Enhanced Reasoning for Biomedical Document-Level Relation Extraction via a Novel Cascade Language Model Framework

Anonymous ACL submission

Abstract

Biomedical document-level relation extraction poses significant challenges beyond sentence-level tasks, as it necessitates the integration of evidence from entire documents and the ability for coherent cross-sentence reasoning. While pretrained language models (PLMs) demonstrate efficiency in handling local contexts, they often struggle with global dependency modeling. Conversely, large language models (LLMs) exhibit strong reasoning capabilities but tend to generate hallucinations in knowledge-intensive biomedical tasks. This paper introduces CoRE, a novel cascade framework that leverages the complementary strengths of PLMs and LLMs through a *detect-then-rethink* paradigm. The PLM serves as an efficient detector for high-confidence relations, while challenging cases are forwarded to an LLM enhanced with semantic retrieval and iterative reasoning mechanisms. Experimental results on the BioRED and CDR datasets show that CoRE achieves substantial improvements over state-of-the-art baselines, validating the effectiveness of the proposed cascade paradigm for complex biomedical relation extraction.

1 Introduction

Biomedical document-level relation extraction (BioDocRE) is a critical task that identifies semantic relations between entities across entire scientific documents, forming the foundation for deriving structured knowledge from large-scale unstructured literature. This task poses substantially greater challenges than sentence-level extraction, owing to its inherent complexity. Specifically, it demands the integration of long-range semantic dependencies scattered across documents, robustness to noise from domain-specific terminology variations, and the ability to process dense specialized knowledge beyond the reach of general-purpose language models. The accurate extraction of such relations is crucial for advancing biomedical research, as it directly supports knowledge discovery and accelerates progress in areas including drug development, disease mechanism interpretation, and precision medicine (Luo et al., 2022).

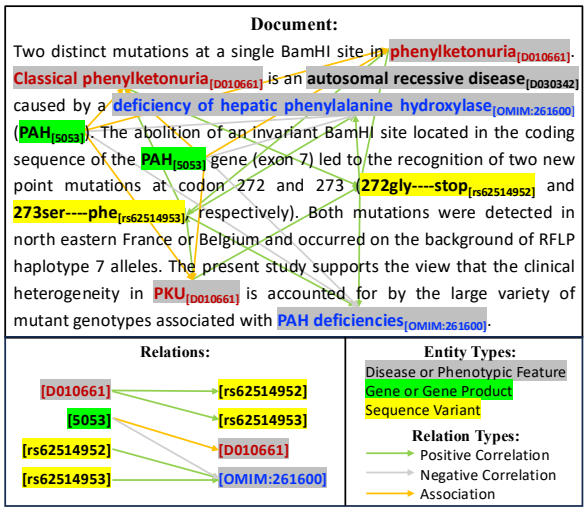

Figure 1: An illustrative example of BioDocRE, in which entities sharing the same ID but varying synonyms are in color. The colored boxes and lines denote different entity types and relation types, respectively.

Pre-trained language models (PLMs) have emerged as the leading method in BioDocRE, surpassing earlier sequence models with self-attention and domain-specific pre-training. These advancements primarily follow three directions: graph-based structural dependency modeling (Li et al., 2025), attention-based entity-pair contextualization (Xu et al., 2021), and novel task reformulation (Wang et al., 2024). Nonetheless, PLMs remain constrained by heavy reliance on fine-tuning and limited reasoning capacity, particularly for implicit relations or low-resource settings. In parallel, large language models (LLMs) offer a new paradigm with strong in-context learning (ICL) (Brown et al., 2020) and reasoning abilities, reducing the need for task-specific annotations (Xu et al., 2024). However, in the precise biomedical domain, LLMs are

prone to hallucination, often generating unsubstantiated relations that inflate recall at the expense of precision (Huang et al., 2025). Their performance still lags behind fully-supervised PLMs (Rehana et al., 2024), and their high computational cost further hinders large-scale deployment.

Consider the example in Figure 1, where determining the relation between the entity `D010661` and the entity `rs62514952` requires cross-sentence reasoning, as the entities are linked indirectly through a bridge entity `5053`. Specifically, the second sentence states that the disease `D010661` is caused by a deficiency of the gene `5053`, while the third sentence notes that the variant `rs62514952` is located on the `5053` gene sequence. Moreover, the disease entity `D010661` appears with multiple synonyms, such as *phenylketonuria* and *PKU*, which necessitates both entity disambiguation and evidence integration.

To simultaneously overcome the reasoning limitations of PLMs on low-confidence instances and curb the hallucination bias of LLMs, we propose CoRE: an innovative cascade method that synergizes the strengths of domain-specific PLMs and LLMs, improves accuracy while optimizing computational efficiency in BioDocRE through confidence-based sample routing. Given the document and entity pairs, a domain-specific PLM first generates initial relation predictions and corresponding confidence scores. Instances yielding high-confidence predictions are deemed reliably resolved and accepted, whereas ambiguous, low-confidence samples are selectively routed to an LLM for refined prediction. For the LLM stage, we employ a semantic retriever to select relevant training demonstrations and construct a few-shot prompt, and further introduce a tailored iterative chain-of-thought (ItCoT) mechanism to encourage more grounded, multi-step reasoning. Finally, predictions from both routes are aggregated to form the final output, allowing the PLM to handle the majority of high-confidence cases while reserving the LLM's advanced reasoning only on intricate or long-tail cases.

The main contributions of this work are summarized as follows: (1) We propose CoRE, a novel cascade framework for BioDocRE that leverages the complementary strengths of PLMs and LLMs via a detect-then-rethink paradigm to achieve efficient state-of-the-art (SOTA) performance; (2) We design a robust LLM reasoning mechanism enhanced with semantic retrieval and iterative reasoning, significantly reducing hallucinations for more reliable extraction; (3) Experiments on BioRED and CDR show that CoRE substantially outperforms PLM-only and LLM-only baselines with practical computational costs.

