioEL datasets. The † symbol indicates that the results have been reproduced. Our ANGEL framework is applied to generative BioEL models during fine-tuning (ANGEL$_{FT}$) and both pre-training and fine-tuning (ANGEL$_{PT+FT}$). We exclude the performance of similarity-based models on BC5CDR, as they were evaluated separately on the chemical and disease subsets, differing from our settings.

mentions that overlap or are missing from the target KB. The best hyperparameter configurations are detailed in Appendix C. We used the source codes provided by Yuan et al. (2022b)[3] and alignment handbook (Tunstall et al., 2023)[4]. During pre-training stage, we trained our model using eight 80G A100 GPUs for 12 hours. During fine-tuning stage, we used a single A100 GPU.

4.4 Results

Consistent with previous studies (Sung et al., 2020; Liu et al., 2021), we use accuracy at top-1 (Acc@1) as our evaluation metric. This metric measures the percentage of mentions where the model correctly ranks the gold standard identifier as the top choice. Table 1 demonstrates that our framework consistently improves the performance of generative models. Specifically, our fine-tuning method (i.e., ANGEL$_{FT}$) improves the Acc@1 scores of BART, BioBART, and GenBioEL by 0.9%, 1.4%, and 1.2%, respectively. When pre-training is also applied (i.e., ANGEL$_{PT+FT}$) to GenBioEL, the improvement increases to 1.7%, underscoring the effectiveness of both pre-training and fine-tuning in ANGEL. Our best model (i.e., GenBioEL with ANGEL$_{PT+FT}$) outperforms all baseline models, whether they are similarity-based or generative BioEL models.

[3] https://github.com/Yuanhy1997/GenBioEL

[4] https://github.com/huggingface/alignment-handbook

5 Analysis

5.1 Ablation Study

We conducted detailed analyses on our negative-aware training. Additionally, the impact of the number of synonyms in positive-only training is provided in Appendix D.

Effect of Pre-training Table 2 highlights the effectiveness of ANGEL's pre-training by comparing other pre-training methods. BART, pre-trained using a standard language modeling objective but not specifically tailored for BioEL tasks, shows the lowest performance. In contrast, GenBioEL, pre-trained using synonyms from UMLS in a similar manner to our positive-only training, initially demonstrates a substantial performance advantage over BART. However, this gap narrows considerably after fine-tuning, to the point where it is no longer statistically significant. When ANGEL's negative-aware training is applied to GenBioEL, its performance improves significantly, achieving gains of 16.6% on BC5CDR and 10.9% on AAP. Even after fine-tuning, the performance gap remains noticeable, with a difference of 1.4% on BC5CDR and 0.9% on AAP.

Model	FT	BC5CDR	AAP
BART	✗	0.8	15.6
GenBioEL	✗	33.1	50.6
+ ANGEL (**Ours**)	✗	**49.7**	**61.5**
BART	✓	93.0	88.7
GenBioEL	✓	93.1	89.3
+ ANGEL (**Ours**)	✓	**94.5**	**90.2**

Table 2: The top-1 accuracy of models with different pre-training strategies, along with the fine-tuned scores. 'FT' denotes fine-tuning, with ✗ representing pre-trained models without fine-tuning, and ✓ indicating models fine-tuned on human-annotated training sets.

Method	BC5CDR	AAP
ANGEL (**Ours**)	**94.5**	**90.2**
GenBioEL	93.1 (-1.4)	89.3 (-0.9)
Prediction-based $\mathbf{e}_l$ ⇒ TF-IDF-based $\mathbf{e}_l$	94.4 (-0.1)	90.0 (-0.2)
$p_\theta(\mathbf{e}_l) > p_\theta(\mathbf{e}_w)$ Pairs ⇒ All Possible Pairs	94.0 (-0.5)	90.0 (-0.2)
$\mathbf{e}_l$ within Top-5 ⇒ Top-10 Predictions	94.4 (-0.1)	89.9 (-0.3)

Table 3: The ablation study on positive ($\mathbf{e}_w$) and negative ($\mathbf{e}_l$) pair selection during negative-aware fine-tuning. '⇒' indicates a modification in our method, specifically in the selection of either negative samples or pairs.

