# How to Detect and Defeat Molecular Mirage: A Metric-Driven Benchmark for Hallucination in LLM-based Molecular Comprehension

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## Abstract

Large language models are increasingly used in scientific domains, especially for molecular understanding and analysis. However, existing models are affected by hallucination issues, resulting in errors in drug design and utilization. In this paper, we first analyze the sources of hallucination in LLMs for molecular comprehension tasks, specifically the knowledge shortcut phenomenon observed in the PubChem dataset. To evaluate hallucination in molecular comprehension tasks with computational efficiency, we introduce **Mol-Hallu**, a novel free-form evaluation metric that quantifies the degree of hallucination based on the scientific entailment relationship between generated text and actual molecular properties. Utilizing the Mol-Hallu metric, we reassess and analyze the extent of hallucination in various LLMs performing molecular comprehension tasks. Furthermore, the Hallucination Reduction Post-processing stage (HRPP) is proposed to alleviate molecular hallucinations. Experiments show the effectiveness of HRPP on decoder-only and encoder-decoder molecular LLMs. Our findings offer critical insights into mitigating hallucinations and enhancing the reliability of LLMs in scientific applications.

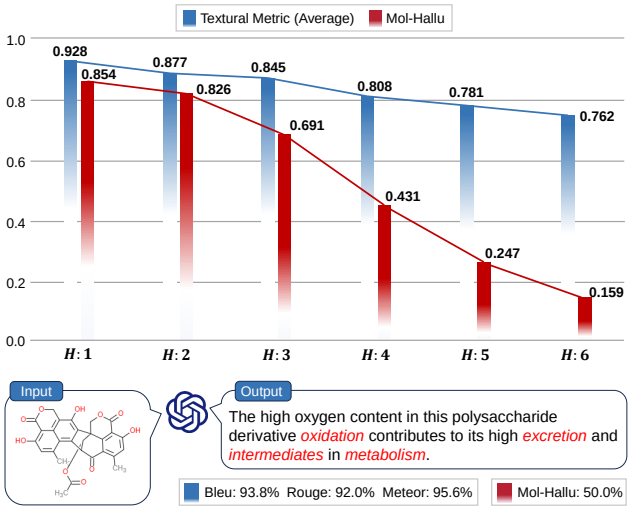


Figure 1: ***Top:*** the scoring curves of Mol-Hallu v.s. traditional metrics (BLEU, ROUGE, METEOR, etc) across varying degrees of hallucination. $H : n$ indicates that samples contain $n$ counterfactual errors, Mol-Hallu imposes an exponential penalty on hallucination errors in text, whereas traditional metrics fail to evaluate biochemical hallucination in texts reasonably. ***Bottom:*** a biochemical sample that suffers severe hallucination (red are counterfactual entities) as an example. Mol-Hallu precisely reflects the hallucination degree in scientific texts compared to traditional metrics.

Submitted to 39th Conference on Neural Information Processing Systems (NeurIPS 2025). Do not distribute.

# 1 Introduction

Large language models (LLMs) are regarded as foundation models in scientific fields due to their outstanding cross-domain generalization capability [39, 65]. In chemistry, LLMs are used for molecular property prediction [38, 50] and molecular design [16, 19]. These models bridge the gap between molecular structural and property features and the natural language descriptions, facilitating multiple chemical applications, including virtual screening, drug design, retrosynthesis planning, etc.

Although LLMs have shown powerful generation capability in biochemistry domains, they suffer from hallucinations [3], which leads to the fabrication of non-existent facts or inappropriate molecular properties [61]. Hallucinations often arise when new biochemical knowledge is introduced during the supervised fine-tuning (SFT) stage conflicts with the model's pretrained knowledge [18]. The risky SFT strategy is frequently employed in various molecular LLMs [14, 48, 64], demonstrating the ubiquity of hallucinations.

Several studies on molecular LLMs analyze the hallucination phenomenon in molecule comprehension tasks. MoleculeQA [36] and MoleculeTextQA [26] construct multi-choice QA datasets to assess the hallucination issues in molecular LLMs. However, these approaches require additional datasets for fine-tuning in the context of fixed-form evaluation [29], and their multiple-choice question format is ill-suited for assessing the open-ended generation capabilities of large language models [59]. To address this limitation, we propose a free-form evaluation metric to quantify the degree of hallucination in molecular LLMs. Moreover, existing research has not yet analyzed the sources of hallucination in molecular LLMs or explored how to effectively mitigate these hallucinations.