2 Related Work

2.1 Document-level Relation Extraction

Document-level relation extraction (DocRE) aims to identify semantic relations between entities across an entire document, presenting unique challenges beyond sentence-level extraction (Yao et al., 2019). Recent PLM-based approaches have advanced along multiple directions. FILR (Li et al., 2022) performs multi-granularity inference at both mention-pair and entity-pair levels with bridge nodes, KG-DGAN(Li et al., 2025) explicitly incorporates external knowledge by constructing a knowledge-enhanced graph, and employs a dynamic generative adversarial network to refine node representations. Regarding attention optimization, BERT-GT (Lai and Lu, 2021) employs graph Transformers (Yun et al., 2019) with neighbor attention to reduce irrelevant noise, ATLOP (Zhou et al., 2021) utilizes adaptive thresholding and localized pooling for discriminative representations. SSAN (Xu et al., 2021) integrates co-occurrence and coreference dependencies via learnable bias terms. From a paradigm perspective, DocuNet (Zhang et al., 2021) treats the relation matrix as an image input and applies U-Net (Ronneberger et al., 2015) to capture global dependencies, Bio-RFX (Wang et al., 2024) decomposes DocRE into predicting potential relation types followed by entity pair extraction via a Question-Answering framework.

Despite these innovations, existing PLM-based methods heavily rely on statistical co-occurrence patterns and shallow semantic matching rather than genuine multi-step reasoning. Consequently, their performance degrades in low-resource scenarios or when processing samples with implicitly expressed relationships.

2.2 LLM-enhanced Reasoning

LLMs have demonstrated promising performance on Information Extraction (IE) tasks through ICL (Dong et al., 2024). To further augment adaptability and reliability, researchers widely adopt retrieval-augmented generation (Lewis et al., 2020) to mitigate hallucinations by retrieving external knowledge, alongside chain-of-thought prompting (Wei

et al., 2022) which induces intermediate reasoning steps. Specific to relation extraction, GPT-RE (Wan et al., 2023) combines task-aware retrieval with gold-label-induced reasoning, CoT-ER (Ma et al., 2023a) prompts LLMs to generate evidence using task-specific conceptual knowledge and then explicitly integrates this evidence into a CoT prompt.

Despite these advances, their performance on biomedical RE tasks still lags behind fully supervised PLMs (Rehana et al., 2024), especially in BioDocRE where long-range dependencies, implicit relations, and specialized knowledge pose compounded challenges. Existing retrieval mechanisms fail to adequately aggregate evidence spanning multiple sentences, and standard CoT methods generate reasoning paths in a single forward pass without error detection or correction mechanisms. Additionally, applying LLMs directly to all samples is often infeasible due to prohibitive computational costs and low processing efficiency. While cascade strategy (Ma et al., 2023b) have shown promise in sentence-level IE tasks, it has not yet been adapted to the complexity of document-level reasoning. To bridge these gaps, we propose CoRE, a cascade framework that synergizes domain-specific PLMs with LLMs through confidence-based routing. Our approach incorporates a document-level semantic retriever optimized for cross-sentence evidence aggregation, and an iterative reasoning mechanism utilizing a dynamic error experience library, enabling reflection and correction during inference.

3 Method

3.1 Task Definition

The BioDocRE task can be formalized as follows: given a biomedical document $\mathcal{D}$, containing a set of entities $\mathcal{E} = \{e_1, e_2, \ldots, e_N\}$, each entity e corresponds to a set of synonyms $\mathcal{M}_e = \{m_1, m_2, \ldots, m_k\}$. For a target pair of entities (e_s, e_o), where $e_s, e_o \in \mathcal{E}$, the objective is to infer the corresponding semantic relation $r \in \mathcal{R}$, where $\mathcal{R}$ denotes a predefined set of biomedical relation types. The final output forms a set of triples $\{(e_s, r, e_o)\}$ derived from the semantic information within $\mathcal{D}$.

3.2 Preliminary Study

The proposed method is motivated by an empirical observation regarding the correlation between model confidence and reliability. We define the confidence score as the maximum probability assigned by the model across all possible relation types:

$$\mathcal{C}(e_s, e_o) = \max_{r \in \mathcal{R}} P(r \mid \mathcal{D}, e_s, e_o) \quad (1)$$

As illustrated in Figure 2, the performance of PLM DocuNet on the CDR development set demonstrates a strong correlation between confidence and reliability. Higher-confidence predictions yield significantly greater accuracy and F1-scores, while lower-confidence ones are notably less reliable. In contrast, LLMs show stable performance across the same confidence intervals, but their performance declines in high-confidence regions due to the prevalence of "no-relation" samples. The LLM has a bias toward predicting the existence of a relation, which leads to a higher rate of false positives and poorer performance on these specific samples.

3.3 Model Architecture

The overall architecture is illustrated in Figure 3. To synergize the exceptional performance of PLMs on high-confidence predictions with the superior generalization capabilities of LLMs, the proposed CoRE adopts a two-stage prediction paradigm to deal with the BioDocRE task, the PLM efficiently handles reliable high-confidence samples, while routing only the intricate, low-confidence instances to the LLM for refined inference. The following subsections describe each stage in detail.

3.4 Initial Prediction by PLM

The first stage employs a fine-tuned biomedical PLM to efficiently process documents and assign confidence scores for subsequent routing. For each target entity pair (e_s, e_o) within the document $\mathcal{D}$, the PLM predicts the relation type r_{os} and the confidence score c_{os}. To decide which predictions should be trusted, we introduce a confidence threshold τ, which is empirically optimized on the development set via grid search to maximize the overall system performance. For high-confidence samples with confidence score c_{os} satisfying $c_{os} \geq \tau$, the fully supervised PLM's predictions are generally reliable, indicating that the model has successfully captured the relevant relational patterns from the training data; thus, these predictions can be accepted directly. Conversely, instances with scores below τ are considered challenging for the PLM, which are routed to the second stage for enhanced reasoning.

