DRUGAGENT: EXPLAINABLE DRUG REPURPOSING AGENT WITH LARGE LANGUAGE MODEL-BASED REASONING

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ABSTRACT

Drug repurposing offers a promising avenue for accelerating drug development by identifying new therapeutic potentials of existing drugs. In this paper, we propose a multi-agent framework to enhance the drug repurposing process using state-of-the-art machine learning techniques and knowledge integration. Our framework comprises several specialized agents: an AI Agent trains robust drug-target interaction (DTI) models; a Knowledge Graph Agent utilizes the drug-gene interaction database (DGIdb), DrugBank, Comparative Toxicogenomics Database (CTD), and Search Tool for Interactions of Chemicals (STITCH) to systematically extract DTIs; and a Search Agent interacts with biomedical literature to annotate and verify computational predictions. By integrating outputs from these agents, our system effectively harnesses diverse data sources, including external databases, to propose viable repurposing candidates. Preliminary results demonstrate the potential of our approach in not only predicting drug-disease interactions but also in reducing the time and cost associated with traditional drug discovery methods. This paper highlights the scalability of multi-agent systems in biomedical research and their role in driving innovation in drug repurposing. Our approach not only outperforms existing methods in predicting drug repurposing potential but also provides interpretable results, paving the way for more efficient and cost-effective drug discovery processes. Code is available https: //anonymous.4open.science/r/DrugRepurposeLLM-E0B5/.

1 Introduction

Drug repurposing, also known as drug repositioning, is a strategy for identifying new uses outside the scope of the original medical indication of existing drugs. This approach has gained significant attention due to its potential to reduce the time, cost, and risk associated with drug development (Pushpakom et al., 2019; Chen et al., 2024b; Fu et al., 2022b). With the growing complexity of biological data and the increasing availability of diverse biomedical information sources (Chen et al., 2024a; Wu et al., 2022b), there is a pressing need for innovative computational strategies that can efficiently integrate and analyze these vast datasets (Huang et al., 2021; Lu, 2018).

Recent advances in artificial intelligence (AI), particularly in machine learning and knowledge graphs (Gyori et al., 2017), have shown great promise in addressing these challenges (Vamathevan et al., 2019). However, the integration of heterogeneous data sources and the effective interpretation of their interrelations remain significant hurdles. To overcome these obstacles, we propose a multi-agent

system framework, where each agent specializes in a specific aspect of the drug repurposing process. This approach not only enhances the scalability and flexibility of the analysis but also allows for more robust and accurate predictions.

Our framework includes three primary agents: the AI agent, the Knowledge Graph Agent, and the Search Agent. The AI agent employs the DeepPurpose package (Huang et al., 2020) to develop and refine drug-target interaction (DTI) models. The knowledge graph Agent utilizes the drug-gene interaction database (DGIdb) (Cannon et al., 2024), DrugBank (Knox et al., 2024), Comparative Toxicogenomics Database (CTD) (Davis et al., 2023), and Search Tool for Interactions of Chemicals (STITCH) (Kuhn et al., 2007) to extract and synthesize information on DTIs. The search Agent engages with biomedical literature, specifically leveraging large language models for automated data labeling and validation, a process typically resource-intensive and costly.

This paper details the design, implementation, and initial outcomes of this multi-agent system. By demonstrating the system's ability to leverage AI for effective drug repurposing, we aim to contribute to the broader field of computational drug discovery, offering a scalable model that can be adapted and extended to other areas of biomedical research.

Unlike previous approaches that rely on single models or data sources, our multi-agent system leverages diverse perspectives and methodologies, mirroring the collaborative nature of real-world drug discovery teams. This novel integration of AI agents with specialized roles represents a significant advancement in the field of computational drug repurposing.

2 RELATED WORKS

The concept of drug repurposing has evolved significantly with the advancements in computational tools, leading to a growing body of literature that explores various methodologies. Here, we highlight key developments in the field that align with our multi-agent system approach.

Machine Learning in Drug Repurposing. Machine learning techniques have increasingly been applied to drug repurposing, demonstrating significant potential in predicting drug-disease interactions (Issa et al., 2021). Similarly, our AI Agent leverages the DeepPurpose toolkit, which has been extensively validated for its efficiency in drug-target interaction (DTI) predictions (Huang et al., 2020).

Knowledge Graphs for Integrative Analysis. Knowledge graphs have been instrumental in providing a structured way of integrating diverse biological data. For instance, the DRKG, as employed by our Knowledge Graph Agent, integrates data from several sources, including DrugBank (Knox et al., 2024), Hetionet (Himmelstein et al., 2017), and STRING (Szklarczyk et al., 2023), to offer comprehensive insights into possible drug-disease links (Ioannidis et al., 2020). This structured integration facilitates the systematic exploration of potential drug repurposing candidates.

Literature Search for Drug Repurposing. The automation of literature review and data extraction using AI tools, particularly large language models (LLMs), has become an essential component of modern drug discovery (Chakraborty et al., 2023). This trend is especially relevant in the field of drug repurposing, where efficient processing of vast amounts of scientific literature is crucial. Recent studies have demonstrated that LLM-based search tools can significantly enhance the efficiency and complexity of queries compared to traditional search engines (Spatharioti et al., 2023). In our framework, we leverage this approach by implementing a Search Agent that utilizes search engines as a data source for the LLM, aligning with current trends in AI-assisted literature review for drug discovery and repurposing.

