

# ***Biomedical knowledge graph-optimized prompt generation for large language models***

Karthik Soman<sup>1</sup>, Peter W Rose<sup>2</sup>, John H Morris<sup>3</sup>, Rabia E Akbas<sup>1</sup>, Brett Smith<sup>4</sup>, Braian Peetoom<sup>1</sup>, Catalina Villouta-Reyes<sup>1</sup>, Gabriel Cerono<sup>1</sup>, Yongmei Shi<sup>5</sup>, Angela Rizk-Jackson<sup>5</sup>, Sharat Israni<sup>5</sup>, Charlotte A Nelson<sup>6</sup>, Sui Huang<sup>4</sup>, Sergio E Baranzini<sup>1\*</sup>

<sup>1</sup> Department of Neurology. Weill Institute for Neurosciences. University of California San Francisco. San Francisco, CA, USA.

<sup>2</sup> San Diego Supercomputer Center, University of California, San Diego, La Jolla, CA, USA.

<sup>3</sup> Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, San Francisco, CA, USA.

<sup>4</sup> Institute for Systems Biology, Seattle, WA, USA.

<sup>5</sup> Bakar Computational Health Sciences Institute, University of California, San Francisco, San Francisco, CA, USA.

<sup>6</sup> Mate Bioservices, Inc. Swallowtail Ct. Brisbane, CA, USA.

Short title: Empowering large language models using biomedical knowledge graph

\* Corresponding author

E-mail: sergio.baranzini@ucsf.edu (SEB)

# Abstract

Large Language Models (LLMs) are being adopted at an unprecedented rate, yet still face challenges in knowledge-intensive domains like biomedicine. Solutions such as pre-training and domain-specific fine-tuning add substantial computational overhead, requiring further domain-expertise. Here, we introduce a token-optimized and robust Knowledge Graph-based Retrieval Augmented Generation (KG-RAG) framework by leveraging a massive biomedical KG (SPOKE) with LLMs such as Llama-2-13b, GPT-3.5-Turbo and GPT-4, to generate meaningful biomedical text rooted in established knowledge. Compared to the existing RAG technique for Knowledge Graphs, the proposed method utilizes minimal graph schema for context extraction and uses embedding methods for context pruning. This optimization in context extraction results in more than 50% reduction in token consumption without compromising the accuracy, making a cost-effective and robust RAG implementation on proprietary LLMs. KG-RAG consistently enhanced the performance of LLMs across diverse biomedical prompts by generating responses rooted in established knowledge, accompanied by accurate provenance and statistical evidence (if available) to substantiate the claims. Further benchmarking on human curated datasets, such as biomedical true/false and multiple-choice questions (MCQ), showed a remarkable 71% boost in the performance of the Llama-2 model on the challenging MCQ dataset, demonstrating the framework's capacity to empower open-source models with fewer parameters for domain-specific questions. Furthermore, KG-RAG enhanced the performance of proprietary GPT models, such as GPT-3.5 and GPT-4. In summary, the proposed framework combines explicit and implicit knowledge of KG and LLM in a token optimized fashion, thus enhancing the adaptability of general-purpose LLMs to tackle domain-specific questions in a cost-effective fashion.

# Introduction

Large language models (LLM) have shown impressive performance in solving complex tasks across various domains that involve language modeling and processing (Zhao et al. 2023). LLMs are pre-trained on a large corpora of text data in a self-supervised learning framework which can be either Masked Language Modeling (e.g. BERT like models) (Devlin et al. 2018; Liu et al. 2019) or Auto-Regressive framework (GPT like models) (Brown et al. 2020; R. Luo et al. 2022). This pre-training encodes knowledge about the language in the model parameters. Similar to the transfer learning approach commonly used in deep neural networks, this implicit knowledge can be refined through supervised training to excel in a range of domain-specific tasks (Wei et al. 2021; R. Luo et al. 2022). Nevertheless, the “implicit representation” of knowledge in LLM has also been shown to generate non-factual information despite linguistically coherent answers (i.e. “hallucination”) as a response to the input prompt (Ji et al. 2022; Maynez et al. 2020; Raunak, Menezes, and Junczys-Dowmunt 2021). This issue poses a significant challenge for the adoption of LLM models in domains with stringent requirements for accuracy, such as biomedicine. Various strategies have been introduced to address hallucinations in LLMs. One such solution involves the utilization of domain-specific data for pre-training the LLM, rather than relying on generic text corpora. This approach has led to the creation of models such as PubMedBERT (Yu Gu Microsoft Research, Redmond, WA et al. 2021), BioBERT (Lee et al. 2019), BlueBERT (Lee et al. 2019; Peng, Yan, and Lu 2019), SciBERT (Beltagy, Lo, and Cohan 2019), ClinicalBERT (Huang, Altosaar, and Ranganath 2019), BioGPT (R. Luo et al. 2022), Med-PaLM (Singhal et al. 2023), and BioMedGPT (Y. Luo et al. 2023). However, pre-training an LLM from scratch imposes a significant computational cost and time overhead to attain the desired human-like performance. An alternative approach, known as prompt tuning, was recently proposed as a means to enhance LLM performance, for instance through the use of zero-shot

(Kojima et al. 2022), few-shot (Brown et al. 2020) and Chain-of-Thought (Wei, Wang, et al. 2022) prompting strategies.

Although prompt tuning methods have proven to be effective, their performance is restricted on knowledge-intensive tasks that require providing provenance and up-to-date knowledge about the world to address the user prompt. To address such knowledge-intensive tasks, an alternative approach that integrates knowledge graphs (KG) with language models was recently introduced (Feng et al. 2020; Lin et al. 2019; Wang et al. 2019; Yang et al. 2019; Yasunaga et al. 2021; Lv et al. 2019; Yasunaga et al. 2022). This approach was primarily implemented in question-answering tasks, where the structured information contained within the KG was used to provide context for predicting the answer to the question. While such multimodal integrative approach showed promise, its downstream supervised training was tailored to a specific task, limiting its versatility and broad applicability, thereby constraining its ability to fully harness the "emergent capabilities" of LLMs (Wei, Tay, et al. 2022). Retrieval-Augmented Generation (RAG) involves enhancing a parametric pre-trained LLM with the ability to access a non-parametric memory containing updated knowledge about the world (for e.g., Wikipedia or SPOKE) (Lewis et al. 2020).

In this paper, we propose a robust and token-optimized framework called KG-RAG that integrates a KG with a pre-trained LLM within a RAG framework, thus capturing the best of both worlds. To achieve this, we make use of the biomedical KG called SPOKE (Morris et al. 2023) that integrates more than 40 publicly available biomedical knowledge sources of separate domains where each source is centered around a biomedical concept, such as genes, proteins, drugs, compounds, diseases, and one or more of their known relationships. Because these concepts are recurrent entities forming defined sets (e.g., all named human genes, all FDA

approved drugs, etc.) the integration of these concepts into a single graph exposes novel multi-hop factual relationships that connect the knowledge sources and provides the biological and ontological context for each concept. Unlike other RAG approaches, the proposed framework performs an optimized retrieval, specifically obtaining only the essential biomedical context from SPOKE, referred to as 'prompt-aware context', which is adequate enough to address the user prompt with accurate provenance and statistical evidence. This enriched prompt is further used as input for the LLM in the RAG framework for meaningful biomedical text generation. We evaluated this approach using various pre-trained LLMs including Llama-2-13b, GPT-3.5-Turbo and GPT-4.