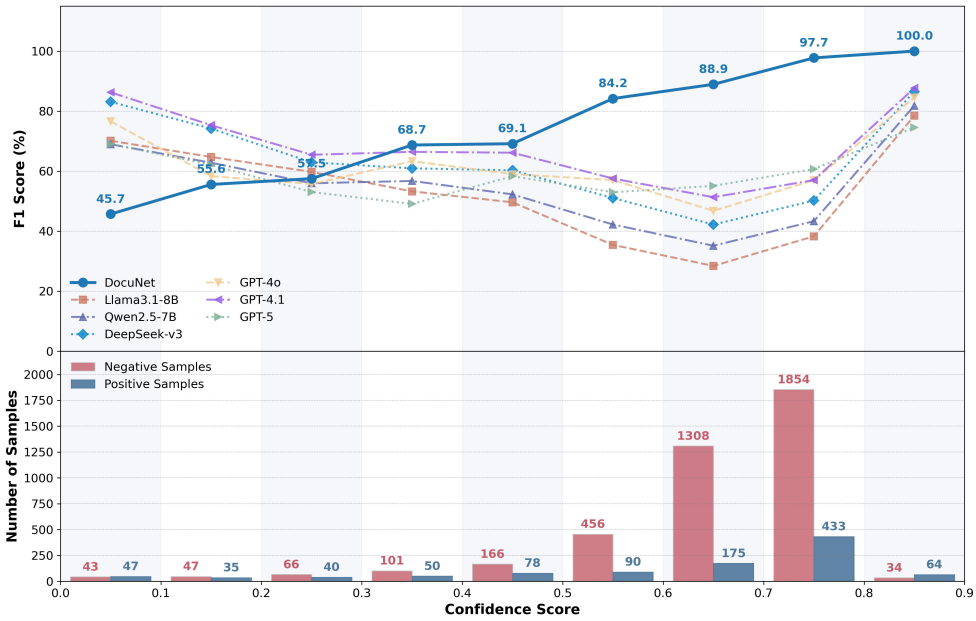

Figure 2: Performance comparison across confidence score intervals on the CDR development set. The higher panel illustrates the F1 scores of DocuNet (solid line) and various LLMs (dashed lines) across different confidence score intervals, revealing the correlation between performance and confidence. The lower panel displays the distribution of positive and negative samples within each confidence interval for DocuNet, highlighting the data class imbalance and its impact on models' performance.

3.5 Mention-Aggregation-based Semantic Retrieval

To mitigate the inherent over-prediction bias of LLMs, where models tend to fabricate relations between uncorrelated entities, we introduce a novel context-aware semantic retriever that augments the LLM with contextually relevant demonstrations from the training set.

In BioDocRE, a significant challenge arises from the dispersed nature of entity mentions, where a single entity often appears multiple times in different sentences, each providing partial evidence. Relying on isolated mention contexts fails to capture the global relational semantics. To address this, we propose a Mention-Aggregation-based strategy that encodes all occurrences of the two target entities, and aggregates them into a unified relation vector, thereby naturally integrating cross-sentence evidence for retrieval.

Given a document $\mathcal{D}$ and a target entity pair (e_s, e_o), we first construct a document-level semantic representation for each entity. We segment $\mathcal{D}$ into sentences, and let $\mathcal{M}_e = \{m_1, m_2, \ldots, m_k\}$ denote the set of mentions for entity e within these sentences. For each mention m_i, we extract its local context as s_i. Subsequently, we employ a pre-trained Sentence-Transformer (Reimers and Gurevych, 2019) model all-mpnet-base-v2[1] to encode the local context sentence of each mention. This generates a context-aware mention vector:

$$\mathbf{h}_i = \text{Encoder}(s_i), \quad \forall m_i \in \mathcal{M}_e \tag{2}$$

where $\mathbf{h}_i \in \mathbb{R}^d$ encapsulates the local semantic features of the i-th mention. While a target entity may appear multiple times within a document, decisive relational evidence is often sparse. Standard average pooling dilutes these specific signals. To address this, we adopt a LogSumExp (LSE) pooling strategy to synthesize the mention vectors into a unified entity representation $\mathbf{v}_e \in \mathbb{R}^d$. LSE serves as a smooth approximation of the max operator, enabling the model to selectively emphasize the most salient contextual features while maintaining numerical stability:

$$\mathbf{v}_e = \text{LSE}(\{\mathbf{h}_1, \ldots, \mathbf{h}_k\}) = \log\left(\sum_{i=1}^{k} \exp(\mathbf{h}_i)\right) \tag{3}$$

After obtaining the aggregated vectors, for document $\mathcal{D}$ and target entities e_s and e_o, we concatenate their aggregated vectors $\mathbf{v_s}$ and $\mathbf{v_o}$, then apply L2 normalization to form the final relation representation, which removes magnitude differences and ensures a consistent basis for similarity measurement:

$$\mathbf{v}_{os} = \frac{[\mathbf{v_s} \oplus \mathbf{v_o}]}{\left\|[\mathbf{v_s} \oplus \mathbf{v_o}]\right\|_2} \tag{4}$$