Multi-Agent Systems in Biomedical Applications. While individual AI applications have shown promise, the integration of these technologies through a multi-agent system is less explored in the field of drug repurposing. However, similar multi-agent frameworks have been successfully implemented in other areas of biomedical research, such as clinical trials (Yue & Fu, 2024). These studies provide a foundation for the application of multi-agent systems in drug repurposing, suggesting that such frameworks can enhance the predictive accuracy and efficiency of computational drug discovery.

3 METHODS

Our DrugAgent framework is designed to mimic the collaborative and multidisciplinary nature of drug discovery teams. Each agent in the system is specialized to handle specific aspects of the drug repurposing process, allowing for a more comprehensive and nuanced analysis than traditional single-model approaches.

3.1 OVERVIEW OF DRUGAGENT

Our proposed system is a conversational multi-agent framework analogous to a specialized research team focused on drug repurposing. Each agent within this system plays a distinct role, mirroring the specialization seen in pharmaceutical research—some focus on machine learning models, others on search-based analysis, and another is dedicated to knowledge graph exploration.

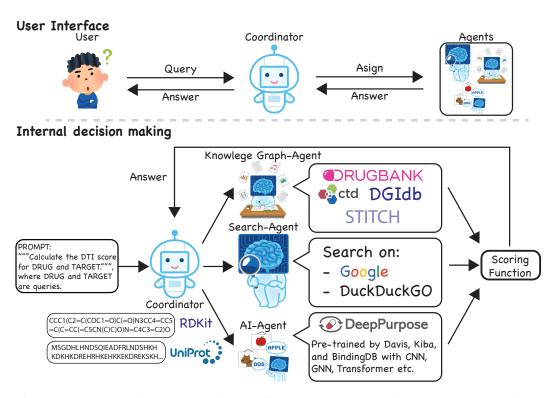


Figure 1: DrugAgent framework architecture for advanced DTI analysis. This system combines a user-friendly interface with sophisticated internal decision-making processes. It features a central "Coordinator" managing specialized agents: a "Knowledge Graph Agent" accessing biomedical databases (DrugBank, CTD, DGIdb, STITCH), a "Search Agent" utilizing web search engines, and an "AI Agent" employing deep learning models (trained on Davis, Kiba, BindingDB datasets with GNN, CNN, Transformers, etc). The system integrates RDKit and UniProt ID for chemical and protein data processing, culminating in a scoring function that synthesizes multi-source information to generate comprehensive answers for complex drug-target queries.

The system comprises the following key agents:

- 1. A Coordinator Agent that oversees the specialized agents and integrates their findings.
- 2. An AI Agent specializing in predicting drug repurposing potential using machine learning models.
- 3. A Search Agent focusing on analyzing existing literature and data for repurposing opportunities.
- 4. A Knowledge Graph (KG) Agent dedicated to exploring connections between drugs, diseases, and biological pathways.

To process natural language inputs and generate responses that are coherent and contextually appropriate, each agent utilizes large language models. The system's reasoning capabilities are enhanced by incorporating methodologies that allow for step-by-step problem-solving and decision-making.

Following the reasoning process, the system is capable of taking actions such as calculating repurposing scores, performing literature-based analyses, and querying knowledge graphs for novel drug-disease associations. By integrating this information through a weighted average approach, the system effectively simulates a highly knowledgeable drug repurposing researcher.

Working in concert, these agents can deliver precise, explainable assessments of drug repurposing potential in response to user inquiries about specific drugs or diseases. This framework's modular nature allows for easy expansion and refinement of the system's capabilities in the context of drug repurposing research.

3.2 AGENT ROLES AND RESPONSIBILITIES

The DrugAgent framework integrates a diverse array of specialized agents, each employing the Re-Act (Yao et al., 2022) and LEAST-TO-MOST (Zhou et al., 2022) reasoning methods to meticulously plan their actions. Through the use of advanced search capabilities, access to specialist models, and indexing in databases, these agents can execute a wide range of tasks effectively. Below, we delve into the specific roles and responsibilities assigned to each agent within the system.

3.3 AI AGENT

Our approach begins with the AI Agent, which utilizes the MPNN_CNN_BindingDB model from DeepPurpose (Huang et al., 2020) to predict potential drug repurposing opportunities. This model combines Message Passing Neural Networks (MPNN) (Gilmer et al., 2017) for processing molecular structures with Convolutional Neural Networks (CNN) for capturing binding site features. It is trained on the comprehensive BindingDB dataset, which contains a wealth of binding affinity data for DTIs.

The MPNN_CNN_BindingDB model operates as follows:

- 1. The MPNN component processes the molecular graph of the drug, capturing its structural features.
- 2. The CNN component analyzes the binding site information of the target protein.
- 3. These features are then combined and processed through fully connected layers to predict binding affinity or repurposing potential.

The AI Agent's predictions are continually refined through an iterative training and validation process, using cross-validation techniques to ensure accuracy and robustness.