Selection of Positive and Negative Pairs Table 3 presents various methods for constructing positive-negative pairs in negative-aware training. We investigated the effects of three different aspects: negative sampling techniques, the ranking of negative samples, and top-k selection, on the BC5CDR and AAP datasets. Notably, all three model variants significantly improved performance compared to the baseline GenBioEL model, highlighting the effectiveness of our negative-aware training, irrespective of the specific techniques used for selecting positive-negative pairs. (1) First, when we modified our approach to extract negative samples based on TF-IDF, similar to the method used during pre-training, performance declined by 0.1% on the BC5CDR and by 0.2% on the AAP. This indicates that our approach, which allows the model to learn from its errors, is more effective than relying on TF-IDF similarity. While the TF-IDF-based method tends to select pairs where the positive and negative examples have similar surface forms, our error-driven approach enables the selection of more diverse negative samples without such constraints. (2) Additionally, when we substituted our

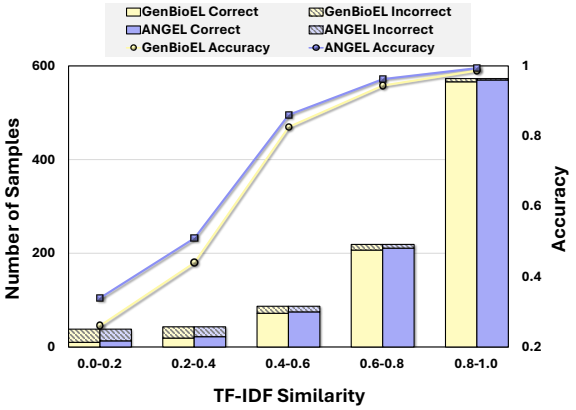

Figure 3: In-depth evalution of GenBioEL and our ANGEL models based on the TF-IDF similarity between the input mentions and gold-standard entities. The NCBI-disease dataset was used. Further analysis is provided in Appendix E.

negative selection method—where negative samples are ranked higher than positive ones—with an approach that includes all positive-negative pairs regardless of rank, the performance dropped by 0.5% on the BC5CDR and by 0.2% on the AAP. (3) Finally, increasing the top-k selection from the top-5 to the top-10 predictions resulted in a performance decline of 0.1% on the BC5CDR and 0.3% on the AAP. Increasing the top-k can indeed gather more diverse negative samples; however, it may also increase the collection of typical samples that the model finds less confusing, potentially degrading performance. Therefore, maintaining a proper balance between diversity and difficulty in sample selection is crucial.

5.2 Error Analysis

We conducted an in-depth evaluation of the models based on the similarity between the input mentions and the gold-standard entities. Similarity was calculated using tri-gram TF-IDF, with the gold-standard entity determined as the candidate synonym with the highest similarity score to the input mention. The similarity scores, ranging from 0 to 1.0, were divided into five bins, and accuracy was measured for each bin. As shown in Figure 3, errors predominantly occurred in the 0-0.2 and 0.2–0.4 bins. This suggests that models tend to struggle when the surface forms of the input mentions are not closely aligned with those of the gold-standard entities. Our method improves the generalizability of the model, leading to an overall reduction in GenBioEL's errors across all bins, with particularly notable improvements in cases of low similarity.