To alleviate these issues, we first analyze the source of hallucinations in molecular LLMs and propose **Mol-Hallu**, the first free-form evaluation metric specifically designed to assess hallucination. Our investigation focuses on the PubChemQA dataset [28], a widely recognized benchmark source from the PubChem database [58] that aligns molecular structures with textual descriptions. We identify that knowledge shortcuts in this dataset hinder the alignment between molecular structures and biochemical entities, resulting in increased hallucinations. To quantify the extent of hallucinations, Mol-Hallu leverages the union of the answer and the molecular general description, rewarding correct biomedical entities. The union and intersection are computed using an entailment model to determine whether the molecular descriptions entail a given text n-gram. To enhance evaluation, we curated a chemical entity database by automatically annotating PubChem and ChEMBL [42] datasets to accurately retrieve biomedical entities from predicted texts. Fig.1 demonstrates the rationality of Mol-Hallu for hallucination evaluation compared to traditional metrics including BLEU [44], ROUGE [30], and METEOR [2].

To mitigate the hallucination in current molecular LLMs, we propose the Hallucination Reduction Post-processing (HRPP) stage, which constructs a hallucination-sensitive preference dataset by leveraging our chemical entity database, thereby optimizing the accuracy of scientific entities in text generated by molecular LLMs. The HRPP approach has validated its effectiveness and generalizability under decoder-only and encoder-decoder language models, two fundamental paradigms of molecular language models. Our contributions are summarized as follows:

- We dive into the molecular hallucination issue and identify that bio-knowledge shortcuts in the dataset exacerbate LLM hallucination.
- To measure the hallucination in molecular comprehension with efficiency, we propose the first free-form evaluation metric, Mol-Hallu, which calculates the F1-score of scientific entities using entailment probability.
- We further propose the hallucination reduction post-processing stage to alleviate the molecular hallucination using the hallucination-sensitive preference dataset.

# 2 Related Works

## 2.1 LLMs for Molecular Comprehension

Pretrained biochemical LLMs excel in molecular comprehension, capturing 1D sequential [13, 14, 21, 57], 2D topological [34, 47, 53, 60, 63], and 3D structural features [25, 32, 35, 66]. Two strategies bridge molecular-textual heterogeneity: cross-modal contrastive learning (MoMu [54],

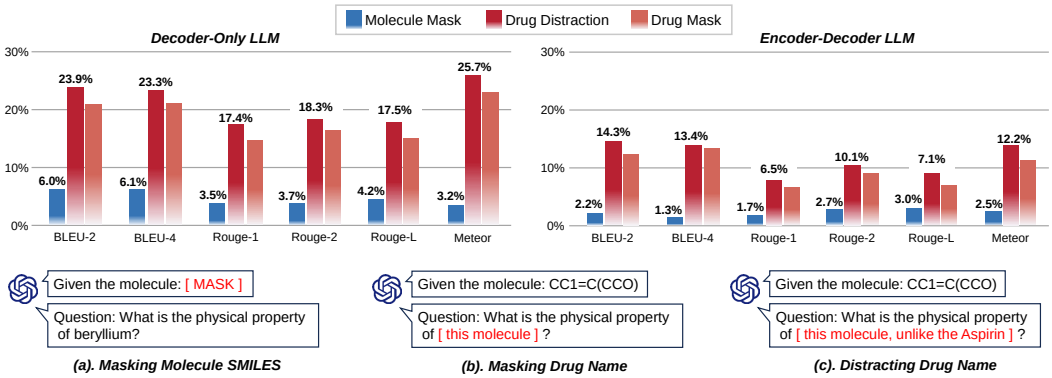


Figure 2: Experiments demonstrate that in both decoder-only LLMs and encoder-decoder LLMs, molecule masking attacking has little impact, while drug masking and distracting attacks lead to a substantial decrease. This indicates that the knowledge shortcut prompts LLMs to establish alignment between molecular properties and drug names instead of molecular structures, thereby deviating from the goal of molecular comprehension.

MoleculeSTM [31], MolCA [33]) and supervised fine-tuning to map molecular representations into textual space (InstructMol [4], PRESTO [6], omni-mol [20]). However, molecular encoder biases and LLM knowledge limitations cause significant hallucination issues.

### 2.2 Hallucination in Biochemical LLMs

LLMs often generate unfaithful content (*hallucination*) due to source-reference divergence from heuristic data collection [46], imperfect training [15], or erroneous decoding [12]. In molecular tasks, counterfactual outputs mislead users and undermine scientific reliability [36].

Hallucination evaluation includes: (1) Fixed-form (multi-choice QA, requires fine-tuning, limited open-ended relevance) and (2) Free-form (automated, computationally efficient). Detection methods comprise: (1) Fact-checking (external [7, 43] or internal knowledge [10, 23]) and (2) Uncertainty estimation (model confidence quantification [40, 56]).