3.4 KNOWLEDGE GRAPH (KG) AGENT

Concurrently, the Knowledge Graph (KG) Agent employs DGIdb (Cannon et al., 2024), Drug-Bank (Knox et al., 2024), CTD (Davis et al., 2023), and STITCH (Kuhn et al., 2007). From these datasets, we make use of the DTI table and then create the vast drug-gene interaction table. From this, we calculate the number of hops to reach from the drug to the target using the below formula,

$$DTI_{score}(d,t) = \begin{cases} 0 & \text{if } d \notin G \text{ or } t \notin G, \\ 0 & \text{if } h(d,t) = -1, \\ 1 & \text{if } h(d,t) = 1, \\ \frac{1}{\ln(1+h(d,t))} & \text{otherwise,} \end{cases}$$
 (1)

where d is a drug, t is a target G is a knowledge graph h(d,t) is a number of hops in the shortest path between d and t in G and $\ln(\cdot)$ is a natural logarithm.

3.5 SEARCH AGENT: INFORMATION EXTRACTION FROM BIOMEDICAL LITERATURE

Parallel to these processes, the Search Agent leverages large language models to automate the extraction of relevant information from biomedical literature, including new findings published in

databases like PubMed. This agent applies natural language processing techniques to extract and annotate data regarding drug efficacy, safety, and novel interactions, which are critical for validating and updating the predictions generated by the other agents.

The search agent's core functionality can be summarized as follows:

- 1. **Google Search Query**: The agent formulates a search query combining the drug name and target name, along with the term "interaction".
- 2. **Web Scraping**: It performs a Google search using this query and scrapes the search results, including titles, links, and snippets.
- Text Analysis: The agent analyzes the scraped text for the presence of the drug name, target name, and predefined keywords related to interactions and efficacy.
- 4. **Scoring**: Based on the presence of these elements, it assigns a score to each search result. The scoring system considers: (1) Presence of both drug and target names; (2) Occurrence of interaction-related keywords; (3) The presence of words indicating strong or significant effects.
- 5. **DTI Score Calculation**: Finally, it calculates an overall DTI score by aggregating individual result scores and normalizing the total.

This simplified approach allows for rapid information gathering from publicly available sources. However, it is important to note that this method relies heavily on the quality and relevance of Google search results, and does not directly access or analyze full scientific papers or curated databases. As such, it serves as a preliminary screening tool rather than a comprehensive literature review system.

The DTI score calculation is as follows: Let $R = \{r_1, r_2, ..., r_n\}$ be the set of search results, where n is the number of results (default n is 10). For each result r_i , we define an individual score function $S(r_i)$: $S(r_i) = I(d, t, r_i) + I(p, r_i) + I(s, r_i)$, where

$$I(d, t, r_i) = \begin{cases} 1 & \text{if drug name } d \text{ and target name } t \text{ are in } r_i \\ 0 & \text{otherwise}, \end{cases}$$

$$I(p, r_i) = \begin{cases} 1 & \text{if any positive keyword is in } r_i \\ 0 & \text{otherwise,} \end{cases}$$

and

$$I(s, r_i) = \begin{cases} 1 & \text{if any strong keyword is in } r_i \\ 0 & \text{otherwise.} \end{cases}$$

The positive keywords are "interacts", "binds", "activates", "inhibits", and "modulates". The strong keywords are "strong", "significant", "potent", and "effective".

The total score T is then calculated as $T = \sum_{i=1}^{n} S(r_i)$. The maximum possible score M is M = 3n. Finally, the normalized DTI score D is calculated as:

$$D = \begin{cases} \text{round}\left(\frac{T}{M}, 2\right) & \text{if } M > 0\\ 0 & \text{if } M = 0, \end{cases}$$
 (2)

where round(x, 2) rounds x to 2 decimal places.

3.6 CALLING EXTERNAL TOOLS

GPT supports calling external tools (e.g., function, database retrieval) to leverage external knowledge and enhance its capability. Specifically, suppose we have a couple of toolkits, GPT's API can automatically detect which tool to use, which serves as glue to connect large language models to external tools. Our system integrates a variety of external data sources and predictive AI models to support the agents' functions.

Data Sources The use of professional datasets is pivotal in ensuring the accuracy and reliability of our agents' information retrieval capabilities.

- **DrugBank:** DrugBank (Knox et al., 2024) stands out as a premier resource, offering detailed drug data, including chemical, pharmacological, and pharmaceutical information, with a focus on comprehensive DTIs. DrugBank is not only a repository of drug information but also serves as an invaluable tool for bioinformatics and cheminformatics research. It provides data for over 13,000 drug entries, including FDA-approved small-molecule drugs, FDA-approved biopharmaceuticals (proteins, peptides, vaccines, and allergens), and nutraceuticals.
- Comparative Toxicogenomics Database (CTD): The CTD (Davis et al., 2023) is a robust, manually curated database that provides information about chemical—gene/protein interactions, chemical—disease, and gene-disease relationships. It is particularly valuable for understanding how environmental exposures affect human health, integrating data from various species and linking chemicals, genes, diseases, phenotypes, and pathways (Chang et al., 2019; Wu et al., 2022a).
- Search Tool for Interactions of Chemicals (STITCH): STITCH (Kuhn et al., 2007) is a database of known and predicted interactions between chemicals and proteins. It integrates information from various sources, including experimental data, predictive methods, and text-mining of scientific literature. STITCH is particularly useful for exploring the complex network of interactions between drugs, other chemicals, and proteins.
- Drug-Gene Interaction Database (DGIdb): DGIdb (Cannon et al., 2024) is a web resource that consolidates disparate data sources describing drug-gene interactions and gene druggability. It provides an intuitive interface for searching drug-gene interactions and potentially druggable genes, making it an essential tool for researchers in fields such as cancer informatics, drug repurposing, and personalized medicine (Chen et al., 2021; Wang et al., 2024; Lu et al., 2024b).