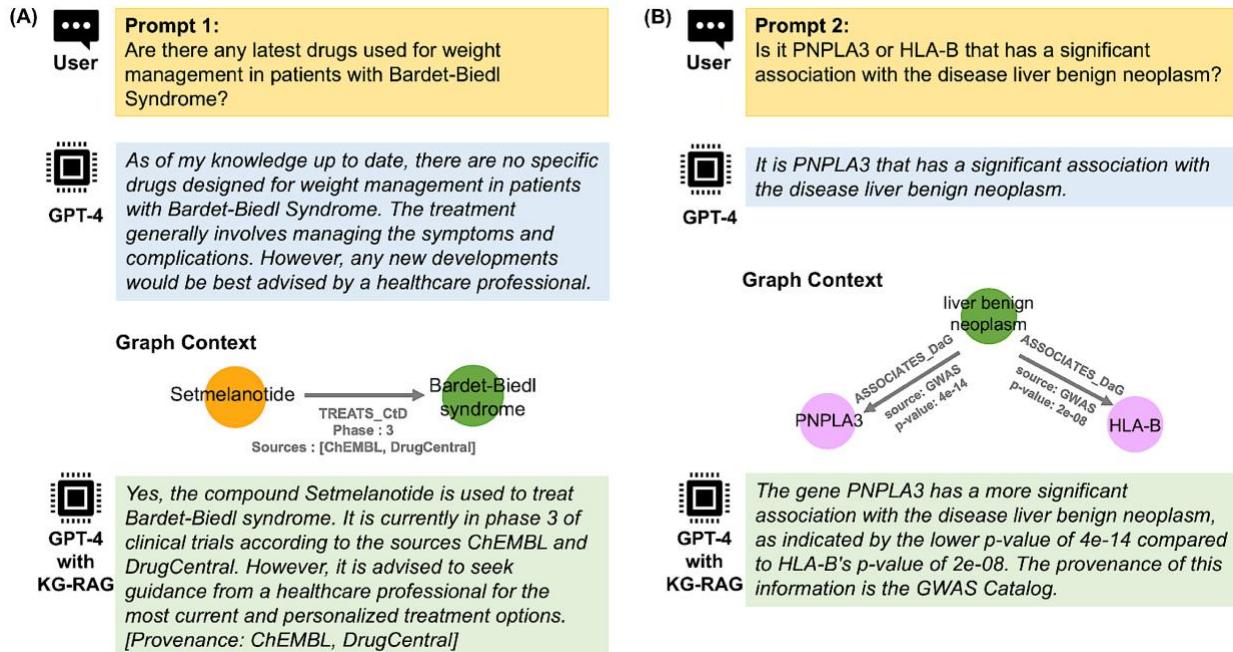
# Results

We developed KG-RAG, a framework that integrates LLMs with the SPOKE knowledge graph. This integration enables accurate biomedical context retrieval and reliable text generation in an optimized and cost-effective manner. This framework involves multiple steps, namely: i) entity recognition from user prompt ii) extraction of biomedical concepts from SPOKE iii) concept embedding iv) prompt-aware context generation v) conversion into natural language vi) prompt assembly and vii) answer generation. The performance of this approach was extensively tested using different scenarios.

## Prompting KG-RAG framework

Fig. 1 shows two biomedical prompts (Fig 1A and B yellow box) given as input to the GPT-4 model using two approaches: (i) prompt based, i.e., without KG-RAG (blue box) and (ii) with KG-RAG (green box). We observed that only KG-RAG was able to provide an accurate answer for both prompts, accompanied by supporting evidence and provenance information. (For more prompting examples refer Supplementary Table C. We have also provided these prompts in a Jupyter notebook which can be accessed at

[https://github.com/BaranziniLab/KG\\_RAG/blob/main/notebooks/kg\\_rag\\_based\\_gpt\\_prompts.ipynb](https://github.com/BaranziniLab/KG_RAG/blob/main/notebooks/kg_rag_based_gpt_prompts.ipynb)



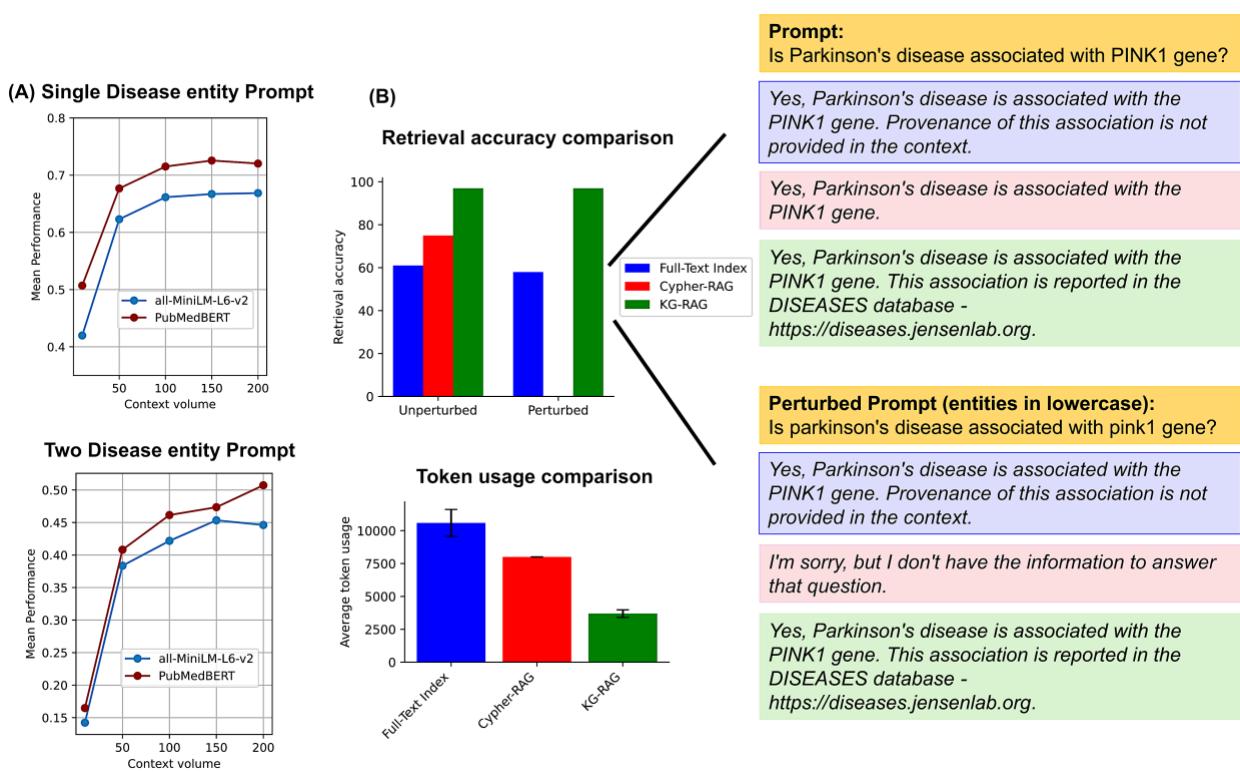
**Fig 1. Prompting examples** Example prompts (yellow boxes) and prompt based (blue boxes)/KG-RAG based (green boxes) responses using GPT-4. **(A)** shows a biomedical prompt to search the drugs used for weight management in patients with ‘Bardet-Biedl Syndrome’ and **(B)** shows another prompt to compare the statistical associations of PNPLA3 and HLA-B genes with the disease liver benign neoplasm. Both **(A)** and **(B)** show the associated ‘prompt aware graph’ context.

## Hyperparameter analysis

KG-RAG has two hyperparameters, (‘context volume’ and ‘context embedding model’), which enable it to conduct optimized context retrieval from a KG. Context volume defines the upper limit on the number of graph connections permitted to flow from the KG to the LLM (See Materials and methods, S1 Text). Context embedding model extracts graph context that shows semantic similarity to the user prompt, facilitating the refinement of extracted context to those that are contextually relevant (See Materials and methods, S1 Text). To optimize these hyperparameters, we used two context embedding models (MiniLM and PubMedBert) with increasing sizes of context volume (Fig 2A). For prompts with single disease entity, the PubMedBert based model exhibited a mean performance (Jaccard similarity) approximately 10%

higher than that of the MiniLM model across all context volume settings (mean performance of PubMedBert = 0.67, mean performance of MiniLM = 0.61). For prompts with two disease entities, PubMedBert achieved a performance that was 8.1% higher than the MiniLM across all context volume settings (mean performance of PubMedBert model = 0.4, performance of MiniLM = 0.37).

Fig 2A shows that the performance curve reaches a plateau for prompts with single disease entity and follows a similar trend for prompts with two disease entities (for both models). Based on these findings, we selected PubMedBert based model as the context embedding model and set the context volume to a value between 100-200 (For most downstream tasks, we opted for a context volume of 150, and for True/False questions, we chose a context volume of 100).



**Fig 2. Hyperparameter analysis and RAG comparison** **(A)** Hyperparameter analysis performance curves using prompts with single (top) and two (below) disease entities mentioned in it. The x-axis denotes the ‘Context volume’ (number of associations from KG) and the y-axis denotes the mean performance (Jaccard similarity) across the prompts. The red curve denotes ‘PubMedBert’ and the blue curve denotes ‘MiniLM’ transformer models. **(B)** shows the comparative analysis between KG-RAG (green color), Cypher-RAG (red color) and Full-Text Index using Apache Lucene (blue color) in terms of retrieval accuracy (top) and token usage (bottom). Insight shows an example where Cypher-RAG fails to retrieve context from the KG when the input prompt is slightly perturbed, but KG-RAG and Full-Text Index remain robust in context retrieval. However, only KG-RAG could extract provenance information linked to the assertion from the context, whereas Full-Text Index could not. It is evident that KG-RAG has significantly lesser token usage when compared to Cypher-RAG and Full-Text Index method (bottom). Error bar in the token utilization bar plot (bottom) represents standard error of the mean (sem).