No existing metrics address biochemical LLM hallucination assessment [52]. We propose the first free-form metric for molecular tasks, focusing on scientific entity entailment without external retrieval or fine-tuning, providing efficient domain-specific hallucination detection.

## 3 Methodology

In this section, we propose the definition, the source, the Mol-Hallu evaluation metric, and the alleviation strategy for the molecular hallucination phenomenon.

### 3.1 Definition of Molecular Hallucination

Before delving into the source and evaluation of molecular hallucination, we first define the **Molecular Hallucination** as prediction texts that do not consist of the pharmacological or chemical properties of the molecule. Formally, given the molecule SMILES $M$ and the question $Q$. The hallucination is that LLM $f_\theta(\cdot)$ outputs non-existent or counterfactual scientific entities $E$ that do not satisfy the reality $\mathbb{T}$, where $\mathbb{T}$ is the ground-truth entity set without any non-existent facts.

### 3.2 Source of Molecular Hallucination

The phenomenon of hallucination in LLMs arises from multiple sources, including inherent divergence and spurious noise within the data [27], as well as input knowledge bias [62] in training paradigms during training and inference processes. LLMs exhibit significant hallucinations in molecular comprehension tasks. Upon analyzing the PubChemQA dataset, we identified that **bio-knowledge shortcuts** exacerbate LLM hallucinations.

*Molecule: Given a molecule* **[SMILES]**.
*Question: What is the role of* **[Drug Name]** *in cellular processes?*

To be more specific, bio-knowledge shortcuts refer to instances where drug names (e.g., beryllium) are present in molecular-related questions, leading the model to establish mappings between drug names and their physicochemical properties during supervised fine-tuning, rather than between molecular structures from SMILES and physicochemical properties, which is the original intent of molecular comprehension tasks. The existence of such shortcuts makes LLMs prone to hallucination due to changes or the absence of drug names and hinders their ability to infer physicochemical properties for novel molecules.

To prove this, we conduct attacks on the drug names contained in the questions within the molecular question-answer samples from the PubchemQA dataset and analyze the sources of hallucinations by observing the changes in hallucinations corresponding to different attack strategies [5]. Specifically, given a sample and its corresponding question $Q$, we replace the drug name $D_j$ in $Q$ with (1) a masked pronoun $[\,\mathrm{this\ molecule}\,]$ and (2) a distracting drug name $[\,\mathrm{unlike\ D_j}\,]$. Fig. 2 shows that two classes of commonly used scientific LLMs, the decoder-only models (e.g., Llama [11, 55]) and the encoder-decoder models (e.g., T5 [51]), both exhibit severe hallucination phenomena (-21% Acc.) under two attack strategies. However, the absence of SMILES input has little influence on both models (-5% Acc.). This indicates that the models rely more on textual cues (e.g., drug names) than on SMILES structural information to infer molecular properties, highlighting their inability to align SMILES with molecular properties. This limits their generalization and reasoning capabilities for accurate molecular question-answering.

### 3.3 Mol-Hallu Metric

To better quantify hallucination in LLMs for molecular comprehension tasks, we introduce the **Mol-Hallu** evaluation metric to assess the extent of hallucination. This metric calculates Recall and Precision by comparing the entity entailment probability between the predicted answer $A_i$, the ground-truth answer $G_i$, and the molecular description $T_i$ corresponding to the molecule $M_i$, thereby evaluating the hallucination rate.

#### 3.3.1 Entity Entailment Probability

We define molecular hallucination as the phenomenon of scientific entity mismatches between predicted text and reference answers. To annotate scientific entities in the text, we employed Meta-llama-3.2 [11] with a 10-shot prompting approach to automatically label scientific entities in captions and QA texts from the PubChem dataset. After filtering based on inclusiveness, length, and semantics, we go through the human evaluation and obtain 97,219 chemical entities as the entity database. To enhance the generalization of our entity database, we employ the same extraction protocol to collect 904 and 12,199 chemical entities from CheF [24] and ChemBench [1], covering diverse molecular domains including pharmaceuticals, chemistry, and materials science. The statistic visualization below shows that nearly half of the entities in our entity database are molecular structural entities, while the entities related to drug application, property, and natural source are nearly balanced.

| Dataset | Appli. | Property | Source | Struct. | Others |
|---|---|---|---|---|---|
| Pubchem | 14.3% | 19.7% | 12.0% | 51.2% | None |
| CheF | 37.16% | 18.47% | 4.6% | 25.0% | 14.7% |
| ChemBench | 15.3% | 13.6% | 22.8% | 28.5% | 19.8% |
| Total | 14.6% | 19.0% | 13.4% | 48.5% | 2.3% |