Predictive AI Models We utilize DeepPurpose (Huang et al., 2020) for the AI Agent. DeepPurpose is a comprehensive and extensible deep learning library for DTI prediction. It integrates multiple state-of-the-art models and datasets, allowing researchers to easily implement and compare various deep learning approaches for drug discovery and repurposing. DeepPurpose facilitates the application of AI in drug development by providing a unified framework for different drug and protein encoding methods.

3.7 Drug Repurposing Agent

The predictions from the AI agent are cross-referenced and enriched with data from the Knowledge Graph Agent and validated against findings from the Search Agent. This integrated workflow allows for a dynamic updating mechanism, wherein feedback from the literature and knowledge graph continually refines the predictions. The entire process is supported by a central data hub that manages data consistency and real-time updates, ensuring that all agents have access to the latest and most accurate data available.

The final prediction score is calculated in this formula:

$$S_{merged} = \alpha S_{ml} + \beta S_{search} + (1 - \alpha - \beta) S_{kg},$$

where S_{merged} is the merged DTI score, S_{ml} is the machine learning DTI score, S_{search} is the search-based DTI score, S_{kg} is the knowledge graph DTI score, α is the weight for the machine learning score, β is the weight for the search score, and $(1 - \alpha - \beta)$ is the weight for the knowledge graph score. Note that $0 < \alpha < 1, 0 < \beta < 1$, and $\alpha + \beta < 1$.

3.8 Workflow

The workflow of our DrugAgent is designed to leverage the strengths of multiple specialized agents to provide comprehensive and accurate DTI scores. The process is structured in several sequential steps, as described below:

Step 1: Query Initialization and Agent Preparation. The workflow begins with the user input, specifying the drug name, target name, and weighting parameters (alpha and beta). The system initializes four specialized agents: the AI Agent, Search Agent, Knowledge Graph (KG) Agent, and Coordinator Agent. Each agent is configured with specific roles and access to relevant functions and databases.

Step 2: Task Allocation to Specialist Agents. The Coordinator Agent, acting as the central manager, allocates specific tasks to each specialist agent:

- The AI Agent is tasked with calculating the DTI score using machine learning models.
- The Search Agent is responsible for analyzing DTI data using search methods and literature analysis.
- The KG Agent is assigned to analyze DTI data using Knowledge Graph techniques.

Step 3: Independent Agent Processing. Each specialist agent processes its assigned task independently, utilizing its specific methodologies and tools:

- The AI Agent applies machine learning models to predict the DTI score.
- The Search Agent conducts literature searches and analyzes the results to derive a DTI score.
- The KG Agent queries and analyzes the knowledge graph to determine the DTI score.

Step 4: Score Collection and Synthesis. After each agent completes its task, the individual DTI scores are reported back to the Coordinator Agent. The Coordinator synthesizes these scores, applying the provided weighting parameters (α and β) to merge the individual scores into a final, comprehensive DTI score.

Step 5: Result Integration and Final Output. The Coordinator Agent integrates all the information, including the individual scores from each method and the merged final score. It formats this information into a structured output, providing a comprehensive view of the DTI prediction from multiple perspectives.

Step 6: Delivery of Solution. The final output, which includes the merged DTI score along with the individual scores from each method, is delivered to the user. This comprehensive result provides not only the final prediction but also insights into how different methods contribute to the overall score, enhancing the user's understanding of the DTI prediction. This structured workflow ensures that our multi-agent DTI prediction system effectively combines multiple analytical approaches, offering a robust and multi-faceted assessment of potential DTIs.

4 EXPERIMENT

4.1 Dataset

In our study, we utilized the Kd (dissociation constant) data from the BindingDB database (Liu et al., 2007) as our experimental dataset. BindingDB is a public repository of measured binding affinities, primarily focusing on interactions between proteins considered as drug targets and small, drug-like molecules.

The Kd dataset comprises 52,284 DTI pairs, involving 10,665 unique drug-like compounds and 1,413 distinct protein targets. Kd values represent the dissociation constant, which quantifies the propensity of a larger complex to separate (dissociate) into smaller components. A lower Kd value indicates a higher binding affinity between the drug and the target protein.

Our regression task involved predicting these Kd values given the target protein's amino acid sequence and the drug compound's SMILES string (a line notation for encoding molecular structures and specific instances) (Weininger, 1988). To evaluate our model's performance, we employed three metrics: Mean Squared Error (MSE), R2 Score, and Correlation. These metrics collectively assess the accuracy of our predictions and the model's capacity to capture the underlying patterns in DTIs.

4.2 PROCEDURE

Each agent in our DrugAgent system was tasked with specific roles, as outlined in the Methods section. The AI Agent applied machine learning models to calculate the DTI score, the Search Agent analyzed literature data to derive a DTI score based on published research, and the KG Agent evaluated DTIs using graph-based techniques. The Coordinator Agent then synthesized these findings into a comprehensive DTI prediction. We conducted experiments to assess the accuracy of the merged DTI scores and the consistency of predictions across different methods.