[1] https://huggingface.co/sentence-transformers/all-mpnet-base-v2

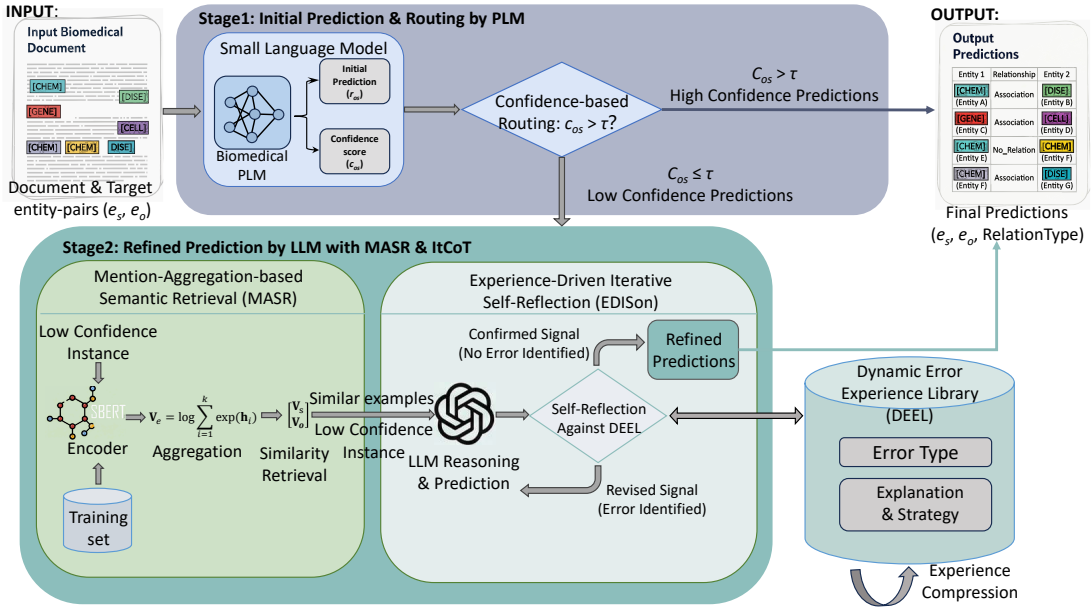

Figure 3: The overall architecture of CoRE.

During the inference phase, $\mathbf{v}_{os}$ is used to query the pre-computed index of the training set. We retrieve the Top-K instances based on cosine similarity, which serve as grounded demonstrations to guide the LLM's subsequent reasoning.

3.6 Iterative Chain-of-Thought Reasoning

Although the semantic retriever identifies contextually relevant demonstrations from the training set, standard ICL and naive CoT prompting tend to treat these demonstrations merely as formatting templates rather than logical guides. This superficial utilization not only fails to exploit the full instructional value of the demonstrations but also renders the reasoning process fragile in complex contexts, where a single logical deviation can easily lead to error propagation.

To explicitly guide the LLM in leveraging the demonstrations while robustly mitigating hallucination in BioDocRE, we propose an iterative ItCoT mechanism. This approach introduces an iterative refinement loop that empowers the LLM to engage in self-reflection and actively rectify its initial conclusions. The core idea is to construct a reasoning system capable of dynamically learning from error experiences, consisting of two collaborating components: a Dynamic Error Experience Library (DEEL) and an Experience-Driven Iterative Self-Reflection (EDISon) process.

3.6.1 Dynamic Error Experience Library

A distinctive feature of the ItCoT mechanism is its capacity for self-improvement. Concretely, before predicting on query instances, we first prompt the LLM to perform a probing inference on the retrieved exemplars and compare its prediction with the gold label. Upon detecting a deviation from the gold label, we provide LLM with the document context, its erroneous reasoning process, and the golden label, then it is tasked with re-reasoning and summarizing the failure by identifying the "Error Type" and formulating a concise "Explanation & Avoidance Strategy". These distilled insights are then structured into a knowledge entry and added to the global Error Experience Library, transferring individual errors into generalizable principles that can guide future reasoning, endowing the system with a capacity for continuous learning in BioDocRE.

Furthermore, to prevent redundancy, unwieldy growth of the library, and mitigate noise, we introduce an LLM-based experience compression mechanism: When the number of entries exceeds a predefined threshold, the LLM is invoked to cluster, deduplicate, and summarize the existing experiences, yielding a compact set of error experiences with improved coverage and reduced noise.

3.6.2 Experience-driven Iterative Self-reflection

Building upon the constructed Error Experience Library, we further instantiate these experiences

as inference constraints via an experience-driven iterative self-reflection procedure. Unlike standard CoT prompting which is strictly feed-forward, our approach induces a iterative "Generate-Reflect-Revise" loop within a single model instance.

Specifically, after obtaining the initial reasoning and prediction from LLM, the LLM is prompted to review its reasoning trace against the entries in the error library, checking for logical errors that match known error patterns. This process compels the LLM to perform a secondary validation of its own thought process and make one of two decisions based on its self-reflection:

- **Confirm**: If the model determines that its reasoning is sound and free of any known error patterns, it outputs a "Confirm" signal. The reasoning process then terminates, and the current prediction is adopted as the final result.
- **Revise**: If the model diagnoses a flaw matching an entry in the library, it is prompted to generate a new, corrected reasoning trace and provide an updated prediction.

This "Generate-Reflect-Revise" loop can be iterated multiple times until the model outputs a "Confirm" signal or a maximum number of iterations is reached. This iterative refinement improves the reliability of the LLM's prediction by ensuring that only thoroughly validated reasoning is ultimately adopted.

4 Experiment

4.1 Datasets

We evaluate CoRE on two publicly available and widely recognized biomedical document-level relation extraction benchmarks: CDR (Li et al., 2016) and BioRED (Luo et al., 2022). The detailed statistics of these datasets are summarized in Table 1.

CDR consists of 1,500 PubMed abstracts, and serves as a benchmark for identifying relations between chemicals and diseases. BioRED is a more recent dataset comprising 600 PubMed documents. Unlike prior datasets restricted to single entity pair or relation type, BioRED features a comprehensive schema with six entity categories and multiple relation types.

Table 1: Statistics of the CDR and BioRED datasets. We report the numbers of documents and relation instances in the training, development, and test sets, together with the numbers of entity types and relation types.

Dataset	Types		Documents			Relation Instances		
	Ent.	Rel.	Train	Dev	Test	Train	Dev	Test
CDR	2	2	500	500	500	1,038	1,012	1,066
BioRED	6	8	400	100	100	4,178	1,162	1,163

4.2 Experimental Settings

We benchmark CoRE against a diverse set of state-of-the-art methods listed in Table 2 and Table 3, and adopt DocuNet and e2eBioMedRE (Sarol et al., 2024) as base PLMs. Their predictions and corresponding confidence scores serve as the basis for the subsequent routing process. For LLMs, we employed Llama3.1-8B (Dubey et al., 2024) and Qwen2.5-7B (Yang et al., 2024), along with larger-scale models including Deepseek-v3.2 (Liu et al., 2024), GPT-4o (Achiam et al., 2023), GPT-4.1 (OpenAI, 2025a), and GPT-5 (OpenAI, 2025b). All LLMs are deployed using default parameters to ensure reproducibility. The optimal routing threshold τ is determined via grid search on the development set to maximize the hybrid F1-score and is fixed for the test set. We utilize *all-mpnet-base-v2* to encode relation instances into vector representations.