Rank	SapBERT	GenBioEL	ANGEL (Ours)
	... aggressive the same way someone with [ST] ***ASPD*** [ET] would be, except teenagers ...		(SNOMED CT:26665006)
1	ASP	Anankastic personality disorder	**Antisocial personality disorder (disorder)***
2	Acquired immune deficiency syndrome (disorder)	Borderline personality disorder	**Antisocial personality disorder***
3	Acquired immune deficiency syndrome	Oppositional defiant disorder	Borderline personality disorder (disorder)
4	Mesalazine	**Antisocial personality disorder***	Obsessive compulsive disorder (disorder)
5	Cryopyrin associated periodic syndrome (disorder)	Oppositional defiant disorder (disorder)	**Dissocial personality disorder***
	... I switched from lantus to [ST] ***basaglar*** [ET] in january and ...		(SNOMED CT:411529005)
1	Beagle	Linagliptin substance	**Insulin glargine substance***
2	Basiliximab sodium	Benzodiazepine substance	**Insulin glargine***
3	Basiliximab substance	Carisoprodol substance	Insulin glulisine substance
4	Albiglutide	Cariprazine	Ulipristal substance
5	Albiglutide substance	Benzocaine containing product	Lansoprazole
	... effects on amino acid (r-aminobutyric acid (GABA), [ST] ***glutamine*** [ET], aspartate and glutathione) levels ...		(MeSH:D018698)
1	Glutamine	Glutamine	L-glutamine
2	**Glutamic acid***	**Glutamic acid***	Glutamine
3	L-glutamine	Glutamylmethionine	D-glutamine
4	**L-glutamic acid***	Glutamylalanine	Glutamic acids
5	Glutamic acids	Glutaminic acids	**Glutamic acid***

Figure 4: The top 5 predictions from different BioEL models are presented. Entity names with correct identifiers are highlighted in boldface with an asterisk. The first and second examples highlight the strengths of our model, while the final example illustrates its limitations. For a detailed explanation, please refer to the main text.

However, significant challenges remain, as the accuracy of our model is only 34.2% in the 0–0.2 bin, highlighting the need for further improvement.

5.3 Case Study

Figure 4 illustrates the predictions of SapBERT, GenBioEL, and ANGEL. In the first example, the mention 'ASPD' is an abbreviation for 'antisocial personality disorder' (also known as 'dissocial personality disorder'). SapBERT incorrectly predicts 'ASP' due to the similarity in surface form. GenBioEL struggles to distinguish between correct entity names and those containing the words 'personality disorder'. In contrast, our model successfully identifies the correct entities, without being misled by false entity names that contain overlapping terms. The second example involves the mention 'basaglar,' a biosimilar medication that contains insulin glargine, a long-acting insulin. The challenge here arises from the fact that product names can differ significantly from the biomedical terms used to describe their active ingredients. This discrepancy leads to failures in both SapBERT and GenBioEL, as they struggle to connect the brand name to its corresponding biomedical entity. Nevertheless, our model successfully identifies the correct entity, showcasing its ability to handle such complex cases effectively. In the final example, our method was less effective. For the mention of 'glutamine,' neither SapBERT nor GenBioEL identified the correct answer, but they did rank 'Glutamic acid,' the correct entity, within the top 5 candidates. Our model, however, ranked the correct answer slightly lower. Consequently, while our model shows a notable improvement in top-1 accuracy, the increase in top-5 accuracy is relatively modest in some datasets. The effectiveness of our method also varies across different datasets. We discuss this limitation in more detail in Appendix F, noting that such cases are an area for further exploration.

6 Conclusions

In this study, we discussed the importance of negative samples in training generative BioEL models and introduced ANGEL, the first framework in this field to effectively incorporate negative-aware training into a generative model. Our models demonstrated the ability to learn subtle distinctions between entities with similar surface forms and contexts. Experimental results showed that ANGEL outperformed existing similarity-based and generative models, with notable performance improvements of 0.9%, 1.4%, and 1.7% for BART, BioBART, and GenBioEL, respectively, while achieving the best performance across five public BioEL datasets.

Limitations

Our method is versatile and applicable to any generative model, but it has only been tested on encoder-decoder models and not on decoder-only models such as BioGPT (Luo et al., 2022). We plan to further investigate the effect of our method on these models. Additionally, it has not been tested on recent open-source large language models (LLMs) (Touvron et al., 2023; Chen et al., 2023). While we acknowledge that incorporating comparisons with LLMs and further assessing the effectiveness of our approach would be an interesting direction, using LLMs for entity linking presents new challenges. The primary concern with larger models is their inefficiency, particularly regarding slower inference speeds and higher memory requirements, which may render them unsuitable for most real-world applications. This issue becomes particularly problematic in fields such as biomedical information extraction, where processing millions of publications to extract meaningful insights is essential.