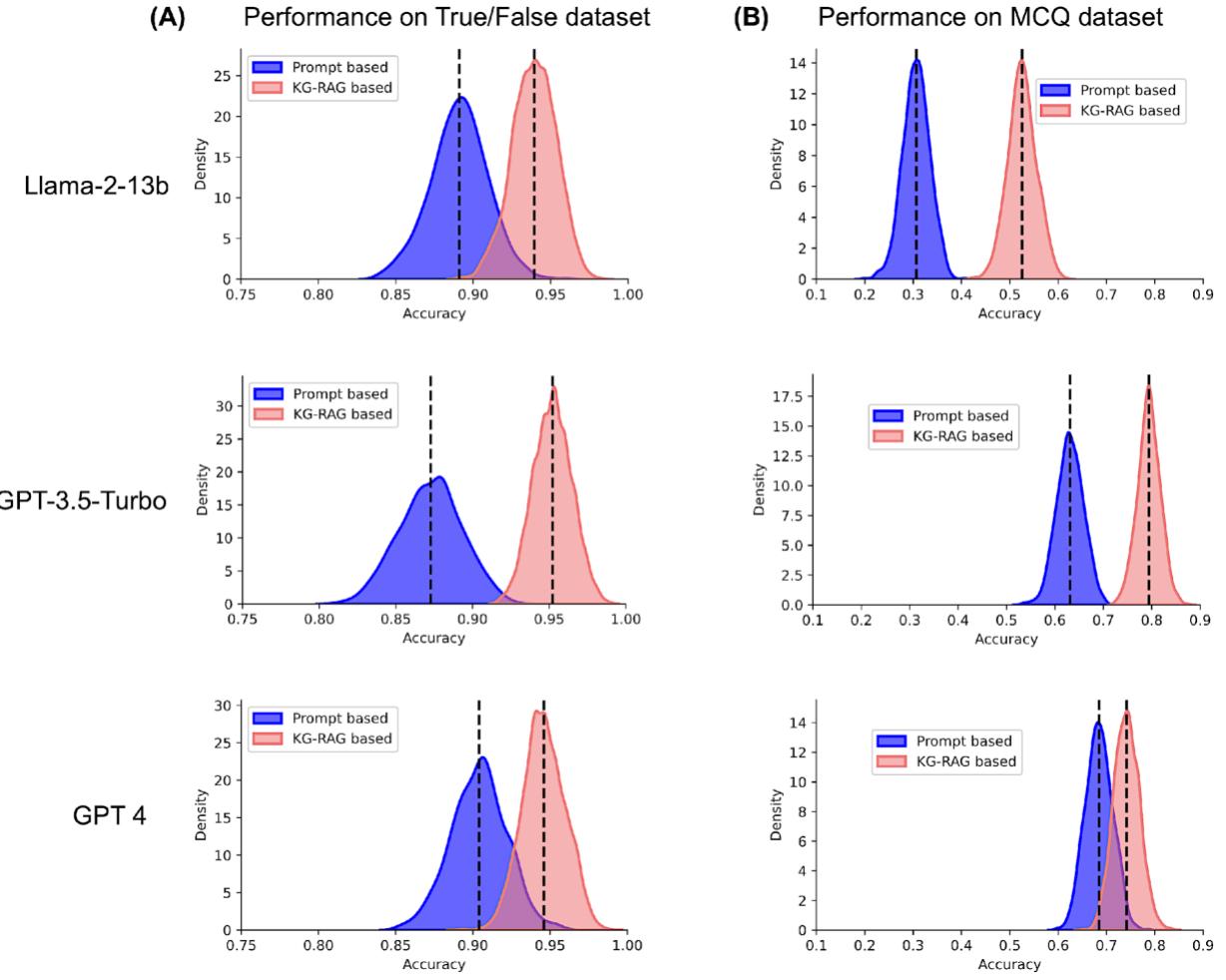
## RAG comparative analysis

Fig 2B shows the comparative analysis between the proposed KG-RAG and the other two methods, such as Cypher-RAG and Full-Text Index approach for context retrieval from a KG (See Materials and Methods). We compared these three frameworks based on their retrieval accuracy, retrieval robustness and token usage. For a test dataset with 100 biomedical questions (S1 Text), Full-Text Index, Cypher-RAG and KG-RAG showed 61%, 75% and 97% retrieval accuracy respectively (Fig 2B top). To test the robustness in context retrieval, we introduced a slight perturbation to the test dataset by converting the entity names to lowercase (Fig 2B insight). We observed a significant decrease in the retrieval accuracy of Cypher-RAG to 0% (indicating failure to retrieve any context from the graph). This mainly occurs because Cypher-RAG utilizes precise matching of the entity keywords provided in the user prompt to formulate the Cypher query for extracting graph context. Compared to Cypher-RAG, Full-Text Index and KG-RAG showed robustness against perturbation. Full-Text Index showed a slight decrease in the accuracy after query perturbation (dropped to 58% from initial 61%), but KG-RAG was able to maintain its retrieval accuracy at 97% which indicates its higher robustness against input perturbation (Fig 2B top). This is because KG-RAG employs a semantic embedding approach to extract graph context, which enhances its ability to effectively handle various representations of entities within user prompts. Next, we analyzed the total token usage of each framework for

generating the response for the same test dataset (Fig 2B bottom). We found that Full-Text Index had an average token usage of 10,590 tokens, while Cypher-RAG averaged 8,006 tokens. However, KG-RAG had an average token usage of only 3,693 tokens (Fig 2B bottom). This represents a 53.9% reduction in the token usage compared to Cypher-RAG and 65.1% reduction compared to Full-Text Index. This highlights the significant cost-effective retrieval ability of KG-RAG.

## Performance on True/False and MCQ datasets

Fig 3 shows bootstrap distributions of performance (accuracy) of the three LLMs using prompt-based and KG-RAG framework on True/False (Fig 3A) and MCQ (Fig 3B) datasets. Table 1 summarizes the performance of the three LLMs across these datasets. We observed a consistent performance enhancement for the LLM models under KG-RAG framework on both True/False and MCQ datasets (Table 1). KG-RAG significantly elevated the performance of Llama-2 by approximately 71% from its initial level ( $0.31 \pm 0.03$  to  $0.53 \pm 0.03$ ) on the more challenging MCQ dataset (Table 1). Intriguingly, we also observed a small but significant drop in the performance of GPT-4 model ( $0.74 \pm 0.03$ ) compared to GPT-3.5-Turbo model ( $0.79 \pm 0.02$ ) on MCQ dataset using KG-RAG framework (T-test, p-value < 0.0001, t-statistic = -47.7, N = 1000) but not in the prompt-based approach. We have also conducted an additional comparative analysis between Cypher-RAG and KG-RAG using the same benchmark datasets, where KG-RAG showed significantly higher performance on both datasets (S1 text, Fig S2, Table B).



**Fig 3. LLM performance on True/False and MCQ datasets** Performance (Accuracy) distributions of LLMs on (A) True/False and (B) MCQ datasets. Blue distribution denotes the performance using prompt-based approach and red distribution denotes the performance using KG-RAG based approach. Black vertical dashed line indicates the mean value of the distribution. The higher the value, the better the performance.

**Table 1. LLM performance (Accuracy: mean  $\pm$  std) on True/False and MCQ dataset**

Model	True/False dataset		MCQ dataset	
	Prompt-	KG-RAG	Prompt-	KG-RAG
	based	based	based	based
Llama-2-13b	0.89±0.02	0.94±0.01	0.31±0.03	0.53±0.03
GPT-3.5-Turbo	0.87±0.02	0.95±0.01	0.63±0.03	0.79±0.02
GPT-4	0.9±0.02	0.95±0.01	0.68±0.03	0.74±0.03

## Discussion

In this work, we introduce a simple but highly effective framework that combines a biomedical knowledge graph with LLM chat models in a token optimized fashion. This integration resulted in a domain-specific generative system whose responses were firmly grounded in well-established biomedical knowledge. We compared the proposed framework with other approaches that utilize Cypher query and Full-Text Indexing and showed that KG-RAG was more robust to prompt perturbation and more efficient in token utilization. In addition, KG-RAG consistently demonstrated superior performance compared to the prompt-based baseline LLM model on all human-curated benchmark datasets. We hypothesize that this performance improvement arises from the fusion of the explicit knowledge from the KG and the implicit knowledge from the LLM. This shows the value of providing domain-specific ground truth at a fine-grained resolution as context at the prompt level.