4.3 Main Results

Table 2 and Table 3 present the comparative performance of baseline PLMs, standalone zero-shot LLMs, and our CoRE method.

Performance of zero-shot LLMs. All LLMs exhibit high recall but significantly lower precision compared to supervised PLMs. This confirms the observation in Section 3.2: LLMs have a strong bias towards predicting the existence of a relation, leading to massive false positives, especially on prevalent "no_relation" samples. Consequently, their F1-scores lag far behind domain-specific SOTA PLMs.

Effectiveness of CoRE. Compared to the original prediction, CoRE consistently boosts the performance of each LLM. Specifically, on the CDR dataset, CoRE achieves an F1 score of 88.20%, surpassing DocuNet by 1.88%. On the BioRED dataset, our method reaches 66.35% F1 score, exceeding e2eBioMedRE by 1.91%. Crucially, these improvements are observed across the full spectrum of LLMs, from 7B-parameter open-source model to the most advanced proprietary model GPT-5. This underscores that the coordination paradigm is a powerful and model-agnostic strategy, rather than an artifact dependent only on a

Table 2: Performance comparison on the CDR test sets. Methods marked with an asterisk (*) indicate our reproduction of the original models.

Method	CDR						
	Validation			Testing			
	P	R	F1	P	R	F1	Δ
Base Group							
BioGPT	–	–	–	–	–	46.17	–
Bio-RFX	–	–	–	–	–	74.49	–
SSAN(SciBert)	–	–	68.40	–	–	68.70	–
KG-DGAN	–	–	–	78.00	74.00	76.00	–
FILR	–	–	–	–	–	85.70	–
ATLOP(SciBert)*	–	–	–	–	–	68.99	–
BERT-GT	–	–	–	64.49	71.79	65.99	–
PubMedBERT	–	–	–	57.84	53.57	55.63	–
DocuNet(SciBert)*	86.38	85.87	86.12	89.03	83.77	**86.32**	–
e2eBioMedRE*	68.11	75.13	71.45	69.97	71.79	70.87	–
Zero-shot LLMs							
Llama3.1-8B	26.16	91.01	40.64	27.34	89.21	41.84	–
Qwen2.5-7B	31.05	89.43	46.09	28.98	92.21	44.10	–
Deepseek-v3.2	37.66	93.67	53.72	39.81	92.02	55.58	–
GPT-4o	45.07	80.53	57.80	48.01	78.14	59.47	–
GPT-4.1	31.64	95.95	47.59	39.75	93.34	55.76	–
GPT-5	56.32	62.55	59.27	62.11	61.82	61.97	–
CoRE Group (Ours)							
Llama3.1-8B + CoRE	88.40	87.35	87.87	88.89	85.55	87.19	+0.87
Qwen2.5-7B + CoRE	88.42	87.55	87.98	90.09	85.27	87.61	+1.29
Deepseek-v3.2 + CoRE	88.09	89.92	89.00	88.75	87.34	88.04	+1.72
GPT-4o + CoRE	90.36	84.29	87.22	89.64	86.02	87.79	+1.47
GPT-4.1 + CoRE	88.87	87.55	88.20	89.39	86.12	87.72	+1.40
GPT-5 + CoRE	88.54	89.33	88.93	89.09	87.34	**88.20**	+1.88

Table 3: Performance comparison on the BioRED test sets. Methods marked with an asterisk (*) indicate our reproduction of the original models.

Method	BioRED						
	Validation			Testing			
	P	R	F1	P	R	F1	Δ
Base Group							
BERT-GT	–	–	–	–	–	56.50	–
PubMedBERT	–	–	–	–	–	58.90	–
DocuNet(SciBert)*	59.19	43.84	50.37	64.29	48.93	55.57	–
e2eBioMedRE*	64.59	59.02	61.68	67.81	61.39	**64.44**	–
Zero-shot LLMs							
Llama3.1-8B	11.40	46.42	18.30	12.13	53.57	19.77	–
Qwen2.5-7B	17.52	53.75	26.43	17.25	59.76	26.77	–
Deepseek-v3.2	18.17	48.40	26.42	21.44	49.96	30.00	–
GPT-4o	19.29	52.11	28.16	20.98	52.88	30.04	–
GPT-4.1	19.22	56.51	28.68	21.03	58.21	30.90	–
GPT-5	27.14	63.68	38.06	28.19	62.42	38.84	–
CoRE Group (Ours)							
Llama3.1-8B + CoRE	65.75	60.14	62.82	68.68	61.65	64.98	+0.54
Qwen2.5-7B + CoRE	67.94	59.62	63.51	70.82	61.56	65.87	+1.43
Deepseek-v3.2 + CoRE	64.98	65.49	65.23	67.65	65.09	**66.35**	+1.91
GPT-4o + CoRE	64.89	66.01	65.44	67.98	63.71	65.78	+1.34
GPT-4.1 + CoRE	64.42	65.92	65.16	66.03	65.35	65.69	+1.25
GPT-5 + CoRE	67.10	67.04	67.07	67.81	64.66	66.20	+1.76

specific LLM's capability. Notably, even smaller LLMs like Llama3.1-8B, when integrated into CoRE, can outperform original results of much larger standalone models, highlighting the framework's effectiveness.