Our negative-aware training method may not be limited to a specific domain, yet we have only evaluated it on biomedical-domain datasets, which restricts the demonstration of its broad applicability. Nevertheless, we would like to emphasize the reasons for focusing on the biomedical domain. Biomedical entity linking has unique characteristics that differentiate it from other domains, making this problem both challenging and interesting. In general domains, ambiguity typically arises between different types of entities (e.g., whether "Liverpool" refers to a city or a sports club). Similarly, in the biomedical domain, ambiguity exists between different types, such as whether "Ebola" in Figure 1 refers to a disease or a virus. Additionally, biomedical entities often exhibit significant variations in their surface forms, even when they share the same identifier, i.e., they refer to the same entity. As shown in Figure 4, "Basaglar" can be expressed as other variations such as "insulin glargine substance" or "insulin glargine." Furthermore, terms like "*substance*" in the entity "insulin glargine substance" overlap with many other entities (e.g., "Basiliximab *substance*," "Linagliptin *substance*," "Benzodiazepine *substance*"), making the task even more complex. Therefore, distinguishing between numerous candidates with similar surface forms is especially crucial in biomedical entity linking. We believe that our method, which trains the model using negative samples with similar structures, is particularly well-suited to tackle this challenge. However, exploring the application of our approach in other domains would be a valuable direction for future research.

Ethical Considerations

This study complies with ethical standards, ensuring that all datasets and models adhere to their respective licenses and usage terms. Biomedical examples are included to illustrate the methodology; however, they serve explanatory purposes and may not fully represent real-world scenarios. While the model achieves notable improvements, its limitations in handling low-similarity cases underscore the importance of rigorous validation prior to deployment, especially in sensitive applications. To minimize risks, the model is recommended as a reference tool rather than for direct decision-making in critical contexts.

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A Details of Pre-training

Our pre-training process follows the KB-Guided Pre-training strategy outlined in the GenBioEL framework (Yuan et al., 2022b). We define clause templates to generate synthetic training examples by incorporating synonyms and definitions from the KB. Specifically, we select pairs of synonyms $\mathbf{s}_a$ and $\mathbf{s}_b$ from the set $\mathcal{S} \subset \mathcal{E}$, along with a definition $\mathbf{d}_y$ corresponding to the identifier y. The synonyms and definitions are integrated into one of the two predefined clause templates as follows:

[BOS] [ST] $\mathbf{s}_a$ [ET] **is defined as** $\mathbf{d}_y$ [EOS]

or

[BOS] $\mathbf{d}_y$ **describes** [ST] $\mathbf{s}_a$ [ET] [EOS].

The input for the decoder is "[BOS] $\mathbf{s}_a$ **is**" and the output should be "$\mathbf{s}_b$ [EOS]". When no definitions are available in the KB, we construct $\mathbf{d}_y$ using alternative synonyms. For concepts with only two synonyms, $\mathbf{s}_a$ and $\mathbf{s}_b$ are used as the synonyms, with $\mathbf{d}_y$ being the same as $\mathbf{s}_b$. For concepts with only one synonym, $\mathbf{s}_a$, $\mathbf{s}_b$, and $\mathbf{d}_y$ are the same, resulting in a straightforward sentence. This strategy effectively creates simulated contexts for the model to learn from, improving its ability to generalize to new entities not included in the downstream datasets. The complete list of templates used in this process is provided in Table A.