A heterogeneous knowledge graph with diverse concepts (the biomedical concepts in this case) interconnected at a massive scale has the potential to generate new knowledge as an “emergent property” (Morris et al. 2023; Baranzini et al. 2022). In fact, as LLMs scale up in various dimensions like model parameters, training data, and training compute, they have been thought to exhibit reasoning or “emerging capabilities” (Wei, Tay, et al. 2022) although this observation could also be explained by “in-context learning” or other aspects of the examples (Min et al. 2022; Brown et al. 2020; Lu et al. 2023). In any case, KG-RAG capitalized this capability and generated biomedical text with rich annotations such as provenance and statistical evidence (if available) thereby resulting in more reliable and knowledge-grounded responses. Additionally, the optimized and fine-grained context retrieval capability of KG-RAG ensured a budget friendly RAG system to apply on proprietary LLMs. This way, KG-RAG democratizes SPOKE’s vast

biomedical knowledge by enabling researchers, clinicians, and other professionals to leverage its comprehensive information through natural language interactions. This approach facilitates access to complex biomedical data without requiring specialized graph query language skills. Previous studies have utilized KG in conjunction with LLM for knowledge intensive tasks such as question-answering (Yasunaga et al. 2021), multi-hop relational reasoning (Feng et al. 2020), commonsense reasoning (Lin et al. 2019; Lv et al. 2019) and model pre-training (Yasunaga et al. 2022; Moiseev et al. 2022). Furthermore, enhancing prompts by incorporating structured knowledge has been described and studied (Lewis et al. 2020; Xiang Chen Zhejiang University, China et al., n.d.; Pan et al. 2023). Naturally, these approaches have bolstered the positive reinforcement between KG and LLM. Nevertheless, it's worth noting that these approaches are often task-specific and, in some cases, the knowledge infusion could grow exponentially with the inclusion of higher-order relations (Bauer, Wang, and Bansal 2018; Lin et al. 2019). Such approaches could compromise the limited token space of the LLM. Alternative methods employed knowledge infusion through the direct use of query languages like SPARQL (Brate et al. 2022). However, this could render the system constraint to the schema of the underlying KG, potentially affecting the flexibility and adaptability of prompts. Moreover, as the KG expands and its schema grows, it could potentially occupy a significant portion of the LLM input token space. This explains why we noticed a greater token usage with the Cypher-RAG method (average usage of 8,006 tokens), as it incorporates the entire graph schema into the input prompt for converting natural language into structured Cypher queries. In contrast, KG-RAG requires minimal graph schema, thus eliminating the need to include it in the prompt and resulting in substantial token savings, with a reduction of over 50% in token utilization compared to Cypher-RAG. This finding suggests that Cypher-RAG, when dealing with a graph as large as SPOKE

(which contains over 40 million nodes), requires LLMs that enable a larger context window. This limitation was also observed with traditional information retrieval frameworks such as full-text indexing using Apache Lucene. In contrast, KG-RAG is capable of managing this with LLMs that require a relatively smaller window size.

To conduct robust benchmarking, we curated datasets that underwent review by domain experts. Given the swift progress in LLM research, we believe that such rigorously vetted datasets could serve as valuable resources not only for evaluating KG-RAG but also for assessing other ongoing LLM endeavors in biomedicine. In our benchmarking analysis, we found an enhancement in LLM performance as a function of the model size in terms of the number of parameters.

Intriguingly, with the KG-RAG framework the performance of GPT-4 on the MCQ dataset, despite its model size, dropped significantly compared to that of the GPT-3.5-Turbo on the MCQ dataset. In fact, the performance of GPT-3.5-Turbo under KG-RAG framework was on par with that of the GPT-4 model on True/False datasets. These results suggest that at present, GPT-3.5 may be a better context listener than GPT-4. In fact, a recent study compared the March 2023 version of GPT-4 with the June 2023 version, shedding light on the drift in the LLM performance over time (Chen, Zaharia, and Zou 2023). The study revealed that, as time progressed, GPT-4 exhibited a reduced tendency to adhere to user instructions (Chen, Zaharia, and Zou 2023). In contrast, there was no consistent alteration observed in the instruction-following behavior of GPT-3.5 over time (Chen, Zaharia, and Zou 2023). Studies have also shown that GPT-4's larger model size and more diverse training data enable it to excel in a multitude of complex reasoning tasks (Baktash and Dawodi 2023; OpenAI et al. 2023). GPT-3.5-Turbo has shown to excel in few-shot learning by context adherence (Brown et al. 2020). We believe that the context adherence nature of GPT-3.5, in contrast to the general application of

GPT-4, might make it more suitable for frameworks like KG-RAG. Therefore, these factors could have contributed to GPT-3.5's superior performance over GPT-4 in the KG-RAG framework.

When the proprietary GPT models were compared to the open-source Llama-2-13b model, they showed a narrow margin in performance on the biomedical True/False dataset. However, on the more challenging MCQ dataset, Llama-2 initially demonstrated lower performance compared to GPT models. Interestingly, the KG-RAG framework provided a substantial performance boost to Llama-2, improving its performance by ~71% from the baseline. Despite this boost that narrowed the performance gap, the performance of Llama-2 remained lower than that of the GPT models. This suggests that the KG-RAG framework has the potential to capitalize the intrinsic context comprehension capabilities of open-source pretrained models like Llama-2, making them more competitive with proprietary models like GPT. The findings underscore the importance of context enrichment techniques for improving the performance of language models on complex tasks in specialized domains.

While the proposed framework has successfully addressed numerous challenges, we recognize there are opportunities for improvement. Currently, this approach is limited to handling biomedical questions centered around diseases, as our focus has been on embedding disease concepts from the SPOKE KG for recognizing disease entities in the prompt. However, we have implemented a proof of concept that extends KG-RAG to non-disease-centric questions by embedding more than 87,000 nodes from SPOKE, including genes, proteins, enzymes, symptoms, compounds, reactions, anatomical structures, and side effects (S1 Text). Future work may expand this scope by including all biomedical concepts (nodes) in SPOKE and other KG. Since SPOKE contains more than 40 million biomedical nodes, this expansion will enable the

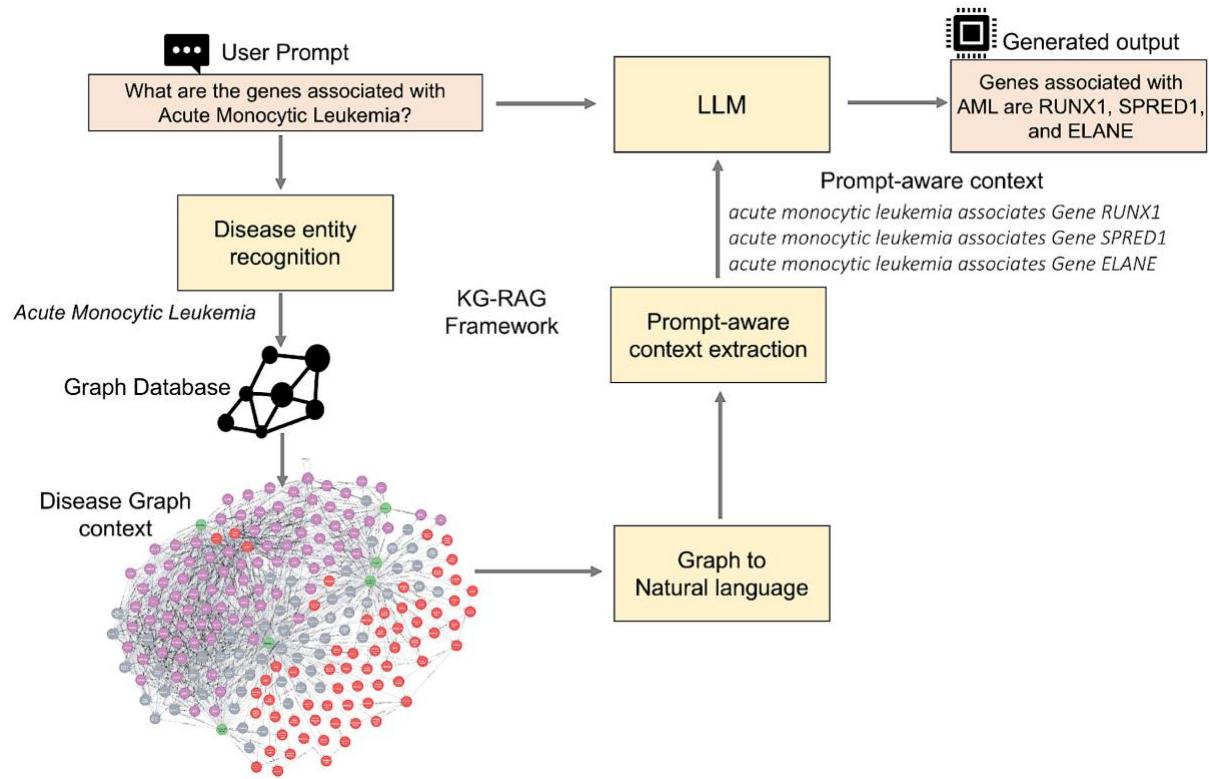
KG-RAG framework to address a broader range of biomedical questions and thereby enhance its versatility. Currently, we have implemented the KG-RAG framework exclusively on the SPOKE biomedical knowledge graph, which is maintained as a Neo4j property graph database. While we utilize embeddings to enhance node and context retrieval, all operations are performed within this Neo4j graph structure. As future work, we plan to extend KG-RAG to other biomedical KGs and domains, demonstrating its versatility and broader applicability. Finally, the quality of the retrieved context relies on the information stored in the underlying graph. In our case, SPOKE utilizes meticulously curated knowledge bases to construct its nodes and edges; however, we do not assert that it is entirely error-free or ready for clinical use. Thus, while SPOKE’s reliability has been demonstrated through its successful application in various biomedical contexts (S1 Text) (Soman, Nelson, Cerono, Goldman, et al. 2023; Nelson, Bove, et al. 2021; Tang et al. 2024; Daniel Scott Himmelstein et al. 2017; Daniel S. Himmelstein and Baranzini 2015; Nelson, Acuna, et al. 2021; Nelson, Butte, and Baranzini 2019; Baranzini et al. 2022; Morris et al. 2023; Soman, Nelson, Cerono, and Baranzini 2023), it is important to note that this work primarily focused on the development of a framework, rather than conducting a rigorous and formal evaluation of the KG itself.