4.4 Ablation study

To analyze the contribution of each component in our method, we visualize the granular performance across seven entity pairs as detailed in Figure 5 (c). The results indicate that naïve CoT with a standard "think step-by-step" instruction does not always

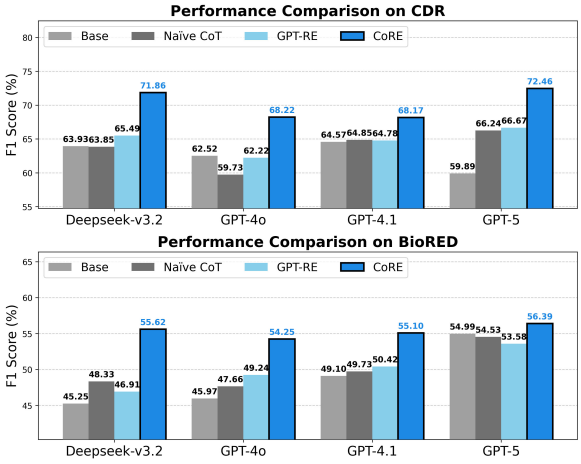

Figure 4: Performance comparison (F1 score) on the low-confidence subsets of CDR (top) and BioRED (bottom). The grouped bars display the performance of four distinct methods: Base, Naïve CoT, GPT-RE (sentence-level retrieval with guided reasoning), and the proposed CoRE method with document-level retrieval and iterative reasoning.

improve LLM performance on the BioDocRE task. For instance, on ⟨Gene-Chemical⟩ pairs, F1 drops from 40.78% to 31.52%. Lacking task-specific guidance, extended reasoning context can occasionally introduce noise, leading to performance degradation. LoRA fine-tuning markedly improves LLM outputs (e.g., Llama3.1-8B F1 rises from 41.84% to 68.47% on CDR), but incurs high computational cost and remains inferior to PLMs specifically designed for DocRE. This validates our premise that direct adaptation of LLMs is not the most efficient path for this task.

In contrast, leveraging pre-trained PLMs in combination with LLMs, with or without CoT, yields substantial gains, surpassing both individual PLM and LLM baselines. Since neither model undergoes further training or fine-tuning, this underscores the effectiveness of the routing-based coordination method. Compared to the full CoRE method, variants lacking semantic mention aggregation and iterative reasoning show an average drop of 6.66% F1 score, confirming the effectiveness of the proposed task-specific retrieval-augmented iterative reasoning components.

4.5 Analysis on Long-tail Relations

To further probe the model's capability on long-tail distributions, we additionally report the performance of models across seven major entity type pairs of BioRED in Figure 5 (detailed in Table 4), enabling a more granular evaluation under complex scenarios involving multiple entity and relation

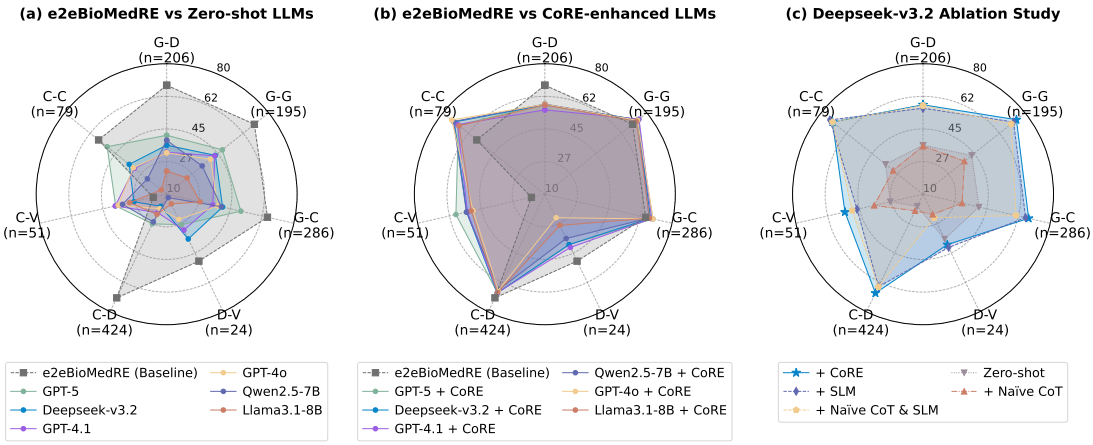

Figure 5: Radar plots comparing F1 scores across seven entity pairs on the BioRED test set. Radial axes correspond to: Gene–Disease (G-D), Gene–Gene (G-G), Gene–Chemical (G-C), Disease–Variant (D-V), Chemical–Disease (C-D), Chemical–Variant (C-V), and Chemical–Chemical (C-C), with sample sizes (n) indicated in parentheses. (a) e2eBioMedRE versus six zero-shot LLMs. (b) e2eBioMedRE versus CoRE-enhanced LLMs. (c) Ablation study of CoRE components on Deepseek-v3.2. Shaded regions indicate coverage area for each method; the radial scale ranges from 10% to 80%.

types. As shown in Figure 5(a), the state-of-the-art PLM e2eBioMedRE demonstrates a significant performance imbalance. While e2eBioMedRE performs well on common pairs like ⟨Gene, Disease⟩, its performance drops precipitously on rare ones such as ⟨Chemical, Variant⟩ (17.39% F1) due to the lack of sufficient training data. In contrast, CoRE (with Deepseek-v3.2) shows substantial improvements in these rare categories (e.g., +35.57% F1 on ⟨Chemical, Variant⟩), often doubling the performance, as shown in Figure 5(b). This demonstrates that the LLM stage, augmented with semantic retrieval and iterative reasoning, is particularly effective for cases requiring nuanced inference while the PLM suffer from data scarcity.

4.6 Comparison with Sentence-level RAG

We focus our evaluation on a low-confidence subset, which corresponds to the most challenging instances typically routed to the LLM stage. We benchmark CoRE against (1) LLMs without CoT (Base); (2) LLMs with naïve CoT; and (3) GPT-RE (2-shots), a representative method employing sentence-level retrieval. Figure 4 shows that GPT-RE generally improves over Base setting, +2.06% and +1.21% F1 on average for CDR and BioRED respectively, suggesting that RAG+CoT can be beneficial for BioDocRE. CoRE further yields consistent gains over GPT-RE across all settings, +5.39% and +5.30% average F1 on CDR and BioRED. We attribute this improvement to two factors: first, CoRE retrieves demonstrations that capture document-wide relational semantics, whereas GPT-RE's sentence-level retrieval may miss critical cross-sentence evidence; second, the iterative self-reflection process encourages the LLM to actively validate its inference and learn from transferable reasoning patterns. These results highlight the importance of retrieval granularity and reasoning design for BioDocRE.