Template	
Encoder Side	**Decoder Side**
$\mathbf{s}_a$ < is defined as > $\mathbf{d}_y$	$\mathbf{s}_a$ is $\mathbf{s}_b$
$\mathbf{s}_a$ < is described as > $\mathbf{d}_y$	
$\mathbf{d}_y$ < are the definitions of > $\mathbf{s}_a$	
$\mathbf{d}_y$ < describe > $\mathbf{s}_a$	
$\mathbf{d}_y$ < define > $\mathbf{s}_a$	
$\mathbf{d}_y$ < are the synonyms of > $\mathbf{s}_a$	
$\mathbf{d}_y$ < indicate the same concept as > $\mathbf{s}_a$	
$\mathbf{s}_a$ < has synonyms such as > $\mathbf{d}_y$	
$\mathbf{s}_a$ < refers to the same concepts as > $\mathbf{d}_y$	
$\mathbf{d}_y$ < is > $\mathbf{s}_a$	
$\mathbf{d}_y$ < is the same as > $\mathbf{s}_a$	
$\mathbf{s}_a$ < is > $\mathbf{d}_y$	
$\mathbf{s}_a$ < is the same as > $\mathbf{d}_y$	

Table A: The templates used for constructing pre-training samples. $\mathbf{s}_a$ is the input synonym, and $\mathbf{s}_b$ is the decoding target. $\mathbf{d}_y$ includes contextual information such as definitions and synonyms. Template words are enclosed in < >.

B Datasets

Table B presents the statistics of the five datasets used, along with their corresponding target knowledge bases.

NCBI-disease (Doğan et al., 2014) The NCBI-disease dataset contains 793 PubMed abstracts annotated with 6,892 disease mentions that are mapped to 790 unique disease concepts using the MEDIC ontology (Davis et al., 2012). MEDIC is a medical dictionary that integrates disease concepts, synonyms, and definitions from both MeSH (Lipscomb, 2000) and OMIM (Hamosh et al., 2004), encompassing a total of 9,700 unique disease entities. This dataset is primarily used for disease recognition and concept normalization tasks.

BC5CDR (Li et al., 2016b) The BC5CDR dataset includes 1,500 PubMed abstracts with 4,409 chemical entities, 5,818 disease entities, and 3,116 chemical-disease interactions. All annotated entities are mapped to the MeSH ontology (Lipscomb, 2000), which is a subset of UMLS (Bodenreider, 2004). This dataset is widely used for biomedical entity recognition and interaction studies. To fit the purpose of our study, we use only the chemical and disease annotations and discard the interaction annotations.

COMETA (Basaldella et al., 2020) COMETA focuses on layman medical terminology, compiled from four years of content across 68 health-related subreddits. This dataset consists of 20,000 biomedical entity mentions annotated with concepts from SNOMED CT (Chang and Mostafa, 2021). It is utilized for the normalization of consumer health expressions into standardized medical terminologies.

AskAPatient (AAP) (Limsopatham and Collier, 2016b) The AskAPatient dataset contains 8,662 phrases from social media language, each mapped to medical concepts from SNOMED CT (Chang and Mostafa, 2021). This dataset does not include contextual information, meaning that mentions are disambiguated solely based on the phrases themselves. Since the AskAPatient dataset lacks a test set, we employed a 10-fold cross-validation approach as outlined in the original paper by Limsopatham and Collier (2016a). The statistics reported are the averages across these folds.

Dataset	NCBI	BC5CDR	COMETA	AAP	MM-ST21pv
Entity types	disease	disease/chemical	medical concepts	medical concepts	21 UMLS types
Data Examples					
Training	5,784	9,285	13,489	15,665	121,498
Validation	787	9,515	2,176	793	40,600
Test	960	9,654	4,350	866	39,922
KB statistics					
Entity names	108,071	809,929	904,798	3,381	203,282
Identifiers	14,967	268,162	350,830	1,036	25,419

Table B: The statistics of the benchmark datasets and their corresponding KBs.