4.3 IMPLEMENTATION DETAILS

In this section, we provide detailed descriptions of the implementation processes to enhance the reproducibility of our study.

Role Assignment to Agents Each agent within our multi-agent framework is designated a specific role, which is integrated directly into the LLM's system prompt for clarity and focus. For instance, the role of the AI Agent is defined as follows:

```
"""Specialized AI Agent for calculating DTI scores using machine learning models. Use the get_ml_score function to obtain the DTI score. Output the score in the following format: { "ml_dti_score": 1.0,}"""
```

This role definition is crucial as it guides the LLM to prioritize responses based on the assigned expert domain, leveraging the model's inherent capability to focus more acutely on instructed tasks than on general information.

Defining External Tools External tools are defined in a structured format to facilitate their integration and usage within the LLM environment. These definitions are crafted in Python functions, specifying the function name, parameters, and return types. Key examples include:

- 1. AI Agent: Utilizes machine learning models for DTI scoring.
- 2. Search Agent: Performs web-based information retrieval to gather relevant DTI data.
- 3. KG Agent: Leverages a knowledge graph (KG) for graph-based DTI scoring.

This structured approach allows for the direct execution of function calls within the system, providing detailed responses, including the function name and arguments. These responses enable the retrieval of results in a structured manner. (See Appendix A for detailed implementations of these agents)

Enhanced Score Integration To improve the model's prediction capabilities, we incorporate a weighted integration method within the Coordinator Agent. This method, known as score merging, aids in synthesizing the outputs from different agents into a comprehensive DTI prediction. The integration is performed using predefined weights (α and β) to balance the contributions of each prediction method:

```
merged\_dti\_score = \alpha * ai\_score + \beta * search\_score + (1 - \alpha - \beta) * kg\_score
```

Here, ai_score, search_score, and kg_score represent the DTI scores from the AI Agent, Search Agent, and KG Agent, respectively. The weights α and β are adjustable hyperparameters that determine the relative importance of each score in the final prediction. This approach enhances the accuracy of the model's outputs and its ability to leverage diverse prediction methods for more robust drug repurposing predictions.

These implementation strategies collectively ensure that each component of our multi-agent system operates effectively and that the integration between different agents and external tools is seamless, fostering an environment conducive to robust, reproducible research in drug repurposing prediction.

4.4 CASE STUDY

We analyze three realistic case studies focusing on drug repurposing for Topotecan, targeting different proteins: TOP1, SLFN11, and SLC26A4 (Tables 1, 2, and 3). Topotecan inhibits TOP1, preventing DNA religation and causing cell death in rapidly dividing cancer cells (Schmidt et al., 2001). While SLFN11 is not the direct target of Topotecan, it has been associated with Topotecan efficacy in some studies (Raynaud et al., 2023). In contrast, SLC26A4, a gene encoding pendrin (an anion exchanger protein), is not directly related to Topotecan's mechanism of action or efficacy. These cases represent a spectrum of DTIs, from well-established to potentially novel and unlikely connections. For each case, the user initiates the process by providing the drug name (Topotecan) and the target protein. The Coordinator Agent then decomposes the complex problem into three subproblems, handled by specialized agents: the AI Agent, the Search Agent, and the Knowledge Graph Agent. Case

Table 1: Case study 1: known drug-target interaction

User Input

Problem: I have designed a drug repurposing study and hope you can help me predict whether this drug works for the target. Features contain (1) **drug**: Topotecan; (2) **target**: TOP1;

Coordinate (Coordinator Agent): Coordinate the problem

Thought: Decompose a complex problem into several easier subproblems.

- Subproblem 1 (AI Agent): Predict the DTI score using pre-trained DeepPurpose model.
- Subproblem 2 (Search Agent): Analyze DTI data using search methods and scientific literature.
- Subproblem 3 (Knowledge Graph Agent): Assess the relationship between Topotecan and TOP1 using knowledge graphs.

Solving Subproblems:

- **Subproblem 1** (**AI Agent**): The ML-based DTI score for Topotecan and TOP1 is calculated as 7.649889945983887. This high score suggests a strong potential interaction.
- Subproblem 2 (Search Agent): Analysis of scientific literature yields a search-based DTI score of 0.27. This low score might indicate limited direct evidence in published research.
- Subproblem 3 (Knowledge Graph Agent): The knowledge graph analysis results in a score of 1, indicating a known connection between Topotecan and TOP1 in existing databases.

Reasoning (Reasoning Agent): Integrating multi-source information

- 1. ML Prediction: The high ML-based score (7.65) suggests that the structural and chemical properties of Topotecan are highly compatible with TOP1 binding, indicating a strong potential for interaction.
- 2. Literature Evidence: The low search-based score (0.27) implies that while there might be some mentions of Topotecan and TOP1 in literature, the direct evidence of their interaction is not extensively documented or studied.
- **3. Known Connections**: The knowledge graph score of 1 confirms that there is an established connection between Topotecan and TOP1 in curated databases.
- 4. Background Information: Topotecan is a known topoisomerase I inhibitor, and TOP1 (DNA topoisomerase I) is its primary target. It is used in cancer treatment, particularly for ovarian and small-cell lung cancers.