In summary, the KG-RAG framework retrieves semantically meaningful context from a knowledge graph using minimal tokens, then combines this explicit knowledge with the parameterized implicit knowledge of an LLM. This knowledge integration results in the generation of domain-specific, reliable and up-to-date meaningful biomedical responses with rich annotations.

# Materials and Methods

## Knowledge Graph based Retrieval Augmented Generation (KG-RAG) Framework

The schema of the proposed KG-RAG framework is shown in Fig 4. The following sections explain each component of this framework.



**Fig 4. Schema for the Knowledge Graph based Retrieval-Augmented Generation (KG-RAG) Framework.**  
The direction of the arrows indicates the flow of the pipeline in this framework

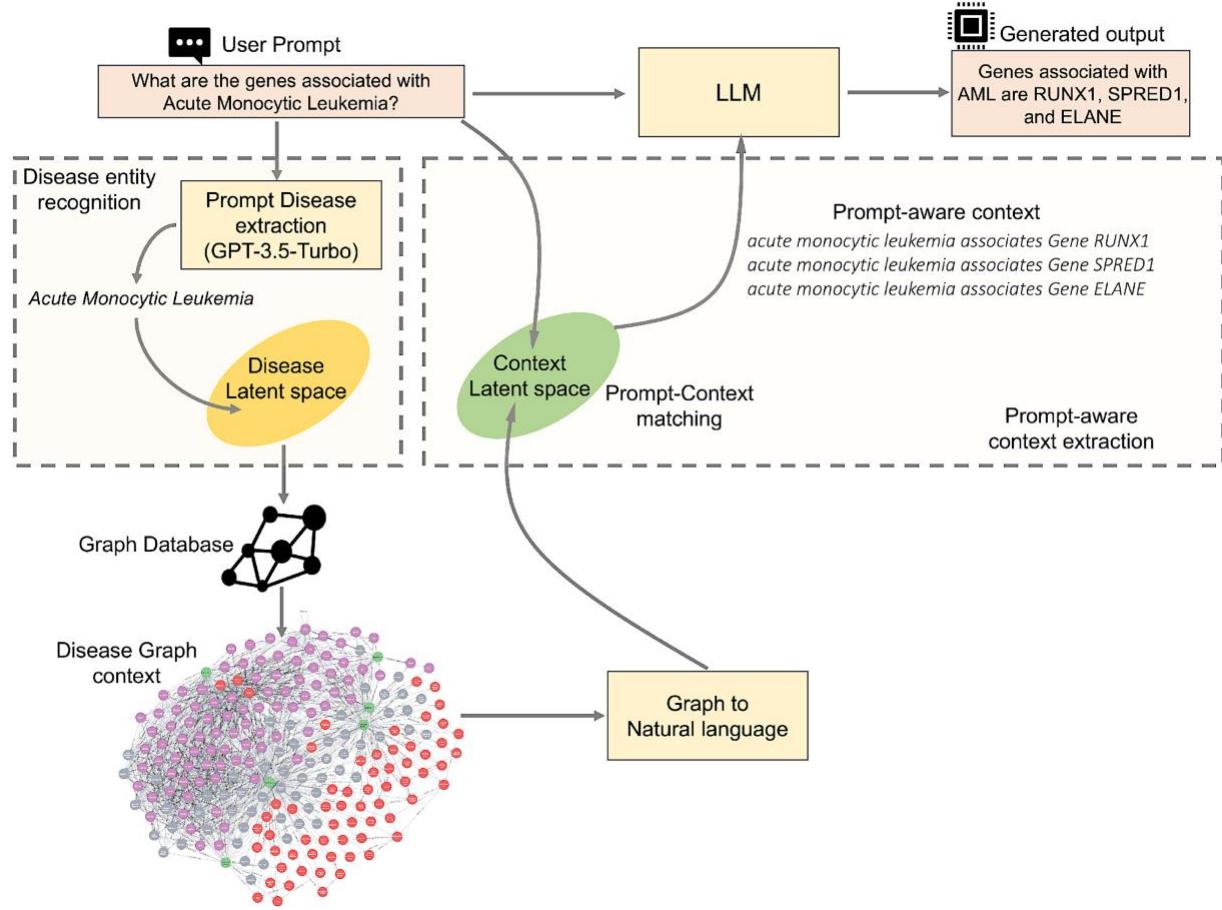
### Disease entity recognition

This is the first step in KG-RAG. The objective of this step is to extract the disease concept (an entity) from the input text prompt and then find the corresponding matching disease node in the KG (a concept in SPOKE graph). This was implemented as a two-step process: i) entity

extraction from prompt and ii) entity matching to SPOKE. Entity extraction identifies and extracts disease entities mentioned in the input text prompt, otherwise called as ‘Prompt Disease extraction’ (Fig 5). To achieve this, zero-shot prompting (Kojima et al. 2022) was used on GPT-3.5-Turbo model (Version: 0613) (Fig 5). Specifically, a system prompt was designed to extract disease entities from the input text and return them in JSON format (S1 Text). We compared the GPT-based entity extraction method with more traditional approaches that use models specifically trained for this task. However, we chose the zero-shot GPT option due to its superior performance in terms of precision and recall (Supplementary Fig S1, Supplementary Table A) and its flexibility in handling various entity types (S1 Text).

Next, entity matching was used to obtain the concept name of the disease as it is represented within the KG. For this, the embeddings for all disease concepts (i.e., nodes) in SPOKE were precomputed using the ‘all-MiniLM-L6-v2’ sentence transformer model (i.e. Disease Latent space in Fig 5) (Reimers and Gurevych 2019). This procedure translates names of the disease concepts into a 384-dimensional dense vector space, making it suitable for semantic search. We chose ‘MiniLM’ for two main reasons: firstly, when combined with entity extraction, it successfully retrieved the disease nodes from the graph with an accuracy of 99.7% (S1 Text). Second, it produced lightweight embeddings (384 dimensions) compared to other sentence transformers like the PubmedBERT model (Yu Gu Microsoft Research, Redmond, WA et al. 2021) (768 dimensions), making it more memory efficient. Next, these newly created disease concept embeddings were stored in the ‘Chroma’ vector database (Dhungana 2023). Disease concepts with the highest vector similarity to the extracted entity are selected for subsequent context retrieval (Fig 5). If the zero-shot approach fails to identify a disease entity in the prompt,

five disease concepts from the vector database with the most significant semantic similarity to the entire input text prompt are selected instead.



**Fig 5. Detailed schema of KG-RAG.** Dashed boxes show the details of ‘Disease entity recognition’ and ‘Prompt-aware context extraction’ from the Knowledge Graph

## Disease context retrieval from SPOKE

The SPOKE KG connects millions of biomedical concepts through semantically meaningful relationships (Morris et al. 2023). The KG consists of 42 million nodes of 28 different types and 160 million edges of 91 types, implemented as a property graph and is assembled by downloading and integrating information from 41 different biomedical databases (Morris et al. 2023). Notably, the vast majority of SPOKE is composed of curated information determined by

systematic experimental measurements, not text mining from the literature. In this study, SPOKE was used as the source of biomedical context for the diseases mentioned in the input prompt.

The process of converting the graph data to natural language involves the following steps:

(a) Context Extraction: We utilize SPOKE's REST-API service, specifically the '/api/v1/neighborhood/' endpoint, to fetch neighbors associated with a disease node (S1 Text). To ensure high-quality context, we apply filters such as restricting treatment associations to those with clinical phase  $\geq 3$ , using only SwissProt-curated protein nodes, and excluding text-mining-based gene-disease associations.

(b) Predicate to Natural Language Transformation: SPOKE uses a specific schema for predicates: `upperCase(predicateName) <upperCase(firstLetter(subjectType))`, `lowerCase(firstLetter(predicateName))`, `upperCase(firstLetter(objectType))`. For example, 'ASSOCIATES\_DaG' is a predicate that connects Disease nodes with Gene nodes.

The context triples (Subject, Predicate, Object) associated with a disease node from SPOKE KG (Morris et al. 2023) follow a specific schema for its predicates (S1 Text):

```
upperCase (predicateName) <upperCase (firstLetter (subjectType)) ,  
lowerCase (firstLetter (predicateName)) ,  
upperCase (firstLetter (objectType)) . For example, 'ASSOCIATES_DaG' is a  
predicate that connects Disease nodes with Gene nodes with the predicate name ASSOCIATES.
```

This schema allowed for the direct conversion of the extracted triples into English language using the following rule (S1 Text):

$$(S, P, O) \rightarrow \text{Subject lowerCase(predicateName) Object}$$

For example:

(Disease hypertension, ASSOCIATES\_DaG, Gene VHL)  $\rightarrow$  `Disease hypertension associates Gene VHL`

This makes it compatible for inputting into the LLM (Fig 4) (S1 Text).

(c) Provenance and Evidence Incorporation: In addition to extracting the connectivity between the disease and its neighbors, we also extracted the provenance information associated with those edges which is given as the edge attribute. Additionally, we've implemented an option ('-e' flag in our KG-RAG script) to include supporting evidence like p-values or z-scores in the output (S1 Text).