MM-ST21pv (Mohan and Li, 2019) The MedMentions dataset is a large-scale resource for biomedical entity recognition. The ST21pv subset includes 4,392 PubMed abstracts with over 200,000 entity mentions linked to 21 selected UMLS semantic types. This dataset provides a comprehensive resource for training and evaluating biomedical entity recognition systems. Unlike the original dataset, we use the 2020AA version of UMLS as the KBs because the 2017AA version of UMLS is not directly accessible. This leads to some differences after preprocessing due to variations between versions. Specifically, our dataset deviates from the original MedMentions dataset by 741 training samples (0.6%), 284 validation samples (0.7%), and 235 test samples (0.6%).

C Hyperparameter Configurations

Table C details the hyperparameters used for positive-only training and negative-aware training across the BioEL benchmark datasets. We search for the hyperparameter settings that are optimized for each dataset. We refer to the study of Yuan et al. (2022b) to determine the range of the hyperparameters. During pre-training, we use the same hyperparameters as in GenBioEL. For positive-only training, we explore a range of training steps between 20K and 40K, a learning rate between 2e-5 and 3e-7, and batch sizes from 8 to 16, except during pre-training. During negative-aware training, we fix the β at 0.1, in accordance with the basic configuration of DPO, and search the hyperparameter space using a learning rate between 1e-5 and 1e-6 and batch sizes ranging from 8 to 64.

D The Number of Synonyms

To evaluate the impact of incorporating multiple synonyms during fine-tuning, we conducted experiments by varying the number of synonyms associated with each mention, testing with 1, 3, and 5 synonyms. As shown in Figure A, the average performance improves when using three synonyms compared to just one, but it declines when expanding to five synonyms. When the number of available synonyms is less than the specified number (e.g., fewer than 3 or 5 synonyms), all available synonyms are used to ensure maximum diversity in learning. Therefore, unlike GenBioEL, which utilized only the top-1 synonym, our approach incorporated up to the top-3 synonyms per mention, which proved to be optimal.

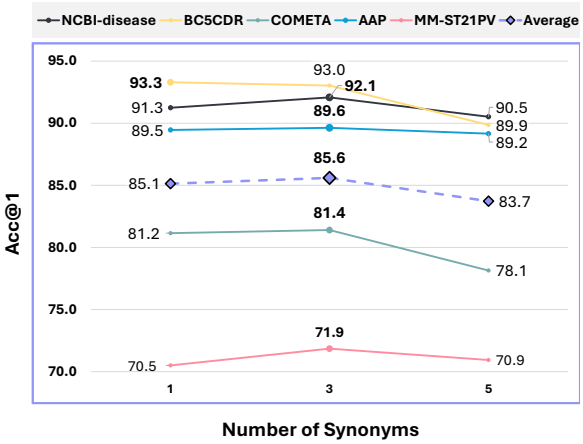

Figure A: The ablation study to determine the optimal number of synonyms. GenBioEL with ANGEL$_{\text{PT}}$ was fine-tuned in this experiment. The scores are generally the highest when $k = 3$.

E Error Cases on COMETA

Similar to the analysis conducted on the NCBI-disease dataset (Figure 3), Figure B shows that the models in COMETA predominantly made the most errors in the 0.0-0.2 bin, where the similarity between input mentions and gold-standard entities is low. Our ANGEL framework improved GenBioEL's performance across all bins, resulting in overall enhancement. Future work will necessitate the development of more advanced methods to

	Pre-training	Fine-tuning				
		NCBI	BC5CDR	COMETA	AAP	MM-ST21pv
Positive-only Training						
Training Steps	80K	20K	30K	40K	30K	40K
Learning Rate	4e-5	3e-7	5e-6	5e-6	5e-6	2e-5
Weight Decay	0.01	0.01	0.01	0.01	0.01	0.01
Batch Size	384	16	16	16	16	16
Adam ϵ	1e-8	1e-8	1e-8	1e-8	1e-8	1e-8
Adam β	(0.9,0.999)	(0.9,0.999)	(0.9,0.999)	(0.9,0.999)	(0.9,0.999)	(0.9,0.999)
Warmup Steps	1,600	0	500	500	0	1,000
Attention Dropout	0.1	0.1	0.1	0.1	0.1	0.1
Clipping Grad	0.1	0.1	0.1	0.1	0.1	0.1
Label Smoothing	0.1	0.1	0.1	0.1	0.1	0.1
Negative-aware Training						
Epochs	5	1	1	1	1	1
Learning Rate	1e-5	1e-5	1e-5	5e-6	5e-6	5e-6
β(DPO)	0.1	0.1	0.1	0.1	0.1	0.1
Weight Decay	0.01	0.01	0.01	0.01	0.01	0.01
Batch Size	1,024	64	16	64	8	64
Warmup Steps	100	100	100	100	100	100