Conclusion: Merging the scores with $\alpha = 0.3$ and $\beta = 0.3$ yields a final drug repurposing score of 4.059966689596993. This moderate-to-high score, combined with the known mechanism of action, strongly suggests that Topotecan is effective against TOP1. (**The ground truth confirms Topotecan's effectiveness against TOP1**)

Table 2: Case study 2: unknown, but might have some relationship drug-target interaction

User Input

Problem: I have designed a drug repurposing study and hope you can help me predict whether this drug works for the target. Features contain (1) **drug**: Topotecan; (2) **target**: SLFN11;

Coordinate (Coordinator Agent): Coordinate the problem **Thought**: Decompose a complex problem into several easier subproblems.

- Subproblem 1 (AI Agent): Predict the DTI score using pre-trained DeepPurpose model.
- Subproblem 2 (Search Agent): Analyze DTI data using search methods and scientific literature.
- Subproblem 3 (Knowledge Graph Agent): Assess the relationship between Topotecan and SLFN11 using knowledge graphs.

Solving Subproblems:

- **Subproblem 1** (**AI Agent**): The ML-based DTI score for Topotecan and SLFN11 is calculated as 7.363409519195557. This high score suggests a strong potential interaction.
- **Subproblem 2 (Search Agent)**: Analysis of scientific literature yields a search-based DTI score of 0.33. This low-to-moderate score might indicate some evidence of interaction in published research, but not extensively documented.
- Subproblem 3 (Knowledge Graph Agent): The knowledge graph analysis results in a score of 0.7213475204444817, indicating a moderate connection between Topotecan and SLFN11 in existing databases.

Reasoning (Reasoning Agent): Integrating multi-source information

- 1. ML Prediction: The high ML-based score (7.36) suggests that the structural and chemical properties of Topotecan are potentially compatible with SLFN11 interaction, indicating a strong potential for some form of relationship.
- 2. Literature Evidence: The low-to-moderate search-based score (0.33) implies that there is some mention of Topotecan and SLFN11 in literature, suggesting a potential relationship, though not as extensively studied as more established DTIs.
- 3. Known Connections: The knowledge graph score of 0.72 indicates a moderate level of established connection between Topotecan and SLFN11 in curated databases, suggesting some recognized relationships in the scientific community.
- 4. Background Information: While Topotecan is primarily known as a topoisomerase I inhibitor, its potential relationship with SLFN11 could be indirect, possibly through DNA damage response pathways that SLFN11 is involved in.

Conclusion: Merging the scores with $\alpha=0.3$ and $\beta=0.3$ yields a final drug repurposing score of 3.1383244829891226. This moderate-to-high score suggests that there might be a meaningful relationship between Topotecan and SLFN11, possibly mediated indirectly through DNA damage response pathways. Further investigation would be warranted to clarify the nature and extent of this potential interaction.

Table 3: Case study 3: unknown drug-target interaction

User Input

Problem: I have designed a drug repurposing study and hope you can help me predict whether this drug works for the target. Features contain (1) **drug**: Topotecan; (2) **target**: SLC26A4;

Coordinate (Coordinator Agent): Coordinate the problem **Thought**: Decompose a complex problem into several easier subproblems.

- Subproblem 1 (AI Agent): Predict the DTI score using pre-trained DeepPurpose model.
- Subproblem 2 (Search Agent): Analyze DTI data using search methods and scientific literature.
- Subproblem 3 (Knowledge Graph Agent): Assess the relationship between Topotecan and SLC26A4 using knowledge graphs.

Solving Subproblems:

- **Subproblem 1** (**AI Agent**): The ML-based DTI score for Topotecan and SLC26A4 is calculated as 7.609444618225098. This high score suggests a strong potential interaction, based on structural and chemical properties.
- Subproblem 2 (Search Agent): Analysis of scientific literature yields a search-based DTI score of 0.07. This very low score indicates extremely limited or no direct evidence of interaction in published research.
- **Subproblem 3 (Knowledge Graph Agent)**: The knowledge graph analysis results in a score of 0.7213475204444817, indicating a moderate connection between Topotecan and SLC26A4 in existing databases.

Reasoning (Reasoning Agent): Integrating multi-source information

- 1. ML Prediction: The high ML-based score (7.61) suggests that the structural and chemical properties of Topotecan might be compatible with SLC26A4 binding. However, this prediction is based solely on molecular features and does not consider biological context.
- 2. Literature Evidence: The extremely low search-based score (0.07) strongly implies that there is little to no documented evidence of direct interaction between Topotecan and SLC26A4 in scientific literature.
- 3. Known Connections: The moderate knowledge graph score (0.72) suggests some indirect connections between Topotecan and SLC26A4 in curated databases, possibly through shared pathways or related molecular processes.
- 4. Background Information: Topotecan is primarily known as a topoisomerase I inhibitor used in cancer treatment. SLC26A4, on the other hand, is a protein involved in iodide transport in the inner ear and thyroid. These functions appear unrelated, which aligns with the low literature evidence score.

Conclusion: Merging the scores with $\alpha=0.3$ and $\beta=0.3$ yields a final drug repurposing score of 2.3765816855913298. This moderate score, primarily driven by the ML prediction and knowledge graph connection, suggests a potential for interaction between Topotecan and SLC26A4. However, the very low literature evidence score indicates that this interaction, if it exists, is not well-studied or documented. The discrepancy between the ML prediction and literature evidence highlights the need for careful interpretation and further experimental validation. Given the known functions of Topotecan and SLC26A4, any potential interaction would likely be indirect or through previously unrecognized mechanisms. Further investigation would be necessary to understand the nature and relevance of any possible interaction between Topotecan and SLC26A4.