## Context Pruning

Next, the extracted disease context was pruned by selecting the most semantically pertinent context that could be used to answer the given prompt. First, the input prompt and all the extracted contextual associations were embedded to the same vector space (Context Latent space in Fig 5) using a sentence transformer model (model selection was done using hyperparameter tuning). Next, for context selection, prompt-context cosine similarity should satisfy two conditions: (i) greater than 75<sup>th</sup> percentile of the similarity distribution encompassing all the context related to the chosen disease node and (ii) having a minimum similarity value of 0.5. This makes the retrieved context more fine-grained and contextually relevant (i.e. ‘prompt-aware context’).

## Large Language Model (LLM)

The input prompt, when combined with the prompt-aware context, resulted in an enriched prompt that was used as input to the LLM for text generation. For that purpose, three pre-trained

chat models were used: Llama-2-13b (Touvron et al. 2023), GPT-3.5-Turbo (Version: 0613) and GPT-4 (Brown et al. 2020). A Llama model with 13 billion parameters and with a token size of 4,096 was downloaded and deployed in the Amazon Elastic Compute Cloud (EC2) GPU P3 instance. GPT models were accessed using the OpenAI API. Since GPT models featured a higher parameter count in comparison to Llama, this gave us the opportunity to compare the performance of KG-RAG as a function of the size of the LLM in terms of its parameter count. In this study, the ‘temperature’ parameter (Brown et al. 2020), governing the level of randomness in the LLM output, was set to 0 for all LLMs.

## **Hyperparameter analysis and validation**

The performance of KG-RAG was evaluated across two sets of hyperparameters such as ‘Context volume’ and ‘Context embedding model’. Context volume defines the upper limit on the number of graph connections permitted to flow from the KG to the LLM. This hyperparameter introduced a balance between context enhancement and input token space utilization of the LLM (S1 Text). Next hyperparameter called ‘Context embedding model’ determined which model exhibited greater proficiency in retrieving the accurate biomedical context from the KG to respond to the input prompt. Since ‘MiniLM’ (Reimers and Gurevych 2019) was used in the disease entity recognition stage, we considered that as a candidate for ‘Context embedding model’. Acknowledging that biomedical contexts often utilize vocabulary that could differ from general domain scenarios, we next considered ‘PubMedBert’ (Yu Gu Microsoft Research, Redmond, WA et al. 2021; Deka, Jurek-Loughrey, and Deepak 2022) as another candidate for this hyperparameter since it was pre-trained on biomedical text. Additionally, two sets of validation data (total 165 questions) were created using prompts

mentioning a single disease (75 questions), while the other set involved prompts mentioning two diseases (90 questions) (S1 Text). The second set of ‘two disease prompts’ were created to see if KG-RAG had the ability to retrieve contexts related to multiple diseases. These prompts were executed using the GPT-4 model in the KG-RAG framework, utilizing specific system prompts to return the results in JSON format (S1 Text). Jaccard similarity was computed by parsing these JSON responses and comparing them with the ground truth. Through these analyses, an empirical selection of hyperparameters for the downstream tasks was made.

## Test dataset

Three types of test datasets were used to quantitatively analyze the performance of the proposed framework (Supplementary Table D): (i) True/False dataset; (ii) Multiple Choice Question (MCQ) dataset; and (iii) RAG comparison dataset. Datasets i and ii were consolidated from external knowledge bases and were further thoroughly reviewed by domain experts to remove any false positives.

A True/False dataset was created from three external data sources, such as DisGeNET (Piñero et al. 2016) MONDO (Vasilevsky et al. 2022) and SemMedDB (Kilicoglu et al. 2012). DisGeNET consolidates data about genes and genetic variants linked to human diseases from curated repositories, the GWAS catalog, animal models, and the scientific literature (Piñero et al. 2016) (S1 Text). MONDO provides information about the ontological classification of Disease entities in the Open Biomedical Ontologies (OBO) format (Vasilevsky et al. 2022) (S1 Text). SemMedDB contains semantic predication extracted from PubMed citations (Kilicoglu et al. 2012) and we used this resource to formulate True/False questions about drugs and diseases (S1 Text). MCQ, comprising five choices with a single correct answer for each question, were

created using data from the Monarch Initiative (Mungall et al. 2017) and ROBOKOP (Reasoning Over Biomedical Objects linked in Knowledge-Oriented Pathways) (Bizon et al. 2019) (S1 Text). To assess the graph context retrieval capabilities of various RAG frameworks, we extracted Disease-Gene associations from the SPOKE graph and designed questions based on these associations. These questions were then used on KG-RAG, Cypher-RAG and Full-Text Indexing frameworks to compare how well they retrieve the associated context from SPOKE graph.

Thus, 311 True/False, 306 MCQ and 100 RAG comparison biomedical question datasets were created for a systematic quantitative analysis of the proposed framework. To assess the performance of LLMs on True/False and MCQ datasets, 150 questions were randomly sampled with replacement 1000 times (using bootstrapping). The accuracy metric was then calculated for each sampling iteration, resulting in a performance distribution.

## Cypher-RAG

Cypher-RAG is a technique utilized for retrieving context associated with a node in a Neo4j graph database (Bratanic 2023). This context can then be leveraged to generate information about the node in natural language using a LLM. The method involves explicitly embedding the schema of the graph into the input prompt, directing the LLM to generate a structured Cypher query based on this schema. The resulting Cypher query is used to make a call to the Neo4j database, and the returned information is utilized as context to respond to the user's prompt. This methodology is integrated into the LangChain python library as *GraphCypherQAChain* class (Bratanic 2023). An advantage of this approach is that it allows for the creation of Cypher queries directly from natural language, eliminating the need for users to have the knowledge of

Cypher query syntax. However, our analysis revealed certain limitations of this approach. We found that the explicit embedding of the graph schema restricts the input token space and increases token usage for this method. As the complexity of the graph schema increases, users may need to utilize LLMs with longer context window sizes for optimal performance. Additionally, we demonstrated that this method can be sensitive to how the prompt is formulated. Even slight perturbations to the prompt can lead to incorrect Cypher queries and subsequently impact downstream generative processes.

## Full-Text Index

Neo4j offers Full-text indexing that is powered by the Apache Lucene indexing and search library. In the context of the SPOKE graph, all nodes were full-text indexed on their ‘name’ and ‘identifier’ properties. This indexing method stores individual words within these string properties and allows semantic interpretation of string data beyond simple exact or substring matching. Hence, this enables content-based matching. When processing user queries, the full-text index procedure in Neo4j was employed to compare the query against the indexed disease names. This comparison yields a proximity score, indicating the semantic closeness between the query and stored values. The disease node with the highest score was selected as the mapped node for subsequent context extraction. Compared to traditional exact or pattern-based matching, this method provides a more nuanced and flexible approach to node matching, potentially improving the information retrieval process.

## Acknowledgements

SEB holds the Heidrich Family and Friends Endowed Chair of Neurology at UCSF. SEB holds the Distinguished Professorship in Neurology I at UCSF. We also acknowledge the Versa team at UCSF for providing the infrastructure to access OpenAI API. The development of SPOKE and its applications are being funded by grants from the National Science Foundation [NSF\_2033569], NIH/NCATS [NIH\_NOA\_1OT2TR003450].

## Data availability

SPOKE KG can be accessed at <https://spoke.rbvi.ucsf.edu/neighborhood.html>. It can also be accessed using REST-API (<https://spoke.rbvi.ucsf.edu/swagger/>). KG-RAG code is made available at [https://github.com/BaranziniLab/KG\\_RAG](https://github.com/BaranziniLab/KG_RAG). Biomedical benchmark datasets used in this study are made available to the research community in the same GitHub repository.

## Conflict of interest:

SEB is a co-founder of Mate Bioservices. CAN is CEO of Mate Bioservices.

## References

Baktash, Jawid Ahmad, and Mursal Dawodi. 2023. “Gpt-4: A Review on Advancements and Opportunities in Natural Language Processing.” <http://arxiv.org/abs/2305.03195>.

Baranzini, Sergio E., Katy Börner, John Morris, Charlotte A. Nelson, Karthik Soman, Erica Schleimer, Michael Keiser, et al. 2022. “A Biomedical Open Knowledge Network Harnesses the Power of AI to Understand Deep Human Biology.” *AI Magazine* 43 (1): 46–58.

Bauer, Lisa, Yicheng Wang, and Mohit Bansal. 2018. “Commonsense for Generative Multi-Hop Question Answering Tasks.” In *Proceedings of the 2018 Conference on Empirical Methods in Natural Language Processing*. Stroudsburg, PA, USA: Association for Computational Linguistics. <https://doi.org/10.18653/v1/d18-1454>.

Beltagy, Iz, Kyle Lo, and Arman Cohan. 2019. “SciBERT: A Pretrained Language Model for Scientific Text.” In *Proceedings of the 2019 Conference on Empirical Methods in Natural Language Processing and the 9th International Joint Conference on Natural Language Processing (EMNLP-IJCNLP)*, 3615–20.