Then, we introduce the entity entailment probability, defined as the probability that the presence of entity list $e$ is correct given the associated molecular descriptions and answers. Inspired by previous entailment works [8], we find that simple models are effective for entailment probability measurement. Here we apply the probability function as $w(\cdot)$,

$$w(e) = \sum\nolimits_{j=1}^{n} \mathbf{1}(e_j \in \bar{\mathbb{T}})/n, \tag{1}$$

where $\mathbf{1}$ is the indicator function, $n$ is the entity number of $e$, and $\bar{\mathbb{T}}$ represents the set of all the entities present in description $T$. Then we compute the precision and the recall of the predicted text.

### 3.3.2 Entailed Precision

The entailed precision aims to represent the correct fraction of the n-gram entities in $mathbbA_i$, where $mathbbA_i$ is the set of all entities in predicted answer $A_i$. An n-gram entity $e$ is treated as correct if it appears in the ground-truth answer or if it appears in the molecular description, which is also a substantial correct answer. We apply $w(e)$ as the reward weight of the second scenario.

$$P_e^{\text{n-gram}} = \sum_{e \in \mathbb{A}_i} [\Pr(e \in \mathbb{G}^{\text{n-gram}}) + w(e)\Pr(e \notin \mathbb{G}^{\text{n-gram}})], \tag{2}$$

Specifically, $P_e^{\text{n-gram}}$ represents the reward of the n-gram entity $e$. It receives a score of 1 if the ground-truth answer entails it. Otherwise, it receives a score of $w(e)$ if $e$ appears in the molecular description. We consider the numerator during the weight calculation of $P_e^{\text{n-gram}}$. Finally, we apply the geometric average to calculate the precision of the total sample group,

$$\bar{P_e} = \exp(\sum_{\text{n-gram}=1}^{4} \frac{1}{4} \log P_e^{\text{n-gram}}), \tag{3}$$

where we select the n-gram order from 1-4 as other metrics [9, 45, 49]. Meanwhile, we calculate the n-gram matching score $\bar{P_\varnothing}$ for non-entity words. To balance the precision $\bar{P_e}$ from scientific entities and $\bar{P_\varnothing}$ from non-entities, we use the entity error count $\gamma$ as a weighting factor,

$$\gamma = 1 - (N_{\text{wrong}}/N_{\text{total}})^{0.5}, \tag{4}$$

$$\text{P} = \gamma\bar{P_\varnothing} + (1-\gamma)\bar{P_e}, \tag{5}$$

where $N_{\text{wrong}}$ and $N_{\text{total}}$ are wrong entity and total entity counts. P represents the final precision score.

### 3.3.3 Entailed Recall

The entailment recall R reflects the extent to which the model misses correct words. R is computed between predicted $A$ and ground truth $G$ to ensure that entities and other n-gram words with high frequency in the ground truth receive a higher score when predicted correctly. We also apply the geometric average to get R from $\text{R}_{1\ldots n}$.

### 3.3.4 Smoothing & Combination

Mol-Hallu employs the geometric average to compute entailed precision due to its ability to reflect compound changes accurately. However, when a component approaches 0, the geometric average also tends to 0. To mitigate this issue, we apply smoothing $\theta$=$10^{-5}$ to components close to 0. After the precision smoothing, we calculate the F1-score based on the entailed precision P and recall R.

$$\text{Mol-Hallu}(A, G, T) = 2\text{P} \cdot \text{R}/(\text{P} + \text{R}), \tag{6}$$

$$\text{Mol-Hallu}(f_\theta) = \frac{1}{N}\sum\nolimits_{i=1}^{N} \text{Mol-Hallu}(A_i, G_i, T_i), \tag{7}$$

where the F1-scores from all samples generated by the model $f_\theta$ are arithmetic averaged to represent the hallucination rate of $f_\theta$.

## 3.4 Hallucination Reduction Post-processing

To mitigate the hallucination in LLM-based molecular comprehension, we propose the Hallucination Reduction Post-processing (HRPP) stage. As shown in Fig. 3, HRPP consists of two main steps: (1) reducing the model's reliance on entity name shortcuts through supervised fine-tuning, and (2) improving response accuracy and reducing hallucination using Direct Preference Optimization (DPO) with a hallucination-sensitive preference dataset.