5 Conclusion

This paper introduces CoRE, a cascade framework that synergizes PLM with LLM via confidence-aware routing. By integrating mention-aggregation semantic retrieval and iterative reasoning, CoRE effectively addresses PLM limitations on hard and long-tail cases while mitigating LLM hallucinations. Experiments on CDR and BioRED confirm that CoRE substantially outperforms SOTA baselines, validating the efficacy of the detect-then-rethink paradigm.

Limitations

Despite the empirical success of CoRE, several limitations remain. First, the effectiveness of our retrieval-augmented prompting relies on the availability of relevant examples in the training set. Second, the confidence-based routing strategy is sensitive to threshold selection, requiring manual calibration for optimal performance across data distributions. Third, while CoRE reduces computational overhead compared to LLM-only approaches, the cascade architecture introduces additional latency for low-confidence samples, potentially limiting its applicability in real-time settings.

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A Detailed Performance Results

Table 4: Overall performance on CDR and BioRED datasets. **Yellow background** indicates the best baseline performance (SOTA). **Green background** indicates the best performance achieved by our CoRE method. The Δ columns show the improvement over the respective best baselines (DocuNet F1=86.32 for CDR, e2eBioMedRE F1=64.44 for BioRED). Teal indicates positive improvement; Red indicates negative difference. Abbreviations: *G=Gene, D=Disease, C=Chemical, V=Variant*.

Method	Variant	CDR Testing Set				BioRED Testing Set				BioRED Testing Set (Detailed F1)						
		P	R	F1	Δ	P	R	F1	Δ	G-D	G-G	G-C	D-V	C-D	C-V	C-C
Base Group																
BioGPT	–	–	–	46.17	–	–	–	–	–	–	–	–	–	–	–	–
Bio-RFX	–	–	–	74.49	–	–	–	–	–	–	–	–	–	–	–	–
SSAN	–	–	–	68.70	–	–	–	–	–	–	–	–	–	–	–	–
KG-DGAN	–	78.00	74.00	76.00	–	–	–	–	–	–	–	–	–	–	–	–
FILR	–	–	–	85.70	–	–	–	–	–	–	–	–	–	–	–	–
ATLOP	*	–	–	68.99	–	–	–	–	–	–	–	–	–	–	–	–
DocuNet	*	89.03	83.77	**86.32**	–	64.29	48.93	55.57	–	–	–	–	–	–	–	–
e2eBioMedRE	*	69.97	71.79	70.87	–	67.81	61.39	**64.44**	–	68.46	70.19	65.47	49.84	71.70	17.39	56.70
BERT-GT	–	64.49	71.79	65.99	–	–	–	56.50	–	54.80	63.50	60.20	42.50	67.00	11.80	52.90
PubMedBERT	–	57.84	53.57	55.63	–	–	–	58.90	–	56.60	66.40	59.90	50.80	65.80	25.80	54.40
Zero-shot LLMs																
Llama3.1-8B	Zero-shot	27.34	89.21	41.84	–	12.13	53.57	19.77	–	22.39	24.01	28.40	15.75	21.97	30.39	13.75
Qwen2.5-7B	Zero-shot	28.98	92.21	44.10	–	17.25	59.76	26.77	–	38.91	34.36	40.08	12.00	26.48	34.31	23.21
Deepseek-v3.2	Zero-shot	39.81	92.02	55.58	–	21.44	49.96	30.00	–	36.30	43.41	40.78	36.67	17.19	28.03	35.70
GPT-4o	Zero-shot	48.01	78.14	59.47	–	20.98	52.88	30.04	–	32.22	40.06	38.18	25.00	18.60	36.65	32.84
GPT-4.1	Zero-shot	39.75	93.34	55.76	–	21.03	58.21	30.90	–	32.53	43.07	35.43	31.33	20.96	38.34	32.19
GPT-5	Zero-shot	62.11	61.82	61.97	–	28.19	62.42	38.84	–	41.61	48.21	50.83	28.13	27.60	38.06	50.85
CoRE Group (Ours)																
Llama3.1-8B	+ CoRE	88.89	85.55	87.19	+0.87	68.68	61.65	64.98	+0.54	57.87	72.78	67.63	28.57	68.57	50.49	68.83
Qwen2.5-7B	+ CoRE	90.09	85.27	87.61	+1.29	70.82	61.56	65.87	+1.43	58.33	73.91	67.41	36.36	66.67	53.16	72.61
Deepseek-v3.2	+ CoRE	88.75	87.34	88.04	+1.72	67.65	65.09	**66.35**	+1.91	57.97	74.09	68.10	40.00	68.87	52.96	72.15
GPT-4o	+ CoRE	89.64	86.02	87.79	+1.47	67.98	63.71	65.78	+1.34	58.25	73.63	69.53	24.00	67.25	49.52	73.87
GPT-4.1	+ CoRE	89.39	86.12	87.72	+1.40	66.03	65.35	65.69	+1.25	55.24	74.62	68.77	41.67	68.49	52.60	69.89
GPT-5	+ CoRE	89.09	87.34	**88.20**	+1.88	67.81	64.66	66.20	+1.76	58.33	72.63	69.53	40.00	68.63	58.93	69.36
Ablation Study																
Llama3.1-8B	+ Naïve CoT	27.28	94.37	42.32	–	16.79	60.88	26.32	–	30.77	33.49	35.40	20.56	25.21	34.23	21.40
	+ LoRA	56.58	86.68	68.47	–	–	–	–	–	–	–	–	–	–	–	–
	+ SLM	86.64	86.96	86.80	+0.48	66.29	60.71	63.38	−1.06	56.28	70.59	64.98	26.09	68.34	49.84	66.26
	+ Naïve CoT&SLM	86.84	86.68	86.76	+0.44	66.12	62.25	64.13	−0.31	56.28	72.49	65.73	34.78	66.19	49.52	70.29
Qwen2.5-7B	+ Naïve CoT	28.99	81.89	42.83	–	16.15	55.03	24.97	–	37.99	28.66	40.16	16.39	21.77	33.49	20.29
	+ LoRA	62.32	79.27	69.78	–	–	–	–	–	–	–	–	–	–	–	–
	+ SLM	87.41	86.59	86.99	+0.67	64.29	62.85	63.57	−0.87	58.29	71.98	68.55	25.00	65.64	45.88	69.94
	+ Naïve CoT&SLM	87.81	85.18	86.48	+0.16	62.92	62.17	62.54	−1.90	56.16	68.04	68.53	25.00	64.96	51.05	66.25
Deepseek-v3.2	+ Naïve CoT	38.57	91.74	54.31	–	19.52	57.70	29.16	–	35.82	38.41	31.52	21.98	19.86	36.89	30.51
	+ SLM	87.34	87.34	87.34	+1.02	66.12	62.42	64.22	−0.22	56.16	72.11	66.43	41.67	65.04	46.30	73.89
	+ Naïve CoT&SLM	87.08	87.24	87.16	+0.84	62.93	63.63	63.27	−1.17	57.55	70.53	61.22	24.00	65.19	49.07	72.13
GPT-4o	+ Naïve CoT	44.44	76.54	56.23	–	24.11	55.55	33.63	–	38.89	38.85	43.52	32.84	22.90	38.20	39.94
	+ SLM	89.36	85.08	87.17	+0.85	63.73	61.65	62.67	−1.77	52.43	70.47	66.43	16.67	62.85	52.44	69.66
	+ Naïve CoT&SLM	88.17	85.27	86.70	+0.38	65.94	62.77	64.32	−0.12	55.17	71.54	66.20	25.00	64.22	51.71	73.98
GPT-4.1	+ Naïve CoT	38.08	90.24	53.55	–	24.49	55.80	34.04	–	37.80	45.57	39.19	29.85	23.93	38.62	37.71
	+ SLM	88.16	86.59	87.36	+1.04	64.09	63.37	63.73	−0.71	54.55	71.25	66.67	40.00	65.64	51.71	68.75
	+ Naïve CoT&SLM	88.96	86.21	87.57	+1.25	65.38	62.68	64.00	−0.44	56.31	73.85	65.96	32.00	66.20	49.52	68.66
GPT-5	+ Naïve CoT	55.71	81.43	66.16	–	28.35	59.85	38.47	–	41.08	51.22	48.18	34.38	26.44	40.38	46.76
	+ SLM	90.39	84.71	87.46	+1.14	64.63	64.57	64.60	+0.16	59.62	73.50	69.18	50.00	65.75	49.08	68.62
	+ Naïve CoT&SLM	89.09	85.83	87.43	+1.11	65.91	64.66	65.28	+0.84	57.00	75.00	71.08	32.00	65.40	50.62	71.04