Bizon, Chris, Steven Cox, James Balhoff, Yaphet Kebede, Patrick Wang, Kenneth Morton, Karamarie Fecho, and Alexander Tropsha. 2019. “ROBOKOP KG and KGB: Integrated Knowledge Graphs from Federated Sources.” *Journal of Chemical Information and Modeling* 59 (12): 4968–73.

Bratanic, Tomaz. 2023. “Using a Knowledge Graph to Implement a DevOps RAG Application.” Neo4j Developer Blog. October 18, 2023. <https://medium.com/neo4j/using-a-knowledge-graph-to-implement-a-devops-rag-application-b6ba24831b16>.

Brate, Ryan, Minh-Hoang Dang, Fabian Hoppe, Yuan He, Albert Meroño-Peñuela, and Vijay Sadashivaiah. 2022. “Improving Language Model Predictions via Prompts Enriched with Knowledge Graphs.” <https://doi.org/10.5445/IR/1000151291>.

Brown, Tom B., Benjamin Mann, Nick Ryder, Melanie Subbiah, Jared Kaplan, Prafulla Dhariwal, Arvind Neelakantan, et al. 2020. “Language Models Are Few-Shot Learners.” <http://arxiv.org/abs/2005.14165>.

Chen, Lingjiao, Matei Zaharia, and James Zou. 2023. “How Is ChatGPT’s Behavior Changing over Time?” <http://arxiv.org/abs/2307.09009>.

Deka, Pritam, Anna Jurek-Loughrey, and Deepak. 2022. “Improved Methods to Aid Unsupervised Evidence-Based Fact Checking for Online Heath News.” *Journal of Data Intelligence* 3 (4): 474–504.

Devlin, Jacob, Ming-Wei Chang, Kenton Lee, and Kristina Toutanova. 2018. “BERT: Pre-Training of Deep Bidirectional Transformers for Language Understanding.” <http://arxiv.org/abs/1810.04805>.

Dhungana, Kamal. 2023. “An Overview of ChromaDB: The Vector Database.” Medium. October 2, 2023. <https://medium.com/@kbdhunga/an-overview-of-chromadb-the-vector-database-206437541bdd>.

Feng, Yanlin, Xinyue Chen, Bill Yuchen Lin, Peifeng Wang, Jun Yan, and Xiang Ren. 2020. “Scalable Multi-Hop Relational Reasoning for Knowledge-Aware Question Answering.” In *Proceedings of the 2020 Conference on Empirical Methods in Natural Language Processing (EMNLP)*. Stroudsburg, PA, USA: Association for Computational Linguistics. <https://doi.org/10.18653/v1/2020.emnlp-main.99>.

Himmelstein, Daniel S., and Sergio E. Baranzini. 2015. “Heterogeneous Network Edge Prediction: A Data Integration Approach to Prioritize Disease-Associated Genes.” *PLoS Computational Biology* 11 (7): e1004259.

Himmelstein, Daniel Scott, Antoine Lizée, Christine Hessler, Leo Brueggeman, Sabrina L. Chen, Dexter Hadley, Ari Green, Pouya Khankhanian, and Sergio E. Baranzini. 2017. “Systematic Integration of Biomedical Knowledge Prioritizes Drugs for Repurposing,” September. <https://doi.org/10.7554/eLife.26726>.

Huang, Kexin, Jaan Altosaar, and Rajesh Ranganath. 2019. “ClinicalBERT: Modeling Clinical Notes and Predicting Hospital Readmission.” <http://arxiv.org/abs/1904.05342>.

Ji, Ziwei, Nayeon Lee, Rita Frieske, Tiezheng Yu, Dan Su, Yan Xu, Etsuko Ishii, et al. 2022. “Survey of Hallucination in Natural Language Generation,” February. <https://doi.org/10.1145/3571730>.

Kilicoglu, Halil, Dongwook Shin, Marcelo Fiszman, Graciela Rosemblat, and Thomas C. Rindflesch. 2012. “SemMedDB: A PubMed-Scale Repository of Biomedical Semantic Predications.” *Bioinformatics* 28 (23): 3158–60.

Kojima, Takeshi, Shixiang Shane Gu, Machel Reid, Yutaka Matsuo, and Yusuke Iwasawa. 2022. “Large Language Models Are Zero-Shot Reasoners.” <http://arxiv.org/abs/2205.11916>.

Lee, Jinhyuk, Wonjin Yoon, Sungdong Kim, Donghyeon Kim, Sunkyu Kim, Chan Ho So, and Jaewoo Kang. 2019. “BioBERT: A Pre-Trained Biomedical Language Representation Model for Biomedical Text Mining.” *Bioinformatics* 36 (4): 1234–40.

Lewis, Patrick, Ethan Perez, Aleksandra Piktus, Fabio Petroni, Vladimir Karpukhin, Naman Goyal, Heinrich Küttler, et al. 2020. “Retrieval-Augmented Generation for Knowledge-Intensive NLP Tasks.” *Advances in Neural Information Processing Systems* 33: 9459–74.

Lin, Bill Yuchen, Xinyue Chen, Jamin Chen, and Xiang Ren. 2019. “KagNet: Knowledge-Aware Graph Networks for Commonsense Reasoning.” In *Proceedings of the 2019 Conference on Empirical Methods in Natural Language Processing and the 9th International Joint Conference on Natural Language Processing (EMNLP-IJCNLP)*. Stroudsburg, PA, USA: Association for Computational Linguistics. <https://doi.org/10.18653/v1/d19-1282>.

Liu, Yinhan, Myle Ott, Naman Goyal, Jingfei Du, Mandar Joshi, Danqi Chen, Omer Levy, Mike Lewis, Luke Zettlemoyer, and Veselin Stoyanov. 2019. “RoBERTa: A Robustly Optimized BERT Pretraining Approach.” <http://arxiv.org/abs/1907.11692>.

Luo, Renqian, Lai Sun, Yingce Xia, Tao Qin, Sheng Zhang, Hoifung Poon, and Tie-Yan Liu. 2022. “BioGPT: Generative Pre-Trained Transformer for Biomedical Text Generation and Mining.” *Briefings in Bioinformatics* 23 (6): bbac409.

Luo, Yizhen, Jiahuan Zhang, Siqi Fan, Kai Yang, Yushuai Wu, Mu Qiao, and Zaiqing Nie. 2023. “BioMedGPT: Open Multimodal Generative Pre-Trained Transformer for BioMedicine.” <http://arxiv.org/abs/2308.09442>.

Lu, Sheng, Irina Bigoulaeva, Rachneet Sachdeva, Harish Tayyar Madabushi, and Iryna Gurevych. 2023. “Are Emergent Abilities in Large Language Models Just In-Context Learning?” <http://arxiv.org/abs/2309.01809>.

Lv, Shangwen, Daya Guo, Jingjing Xu, Duyu Tang, Nan Duan, Ming Gong, Linjun Shou, Dixin Jiang, Guihong Cao, and Songlin Hu. 2019. “Graph-Based Reasoning over Heterogeneous External Knowledge for Commonsense Question Answering.” <http://arxiv.org/abs/1909.05311>.

Maynez, Joshua, Shashi Narayan, Bernd Bohnet, and Ryan McDonald. 2020. “On Faithfulness and Factuality in Abstractive Summarization.” <http://arxiv.org/abs/2005.00661>.

Min, Sewon, Xinxi Lyu, Ari Holtzman, Mikel Artetxe, Mike Lewis, Hannaneh Hajishirzi, and Luke Zettlemoyer. 2022. “Rethinking the Role of Demonstrations: What Makes In-Context Learning Work?” <http://arxiv.org/abs/2202.12837>.

Moiseev, Fedor, Zhe Dong, Enrique Alfonseca, and Martin Jaggi. 2022. “SKILL: Structured Knowledge Infusion for Large Language Models.” <http://arxiv.org/abs/2205.08184>.

Morris, John H., Karthik Soman, Rabia E. Akbas, Xiaoyuan Zhou, Brett Smith, Elaine C. Meng, Conrad C. Huang, et al. 2023. “The Scalable Precision Medicine Open Knowledge Engine (SPOKE): A Massive Knowledge Graph of Biomedical Information.” *Bioinformatics* 39 (2): btad080.

Mungall, Christopher J., Julie A. McMurry, Sebastian Köhler, James P. Balhoff, Charles Borromeo, Matthew Brush, Seth Carbon, et al. 2017. “The Monarch Initiative: An Integrative Data and Analytic Platform Connecting Phenotypes to Genotypes across Species.” *Nucleic Acids Research* 45 (D1): D712–22.

Nelson, Charlotte A., Ana Uriarte Acuna, Amber M. Paul, Ryan T. Scott, Atul J. Butte, Egle Cekanaviciute, Sergio E. Baranzini, and Sylvain V. Costes. 2021. “Knowledge Network Embedding of Transcriptomic Data from Spaceflown Mice Uncovers Signs and Symptoms Associated with Terrestrial Diseases.” *Life* 11 (1): 42.