1 (Topotecan-TOP1) represents a known strong interaction. The AI Agent calculates a high score of 7.65, indicating strong potential interaction based on structural properties. The Search Agent yields a relatively low score of 0.27, possibly due to the well-established nature of this interaction not requiring extensive new studies. The Knowledge Graph Agent confirms this with a score of 1, indicating a known connection in existing databases. Case 2 (Topotecan-SLFN11) explores a less understood but potentially relevant interaction. The AI Agent predicts a high score of 7.36, suggesting structural compatibility. The Search Agent's score of 0.33 indicates some literature evidence, while the Knowledge Graph Agent's score of 0.72 suggests moderate established connections. Case 3 (Topotecan-SLC26A4) investigates an unlikely interaction. Despite a high ML score of 7.61, the Search Agent's very low score of 0.07 indicates minimal literature evidence. The Knowledge Graph Agent's score of 0.72 suggests some indirect connections, highlighting the system's ability to detect potential novel interactions while also recognizing the need for careful interpretation. In each case, the Reasoning Agent integrates this multi-source information, considering the ML-based structural compatibility, literature-based evidence, known connections, and relevant background information. The final drug repurposing scores are calculated using weights $\alpha = 0.3$ and $\beta = 0.3$, resulting in scores of 4.06, 3.14, and 2.38 for cases 1, 2, and 3, respectively. These case studies demonstrate the multi-agent system's ability to:

- 1. Handle diverse scenarios, from known interactions to potentially novel discoveries.
- 2. Leverage and integrate various data sources and analytical methods.
- 3. Provide interpretable results with detailed reasoning processes.
- 4. Recognize system limitations, especially when predictions conflict with existing evidence.
- 5. Offer practical insights for drug repurposing research across different levels of prior knowledge.
- 6. Highlight areas requiring further investigation or experimental validation.

This comprehensive approach not only confirms known interactions but also suggests potential new avenues for research, showcasing the system's value in accelerating and refining the drug repurposing process.

5 DISCUSSION

Our study presents a novel multi-agent system for drug repurposing that integrates machine learning, knowledge graphs, and literature search. This approach offers more robust predictions by leveraging diverse data sources and analytical methods.

The system's strength lies in its collaborative approach, which combines each agent's specialized capabilities to evaluate complex DTIs comprehensively. The weighted integration method allows for flexible adjustment of different prediction methods, enhancing overall accuracy.

However, limitations exist. The system still relies on human expertise for initial setup, limiting its scalability. It also lacks autonomous knowledge updating capabilities to keep pace with rapidly evolving pharmacological research. Furthermore, the current model does not adequately account for individual patient characteristics or drug combination effects.

Future research should focus on:

- Integrating autonomous knowledge updating mechanisms to keep the system current with the latest pharmacological research;
- Enhancing the system's ability to predict drug efficacy and handle complex drug combinations;
- Expanding the system's applicability to a broader range of pharmaceutical tasks by incorporating existing models:
 - Adapting the framework for Drug Response Prediction using models like drGAT (Inoue et al., 2024b);
 - Extending to DTI prediction tasks, leveraging the system's existing knowledge graph and AI capabilities;
 - Developing a more flexible prompting system to allow easy adaptation to various pharmaceutical tasks without major architectural changes, such as drug synergy prediction (Huang et al.,

2022), drug property prediction (Xu et al., 2024), adverse drug reaction prediction (Chen et al., 2024a) or drug design (Fu et al., 2021a; 2022a);

- Automating the preprocessing of complex data types, such as scRNA-seq data:
 - Implementing multiple preprocessing functions including Imputation (Inoue et al., 2024a; Inoue, 2024), Quality Control (McCarthy et al., 2017; Lu et al., 2023), and batch effect correction (Li et al., 2020; Fu et al., 2024; Haghverdi et al., 2018);
 - Developing an optimization framework to automatically select and apply the most appropriate preprocessing methods for given datasets;
 - Integrating these preprocessing capabilities seamlessly into the existing multi-agent system;
- Validating the expanded system's predictions through experimental studies and clinical trials to
 ensure real-world applicability across multiple tasks and data types (Lu et al., 2024a; Fu et al.,
 2023).

In conclusion, our DrugAgent shows promise in accelerating AI-driven drug discovery. Continued development addressing both computational and pharmacological challenges could lead to more efficient and cost-effective drug discovery processes (Zhang et al., 2021). Future work should focus on validating the system in real-world drug discovery projects (Fu et al., 2021b) and evaluating its performance with larger, more diverse datasets.

Experimental Setup Our experimental framework was implemented on a Mac computer equipped with an Apple M1 chip and 16GB unified memory, utilizing the built-in GPU cores. We used Python 3.10 for scripting, pyautogen 0.2.31 (Wu et al., 2023), DeepPurpose 0.1.5 (Huang et al., 2020), and RDKit 2023.9.6 (Landrum et al., 2024). For each experiment, we used the same seed to ensure reproducibility across different Mac models.

Aknoeledge We thank the DGIdb and DrugBank team for granting permission to use their logo in this publication.