Table C: The hyperparameters for positive-only training and negative-aware training.

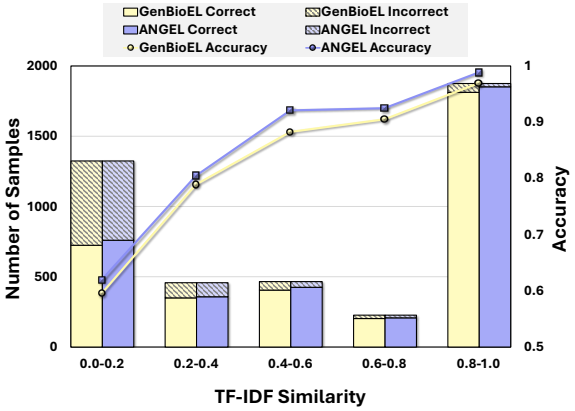

Figure B: In-depth evalution of GenBioEL and our ANGEL models based on the TF-IDF similarity between the input mentions and gold-standard entities. The COMETA dataset was used.

Model	BC5CDR		AAP	
	Acc@1	Acc@5	Acc@1	Acc@5
GenBioEL	93.1	95.7	89.3	**95.4**
+ ANGEL$_{\text{FT}}$	94.4	96.5	89.5	94.7
+ ANGEL$_{\text{PT + FT}}$	**94.5**	**96.8**	**90.2**	95.2

Table D: Comparison of top-1 and top-5 accuracy between the baseline model and models trained with ANGEL method after fine-tuning and pre-training on the BC5CDR and AAP datasets.

specifically address errors in low similarity ranges.

F Top-5 Accuracy

Table D presents our model's top-1 and top-5 accuracy on the BC5CDR and AAP datasets. It compares the performance of our model in its baseline form (GenBioEL) and after fine-tuning (ANGEL$_{\text{FT}}$) and combined pre-training and fine-tuning (ANGEL$_{\text{PT + FT}}$). Our approach consistently boosts top-1 accuracy across all datasets, though the trends in top-5 accuracy are less uniform. In BC5CDR, both top-1 and top-5 accuracy show significant improvements: top-1 accuracy rises by 1.4 percentage points (from 93.1% to 94.5%), and top-5 accuracy increases by 1.1 percentage points (from 95.7% to 96.8%). However, the AAP dataset exhibits a different pattern. While top-1 accuracy improves by 0.9 percentage points (from 89.3% to 90.2%), top-5 accuracy slightly declines: there is a 0.7 percentage points drop (from 95.4% to 94.7%) after fine-tuning and a 0.2 percentage points decrease (from 95.4% to 95.2%) after combined pre-training and fine-tuning. This decline in top-5 accuracy may be due to the AAP dataset's limited contextual information, forcing the model to rely predominantly on the mention form, making it more challenging to maintain high accuracy across multiple predictions. Additionally, the negative sampling strategy could unintentionally bias the model toward optimizing top-1 accuracy, thereby impacting top-5 performance.

In conclusion, while our method consistently improves top-1 accuracy, the occasional slight decreases in top-5 accuracy, as observed in the AAP dataset, underscore the need for further refinement

to maintain balanced accuracy across different ranking levels. Future work should focus on training strategies that preserve or enhance top-5 accuracy alongside top-1 improvements.