B LLM Prompts for Relation Extraction

The following prompts illustrate the primary inference (few-shot), and iterative reasoning.

B.1 Primary Inference Prompt

This prompt concatenates the generated demonstrations with the target task.

Listing 1: Few-Shot Prompt for Main Inference

```
[SYSTEM]
### Task: Given the following biomedical text and two entities, determine the
    relationship between them.

[USER]
Entity 1: E359 K (Entity)
Entity 2: ventricular septal defect|VSD (Entity)
Text: <...Demonstration Text 1 (GATA4)...>
... [Relationship definitions and Options omitted for brevity] ...
Output format: MUST begin with 'Let's think step by step: ', end with 'Final answer:
     X'.

[ASSISTANT]
Let's think step by step: The text discusses the identification of several mutations
    ... <...Model Reasoning...> ...Therefore, the best fit among the provided
    options is 'Association'.
Final answer: Association

[USER]
Entity 1: S429 T (Entity)
Entity 2: ventricular septal defect|VSD (Entity)
Text: <...Demonstration Text 1 (GATA4)...>
... [Relationship definitions and Options omitted for brevity] ...
Output format: MUST begin with 'Let's think step by step: ', end with 'Final answer:
     X'.

[ASSISTANT]
Let's think step by step:
1. The text describes a genetic study... <...Model Reasoning...>
Final answer: Association

[USER]
Entity 1: tachycardia (DiseaseOrPhenotypicFeature)
Entity 2: V1763M (SequenceVariant)
Text: A novel SCN5A mutation manifests as a malignant form of long QT syndrome...
    <...Target Text...> ...
### Relationship definitions:
Positive_Correlation: The variant causally increases disease risk...
Negative_Correlation: The variant is protective...
Association: A general or unclear connection...
no_relation: The sentence mentions both...

### Output format
Answer MUST: begin with 'Let's think step by step: ', end with 'Final choice: X'.
```

B.2 Iterative Reasoning Prompt

This prompt asks the model to review its own reasoning from the previous step.

Listing 2: Prompt for iterative reasoning

```
[USER]
### Task: Review the prediction for biomedical relation extraction. Your goal is to
    critically identify if the prediction is correct or if it contains any errors.

### Context:
- Entity 1: tachycardia (DiseaseOrPhenotypicFeature)
- Entity 2: V1763M (SequenceVariant)
- Text: <...Target Text Content...>

### Relationship definitions:
<Same Definitions as above>

### Current Prediction:
Positive_Correlation

### Reasoning:
```

```
Let's think step by step: The text describes a newborn with ventricular tachycardia
    ... <...Generated CoT from Previous Step...> ...Final choice:
    Positive_Correlation

### Instructions
    1.  Analyze the prediction's reasoning objectively.
    2.  Compare it against the list of common errors.
    < Error types, Explanations and strategys>
    3.  Provide your response in one of the following two formats ONLY:

    'Let's check the reasoning: ..... Final answer: Confirmed.'

    or 'Let's check the reasoning: ..... Revised: <new reasoning and prediction.>'

Response:
```