Nelson, Charlotte A., Riley Bove, Atul J. Butte, and Sergio E. Baranzini. 2021. “Embedding Electronic Health Records onto a Knowledge Network Recognizes Prodromal Features of Multiple Sclerosis and Predicts Diagnosis.” *Journal of the American Medical Informatics Association: JAMIA* 29 (3): 424–34.

Nelson, Charlotte A., Atul J. Butte, and Sergio E. Baranzini. 2019. “Integrating Biomedical Research and Electronic Health Records to Create Knowledge-Based Biologically Meaningful Machine-Readable Embeddings.” *Nature Communications* 10 (1): 1–10.

OpenAI, Josh Achiam, Steven Adler, Sandhini Agarwal, Lama Ahmad, Ilge Akkaya, Florencia Leoni Aleman, et al. 2023. “GPT-4 Technical Report.” <http://arxiv.org/abs/2303.08774>.

Pan, Jeff Z., Simon Razniewski, Jan-Christoph Kalo, Sneha Singhania, Jiaoyan Chen, Stefan Dietze, Hajira Jabeen, et al. 2023. “Large Language Models and Knowledge Graphs: Opportunities and Challenges.” <http://arxiv.org/abs/2308.06374>.

Peng, Yifan, Shankai Yan, and Zhiyong Lu. 2019. “Transfer Learning in Biomedical Natural Language Processing: An Evaluation of BERT and ELMo on Ten Benchmarking Datasets.” In *Proceedings of the 18th BioNLP Workshop and Shared Task*, 58–65.

Piñero, Janet, Àlex Bravo, Núria Queralt-Rosinach, Alba Gutiérrez-Sacristán, Jordi Deu-Pons, Emilio Centeno, Javier García-García, Ferran Sanz, and Laura I. Furlong. 2016. “DisGeNET: A Comprehensive Platform Integrating Information on Human Disease-Associated Genes and Variants.” *Nucleic Acids Research* 45 (D1): D833–39.

Raunak, Vikas, Arul Menezes, and Marcin Junczys-Dowmunt. 2021. “The Curious Case of Hallucinations in Neural Machine Translation.” <http://arxiv.org/abs/2104.06683>.

Reimers, Nils, and Iryna Gurevych. 2019. “Sentence-BERT: Sentence Embeddings Using Siamese BERT-Networks.” <http://arxiv.org/abs/1908.10084>.

Singhal, Karan, Shekoofeh Azizi, Tao Tu, S. Sara Mahdavi, Jason Wei, Hyung Won Chung, Nathan Scales, et al. 2023. “Large Language Models Encode Clinical Knowledge.” *Nature* 620 (7972): 172–80.

Soman, Karthik, Charlotte A. Nelson, Gabriel Cerono, and Sergio E. Baranzini. 2023. “Time-Aware Embeddings of Clinical Data Using a Knowledge Graph.” *Pacific Symposium on Biocomputing. Pacific Symposium on Biocomputing* 28: 97.

Soman, Karthik, Charlotte A. Nelson, Gabriel Cerono, Samuel M. Goldman, Sergio E. Baranzini, and Ethan G. Brown. 2023. “Early Detection of Parkinson’s Disease through Enriching the Electronic Health Record Using a Biomedical Knowledge Graph.” *Frontiers of Medicine* 10 (May): 1081087.

Tang, Alice S., Katherine P. Rankin, Gabriel Cerono, Silvia Miramontes, Hunter Mills, Jacquelyn Roger, Billy Zeng, et al. 2024. “Leveraging Electronic Health Records and Knowledge Networks for Alzheimer’s Disease Prediction and Sex-Specific Biological Insights.” *Nature Aging* 4 (3): 379–95.

Touvron, Hugo, Louis Martin, Kevin Stone, Peter Albert, Amjad Almahairi, Yasmine Babaei, Nikolay Bashlykov, et al. 2023. “Llama 2: Open Foundation and Fine-Tuned Chat Models.” <http://arxiv.org/abs/2307.09288>.

Vasilevsky, Nicole A., Nicolas A. Matentzoglu, Sabrina Toro, Joseph E. Flack, Harshad Hegde, Deepak R. Unni, Gioconda F. Alyea, et al. 2022. “Mondo: Unifying Diseases for the World, by the World.” *medRxiv*. <https://doi.org/10.1101/2022.04.13.22273750>.

Wang, Xiaoyan, Pavan Kapanipathi, Ryan Musa, Mo Yu, Kartik Talamadupula, Ibrahim Abdelaziz, Maria Chang, et al. 2019. “Improving Natural Language Inference Using External Knowledge in the Science Questions Domain.” *Proceedings of the AAAI Conference on Artificial Intelligence* 33 (01): 7208–15.

Wei, Jason, Maarten Bosma, Vincent Y. Zhao, Kelvin Guu, Adams Wei Yu, Brian Lester, Nan Du, Andrew M. Dai, and Quoc V. Le. 2021. “Finetuned Language Models Are Zero-Shot Learners.” <http://arxiv.org/abs/2109.01652>.

Wei, Jason, Yi Tay, Rishi Bommasani, Colin Raffel, Barret Zoph, Sebastian Borgeaud, Dani Yogatama, et al. 2022. “Emergent Abilities of Large Language Models.” <http://arxiv.org/abs/2206.07682>.

Wei, Jason, Xuezhi Wang, Dale Schuurmans, Maarten Bosma, Brian Ichter, Fei Xia, Ed Chi, Quoc Le, and Denny Zhou. 2022. “Chain-of-Thought Prompting Elicits Reasoning in Large Language Models.” <http://arxiv.org/abs/2201.11903>.

Xiang Chen Zhejiang University, China, Ningyu Zhang Zhejiang University, China, Xin Xie Zhejiang University, China, Shumin Deng Zhejiang University, China, Yunzhi Yao Zhejiang University, China, Chuanqi Tan Alibaba Group, China, Fei Huang Alibaba Group, China, Luo Si Alibaba Group, China, and Huajun Chen Zhejiang University, China. n.d. “KnowPrompt: Knowledge-Aware Prompt-Tuning with Synergistic Optimization for Relation Extraction.” Accessed November 6, 2023. <https://doi.org/10.1145/3485447.3511998>.

Yang, An, Quan Wang, Jing Liu, Kai Liu, Yajuan Lyu, Hua Wu, Qiaoqiao She, and Sujian Li. 2019. “Enhancing Pre-Trained Language Representations with Rich Knowledge for Machine Reading Comprehension.” In *Proceedings of the 57th Annual Meeting of the Association for Computational Linguistics*. Stroudsburg, PA, USA: Association for Computational Linguistics. <https://doi.org/10.18653/v1/p19-1226>.

Yasunaga, Michihiro, Antoine Bosselut, Hongyu Ren, Xikun Zhang, Christopher D. Manning, Percy Liang, and Jure Leskovec. 2022. “Deep Bidirectional Language-Knowledge Graph Pretraining.” <http://arxiv.org/abs/2210.09338>.

Yasunaga, Michihiro, Hongyu Ren, Antoine Bosselut, Percy Liang, and Jure Leskovec. 2021. “QA-GNN: Reasoning with Language Models and Knowledge Graphs for Question Answering.” In *Proceedings of the 2021 Conference of the North American Chapter of the Association for Computational Linguistics: Human Language Technologies*. Stroudsburg,

PA, USA: Association for Computational Linguistics.  
<https://doi.org/10.18653/v1/2021.naacl-main.45>.

Yu Gu Microsoft Research, Redmond, WA, Robert Tinn Microsoft Research, Redmond, WA, Hao Cheng Microsoft Research, Redmond, WA, Michael Lucas Microsoft Research, Redmond, WA, Naoto Usuyama Microsoft Research, Redmond, WA, Xiaodong Liu Microsoft Research, Redmond, WA, Tristan Naumann Microsoft Research, Redmond, WA, Jianfeng Gao Microsoft Research, Redmond, WA, and Hoifung Poon Microsoft Research, Redmond, WA. 2021. “Domain-Specific Language Model Pretraining for Biomedical Natural Language Processing.” *ACM Transactions on Computing for Healthcare (HEALTH)*, October. <https://doi.org/10.1145/3458754>.

Zhao, Wayne Xin, Kun Zhou, Junyi Li, Tianyi Tang, Xiaolei Wang, Yupeng Hou, Yingqian Min, et al. 2023. “A Survey of Large Language Models.” <http://arxiv.org/abs/2303.18223>.

## **Supporting information**

**S1 Text : Supplementary information about SPOKE and its applications, semantically pertinent Context extraction from SPOKE, Hyperparameter analysis, Disease entity recognition retrieval analysis, Disease entity extraction comparative analysis, Validation data creation, Test data creation, KG-RAG extended version – A proof of concept, System prompts used, two Supplementary figures and four Supplementary tables: Table A shows the comparative analysis between different methods for disease entity extraction. Table B shows the comparative analysis between Cypher-RAG and KG-RAG using benchmark datasets. Table C displays additional biomedical prompting examples and Table D consolidates sources for the test dataset used in this study.**