To mitigate the model's tendency to generate hallucinated responses due to over-reliance on entity name shortcuts, we employ a supervised fine-tuning approach. Given a training dataset $\mathcal{D} = \{(q_i, G_i)\}_{i=1}^{N}$, where $Q_i$ is the input text and $G_i$ is the corresponding ground truth response, we

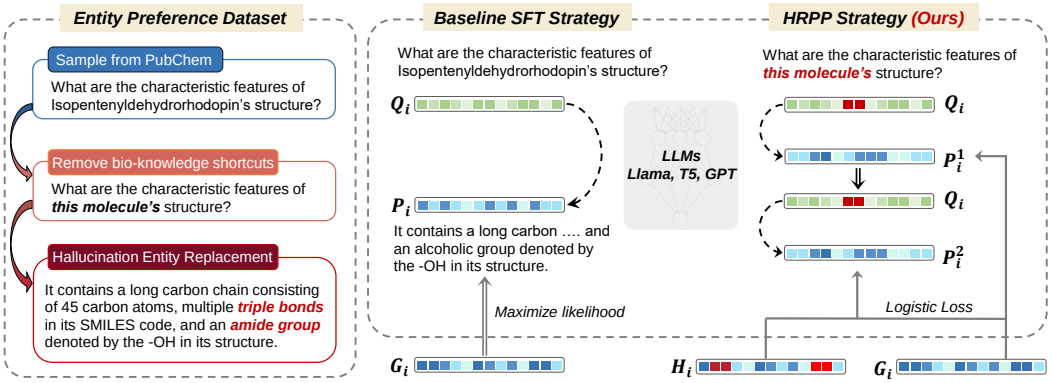


Figure 3: The pipeline of entity preference dataset and our hallucination-reduction post-processing stage. The entity preference dataset is generated by removing bio-knowledge shortcuts and replacing entities with hallucinations. Then we apply the entity preference dataset for scientific-entity hallucination alleviation during the HRPP stage.

preprocess $Q_i$ by masking entity names, replacing them with "this molecule" to prevent shortcut learning. We then optimize the model parameters $\theta$ by minimizing the cross-entropy loss:

$$\mathcal{L}_{\text{CE}}(\theta) = -\sum_{i=1}^{N}\sum_{t=1}^{T}\log P_\theta(G_i^t \mid Q_i, G_i^{<t}) \tag{8}$$

where $T$ is the sequence length, $N$ is the sample number, and $P_\theta$ represents the model's probability distribution over the vocabulary.

To further improve response accuracy and factual consistency of molecular LLMs, we first construct a hallucination-sensitive preference dataset $\mathcal{D}_p = \{(q_i, G_i^+, G_i^-)\}_{i=1}^M$, where $G_i^+$ represents the preferred response, and $G_i^-$ represents the less preferred response. As shown in Fig. 3 left, to construct this dataset, we randomly extract 2000 QA pairs from the training set. The ground truth $G_i$ is designated as $G_i^+$. To generate the negative sample $G_i^-$, we introduce entity perturbations by randomly replacing certain entities in $G_i$ with different ones using our chemical entity database. Additionally, we sample four responses from the model at a high temperature for each $q_i$, incorporating them into the set of $G_i^-$ responses.

We use DPO to optimize the model by maximizing the divergence between the likelihood of preferred and rejected responses:

$$\mathcal{L}(\theta) = -\sum_{i=1}^{M}\log\sigma\left(\beta\log\frac{P_\theta(G_i^+|q_i)P_{\text{r}}(G_i^-|q_i)}{P_\theta(G_i^-|q_i)P_{\text{r}}(G_i^+|q_i)}\right) \tag{9}$$

where $\sigma(\cdot)$ is the sigmoid function, $P_{\text{r}}$ is the reference model, and $\beta$ is a temperature hyperparameter that controls the strength of preference learning. In the experiment section, we apply HRPP to decoder-only LLMs and encoder-decoder LLMs for effectiveness analysis.

# 4 Experiments

## 4.1 Baseline Models and Training Procedures

To comprehensively evaluate the LLM performance in molecular conprehension, we introduce three categories of LLMs as baselines, including scientifically fine-tuned LLMs, general-purpose LLMs, and commercial LLMs. Specifically, LLMs fine-tuned with biochemical knowledge exhibit strong capabilities in modeling molecular SMILES and protein sequences. We evaluate their hallucination levels on the PubChemQA dataset in a zero-shot manner. General-purpose LLMs, trained extensively in natural scenarios, although less adept at modeling molecular SMILES compared to scientifically fine-tuned LLMs, possess stronger reasoning abilities. Commercial LLMs have stronger prior knowledge and reasoning capabilities due to their large parameter sizes. We conduct paid evaluations using the APIs of commercial LLMs, employing 10-shot instruction fine-tuning to generate responses to molecular-related queries.