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A APPENDIX

A.1 WEIGHT OPTIMIZATION FOR SCORE INTEGRATION

To determine the optimal weights for our score integration process, we employed a simple optimization method. We utilized a dataset comprising 3,347 drug-target pairs, each containing scores from our three specialized agents (AI, Knowledge Graph, and Search) along with corresponding ground truth interaction scores from the BindingDB dataset. We formulated the weight optimization as a constrained least squares problem:

$$\underset{\bullet}{\text{arg min}} \quad ||\mathbf{A}\mathbf{x} - \mathbf{b}||_2^2 \quad \text{subject to} \quad \sum_i i = 1^3 x_i = 1 \quad x_i \ge 0, \quad i = 1, 2, 3$$
 (3)

where A is the matrix of agent scores, x is the weight vector we are optimizing, and b is the vector of ground truth scores. The optimization was performed using non-negative least squares (NNLS) followed by Sequential Least Squares Programming (SLSQP) to ensure the weights sum to 1. This approach allows us to determine the relative importance of each agent's score in predicting the true DTI strength. The resulting weights were then used in our merged DTI score calculation:

$$S_{\text{merged}} = x_1 S_{\text{AI}} + x_2 S_{\text{KG}} + x_3 S_{\text{Search}},\tag{4}$$

where x_1 , x_2 , and x_3 represent the optimized weights for the AI Agent, Knowledge Graph Agent, and Search Agent, respectively. This data-driven weight optimization approach ensures that our final predictions leverage the strengths of each agent while accounting for their relative performance on a large set of known DTIs.

A.2 Detailed External Tool Definitions

This appendix provides a comprehensive overview of the implementation details for our three key agents: AI Agent, Search Agent, and KG Agent. Each agent plays a crucial role in our multi-agent system for drug repurposing prediction.

A.2.1 AI AGENT IMPLEMENTATION

The AI Agent utilizes machine learning models to predict DTIs. Its core function, get_ml_dti_score, takes a drug name and a target name as input and returns a float value representing the predicted interaction score.

```
1 # AI Agent
2 def get_ml_dti_score(name: str, target_name: str) -> float:
      target_sequence = get_target_sequence(target_name)
      net = models.model_pretrained(model="MPNN_CNN_BindingDB")
4
5
      X_repurpose, drug_name, drug_cid = load_broad_repurposing_hub(
6
          SAVE_PATH
      idx = drug_name == name
9
      if not any(idx):
10
          print(f"Logging: Drug '{name}' not found.")
11
          return None
13
      res = models.virtual_screening(
14
          X_repurpose[idx], [target_sequence], net,
15
16
          drug_name[idx], [target_name]
17
      return res[0]
18
```

This implementation uses a pre-trained MPNN_CNN model from the BindingDB dataset. It first retrieves the target protein sequence and loads the drug data. If the specified drug is found, it performs virtual screening to predict the interaction score.

A.2.2 SEARCH AGENT IMPLEMENTATION

The Search Agent leverages web-based information to gather relevant data about DTIs. It consists of several functions that work together to perform a Google search, parse the results, and calculate a DTI score based on the search findings.

```
# ... [implementation details]
11
12 def _calculate_individual_score(result: Dict[str, str], drug_name: str,
                                   target_name: str, positive_keywords: List[str],
13
                                   strong_keywords: List[str]) -> int:
14
15
      # ... [implementation details]
16
17 def analyze_dti(name: str, target_name: str) -> float:
18
      search_results = google_search(f"{name} {target_name} interaction")
19
      dti_score = calculate_dti_score(search_results, name, target_name)
20
      return dti_score
```

The main function, analyze_dti, orchestrates the search process and score calculation. It uses a keyword-based scoring system to evaluate the relevance and strength of the interaction based on search results.

A.2.3 KG AGENT IMPLEMENTATION

The KG Agent utilizes a knowledge graph to derive DTI scores based on the structural relationships between drugs and targets in the graph.

```
1 # KG Agent
2 def calculate_dti_score(kg, drug, target):
      if drug not in kg.graph or target not in kg.graph:
3
          return 0  # Return 0 if the drug or target is not in the knowledge graph
4
5
      hops = kg.shortest_path(drug, target)
6
7
      if hops == -1:
          return 0 # No relationship
8
      elif hops == 1:
Q
         return 1 # Direct connection
10
11
      else:
          return 1 / (np.log1p(hops)) # Logarithm-based score
12
13
14 def load_kg(file_path):
      with open(file_path, "rb") as f:
15
16
         kg = pickle.load(f)
      return kg
17
18
19 def get_kg_dti_score(name: str, target_name: str) -> float:
      kg = load_kg("../data/knowledge_graph.pkl")
      score = calculate_dti_score(kg, name, target_name)
21
22
      return score
```

The KG Agent loads a pre-constructed knowledge graph and calculates the DTI score based on the shortest path between the drug and target nodes in the graph. A direct connection yields the highest score, while more distant connections result in lower scores, calculated using a logarithmic scale.

These detailed implementations demonstrate how each agent contributes unique insights to the overall DTI prediction task. The AI Agent provides predictions based on learned patterns from large datasets, the Search Agent incorporates up-to-date information from web sources, and the KG Agent leverages structured knowledge representations. By combining these diverse approaches, our system aims to produce more robust and comprehensive drug repurposing predictions.