| Models | # Params | BLEU-2 | BLEU-4 | ROUGE-1 | ROUGE-L | METEOR | Mol-Hallu↑ |
|---|---|---|---|---|---|---|---|
| *Molecular-LLMs* | | | | | | | |
| MolT5-small | 80M | 49.46 | 41.94 | 55.04 | 51.56 | 55.40 | 59.01 |
| MolT5-base | 250M | 50.21 | 42.53 | **55.70** | **52.07** | 56.00 | 44.74 |
| MolT5-large | 800M | 49.58 | 41.97 | 55.52 | 51.85 | 55.80 | 60.13 |
| MoMu-small | 82M | 50.81 | 42.54 | 52.78 | 51.18 | 55.94 | 55.73 |
| MoMu-base | 252M | 51.07 | 43.29 | 53.71 | 50.98 | 55.59 | **56.29** |
| BioT5-base | 252M | 43.36 | 35.10 | 51.05 | 47.16 | 51.55 | 55.21 |
| MolCA | 1.3B | **51.93** | **44.28** | 55.00 | 51.41 | **56.79** | 55.82 |
| 3D-MoLM | 7B | 32.00 | 26.17 | 40.13 | 34.64 | 52.15 | 53.18 |
| BioMedGPT | 10B | 37.31 | 31.29 | 39.62 | 36.87 | 48.31 | 43.88 |
| *General-LLMs* | | | | | | | |
| T5-small | 60M | 49.97 | 42.40 | 54.88 | 51.16 | 55.47 | 59.07 |
| T5-base | 220M | 51.01 | 43.27 | 55.89 | 52.17 | **56.43** | 60.21 |
| T5-large | 770M | 50.79 | 42.85 | **55.98** | **52.23** | 56.42 | **60.93** |
| Llama-2 | 7B | 28.15 | 23.24 | 35.14 | 30.41 | 46.87 | 53.78 |
| Llama-3.1 | 8B | **52.19** | **43.51** | 55.41 | 51.18 | 57.48 | 60.14 |
| *Universal-LLM-API (Few-shot)* | | | | | | | |
| Qwen-2.5-Instruct | 32B | 35.72 | 27.51 | 43.59 | 38.22 | 49.63 | 49.97 |
| Qwen-Reason (QwQ) | 32B | 18.62 | 13.62 | 27.33 | 23.32 | 35.14 | 25.61 |
| DeepSeek-V3 | 671B | **49.31** | 39.86 | **53.96** | **48.37** | **57.69** | **62.16** |
| DeepSeek-R1 | 671B | 32.12 | 24.17 | 41.77 | 37.56 | 40.65 | 46.65 |
| GPT-4o-20241120 | 1.8T | 47.78 | **41.74** | 51.97 | 46.99 | 51.24 | 55.71 |
| o1-mini | 300B | 40.22 | 31.06 | 46.99 | 41.81 | 51.88 | 51.23 |

Table 1: Experimental results for hallucination evaluation across molecular LLMs (fine-tuned), general LLMs (fine-tuned), and universal LLMs (API-based inference). We report accuracy (%) using both standard textual metrics and our proposed hallucination-specific evaluation metric.

| Molecule-LLMs | BLEU-2 | BLEU-4 | ROUGE-1 | ROUGE-L | METEOR | Mol-Hallu↑ | Expert-Score↑ |
|---|---|---|---|---|---|---|---|
| MolT5 [13] | 34.48 | 26.54 | 45.13 | 41.34 | 37.08 | 46.15 | 50.2 |
| MolT5+SFT | 35.45 | 25.93 | 42.72 | 38.99 | 39.68 | 47.04 | 48.6 |
| MolT5**+HRPP** | 40.65 | 30.73 | 47.47 | 43.54 | 44.31 | **49.03** | **63.9** |
| Mollama-8B [38] | 33.18 | 24.75 | 44.19 | 40.66 | 37.57 | 44.21 | 45.0 |
| Mollama-8B+SFT | 35.14 | 25.62 | 43.42 | 39.43 | 39.14 | 44.71 | 46.8 |
| Mollama-8B**+HRPP** | 38.79 | 28.95 | 46.12 | 42.17 | 43.27 | **46.28** | **61.2** |

Table 2: Hallucination Reduction Post-processing (HRPP) has substantial improvements in textural metrics and our Mol-Hallu metric, demonstrating its effectiveness on both decoder-only models (Mollama) and encoder-decoder-based models (MolT5).

### 4.2 Main Results

We summarize and analyze the baseline performances in Table.1. Several phenomena have been observed as follows.

**Hallucinations in baseline models.** (1) The hallucination metric remains within the range of 40-60%, with an average of 3-4 counterfactual entities present, indicating significant room for improvement. (2) The degree of hallucination is not necessarily positively correlated with model performance. While MolT5-base shows comparable performance to MolT5-small and MolT5-large, its hallucination is notably more severe. However, 3D-MoLM exhibits moderate performance but remains lower hallucination rate.

**LLM Structural Comparison: Encoder-Decoder v.s. Decoder-only.** Encoder-decoder models surpass other structures in molecular comprehension tasks due to their compact size and excellent performance. We observe that T5-based models, represented by T5-finetune, MolT5, and MoMu, exhibit strong performance on the MolecularQA task even in their small versions, surpassing molecular LLMs based on Llama by 2.7% and GPT-4 by 13%. This is attributed to the T5 model's encoder-decoder structure, which employs a span corruption pre-training strategy. Additionally, its smaller parameter count supports full-parameter fine-tuning instead of the LoRA fine-tuning used in Llama, resulting in better generalization in few-shot scenarios within the biochemistry domain.

**Reward strategies in LLMs amplify hallucination.** Deepseek-R1 and o1-mini have widely adopted reinforcement learning as an effective approach to enhance the LLM reasoning capabilities for complex problems. However, this optimization strategy often leads to a hallucination increase [17]. We observe a similar phenomenon in Molecular Comprehension. In the LLM-API part of Table.1, we compare Qwen, Deepseek, and GPT-4, with their reasoning-enhanced versions on scientific QA tasks. The results indicate a significant decline in both prediction quality and factual accuracy, attributed to: (1) the trade-off between improved reasoning in math/code tasks and the reduced reliance on prior knowledge, making it harder to address scientific questions; and (2) the tendency of reasoning-enhanced LLMs to generate chain-of-thought outputs, which often contain more hallucinated entities. Therefore, balancing reasoning and hallucination in domain-specific scenarios remains a critical challenge.

**Extra protein knowledge: no benefit to hallucination.** During pretraining, extending the dataset to include both chemical molecules and protein macromolecules cannot alleviate hallucination. Instead, it leads to a decrease in performance for molecular understanding tasks. In Table. 1, BioMedGPT [37] and BioT5 utilize various protein dataset size (1.8M, 27M) as additional knowledge. However, their performance and hallucination assessment are inferior to the MolT5-based model due to the structural differences between FASTA-based protein inputs and SMILES-based molecular inputs, as well as the significant domain-specific entity differences between proteins and chemical molecules. Consequently, the incorporation of such knowledge fails to enhance generalization or reduce hallucination.

### 4.3 Analysis for Hallucination Reduction

In Table. 2, we dive into the hallucination reduction post-processing (HRPP) and analyze its effectiveness on hallucination alleviation . A chemical-expert evaluation in Table. 2 confirms the HRPP module's efficacy in practical molecular comprehension tasks.

**Effectiveness of HRPP Stage.** Our HRPP stage demonstrates effectiveness across both decoder-only and encoder-decoder models. As shown in Table 2, HRPP substantially improves molecular LLMs, achieving average gains of 4.0% on textual metrics and significant hallucination reduction (2.9%↑ for decoder-only; 2.0%↑ for T5-based structures). To confirm HRPP's gains are not from the preference dataset alone, we conducted SFT on the same data. Results show SFT alone fails to consistently improve performance and even degrades expert-score performance.

Meanwhile, We observe notable BLEU and METEOR improvements (5-7%) with HRPP, versus modest ROUGE gains (1-2%), indicating HRPP-enhanced models generate more precise scientific entities and accurate semantics. Some missing entities persist due to ROUGE's recall sensitivity.

**Chemical-Expert Evaluation.** To validate the scientific plausibility of HRPP in molecular understanding tasks, we engage five chemistry experts to evaluate a subset of PubChemQA for scientific soundness and chemical entity correctness. Specifically, PubChemQA samples are stratified into easy, medium and hard categories based on the precision of the DeepSeek-V3 response, with 20 samples selected from each for evaluation. The Expert-Score in Table. 2 (averaging 1-5 ratings per sample) demonstrates HRPP's effectiveness, showing 13.7% and 16.2% improvements over MolT5 and MolLama respectively.

## 5 Conclusion

In conclusion, our work aims to evaluate and alleviate the LLM's hallucination in molecular comprehension. By attacking the scientific entities in molecule-related questions, we identify the bio-knowledge shortcuts in the PubChem dataset prompt LLMs to establish alignment between molecular properties and drug names instead of molecular structures, which serves as the hallucination source of the molecular comprehension task. We further propose Mol-Hallu, the first free-form hallucination metric for the molecular comprehension task. Mol-Hallu provides a computational efficient way to evaluation the hallucination through scientific entailment relationship. To further alleviate the hallucination, we propose the hallucination reduction post-processing (HRPP) strategy with a self-collected hallucination-sensitive preference dataset constructed based on scientific entity replacement. Experimental results demonstrate that various LLM architectures significantly suppressed hallucinations with our HRPP strategy.

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# A Appendix

## A.1 Full version of Related Works

### A.1.1 LLMs for Molecular Comprehension

LLMs that were pretrained with biochemical scientific data have shown substantial success in molecular comprehension tasks [38]. The molecular encoders capture 1D sequential features [13, 14, 21, 57], 2D topological features [34, 47, 53, 60, 63], and 3D structural patterns [25, 32, 35, 66] from the molecule.

Related studies have adopted two primary strategies to bridge the heterogeneity gap between molecular and textual representations for enhanced comprehension. Firstly, the cross-modal contrastive learning strategy is applied to fine-tune molecular and textual encoders, including MoMu [54], MoleculeSTM [31], and MolCA [33]. As textual encoders grow in parameter size and inferential capability, InstructMol [4], PRESTO [6], and omni-mol [20] have turned to supervised fine-tuning using molecular-text datasets to establish a pooling layer that maps molecular representations into the textual space of LLMs. However, constrained by the feature bias of molecular encoders and the prior knowledge of LLMs, current molecular LLMs are plagued by significant hallucination issues.

### A.1.2 Hallucination in Biochemical LLMs

Alongside the advancement in reasoning, LLMs often generate nonsensical or unfaithful content to the provided source, referred as *hallucination* [3, 41]. The source-reference divergence phenomenon [22] is the main cause of hallucination. The divergence comes from heuristic data collection [46] and imperfect representation learning during the training procedure [15] or erroneous decoding when conducting inference [12]. In molecular comprehension tasks, molecular LLMs often generate counterfactual content, which can lead to adverse consequences such as misleading users and ultimately undermining the reliability of LLMs in scientific applications [36].

The evaluation of hallucinations in LLMs can be categorized into **(1) Fixed-form evaluation** and **(2) Free-form evaluation**. Fixed-form evaluation uses multi-choice QA datasets, such as MoleculeQA and MoleculeTextQA, to assess hallucinations. However, this method requires fine-tuning LLMs on hallucination datasets and uses a multi-choice format that differs from the open-ended nature of LLM tasks, making it less reflective of the true hallucination extent. In contrast, free-form evaluation leverages automated functions for faster, more computationally efficient assessments. Hallucination detection methods also fall into two categories: **(1) Fact-checking-based methods**, which verify accuracy through external [7, 43] or internal knowledge [10, 23], and **(2) Uncertainty estimation methods** [40, 56], which detect hallucinations by quantifying model confidence without external references.

Currently, there are no such metrics for hallucination assessment in biochemical LLMs [52], which limits the effectiveness of large scientific models in drug discovery. To address this, we propose the first free-form evaluation metric for molecular comprehension tasks, focused on the entailment of scientific entities. This method leverages ground truth while avoiding the need for external retrieval or fine-tuning, providing an efficient and domain-specific solution for hallucination detection.

## A.2 Case Studies

We select samples with hallucinations and demonstrate a numerical comparison between our Mol-Hallu metric and traditional textual metrics. Table. 3 shows that Mol-Hallu are more sensitive to hallucinations. When the prediction and ground truth share similar sentence structures but differ in

scientific entities, Mol-Hallu assigns a lower score, whereas traditional evaluation methods consider them semantically similar.

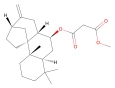
| Molecule | Query | Ground-Truth | Our answer | Metric |
|---|---|---|---|---|
|  | Isolated Area | This compound is isolated from the plants Sorbus cuspidata and Calceolaria dentata. | Hexaen is isolated from the plants pentahydroxy and benzoate. | B: 78.9%<br>R: 86.4%<br>M: 87.9%<br>M-H: 43.3% |
|  | Potential Reactivity | This compound has potential reactivity towards nucleophiles and bases due to the presence of ketone and lactone groups. | This compound has potential reactivity towards aromaticity and methoxy due to the presence of solubility and reactivity groups. | B: 92.2%<br>R: 93.3%<br>M: 93.9%<br>M-H: 66.1% |

Table 3: **Case Studies for Mol-Hallu and Other Textural Metrics**. Our Mol-Hallu exhibits stronger sensitivity to hallucinated outputs under different question types in molecule comprehension.