

Conversational no-code and multi-agentic disease module identification and drug repurposing prediction with ChatDRex

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Abstract

Repurposing approved drugs offers a time-efficient and cost-effective alternative to traditional drug development. However, *in silico* prediction of repurposing candidates is challenging and requires the effective collaboration of specialists in various fields, including pharmacology, medicine, biology, and bioinformatics. Fragmented, specialized algorithms and tools often address only narrow aspects of the overall problem, and heterogeneous, unstructured data landscapes require specialized users to be involved. Hence, these data services do not integrate smoothly across workflows.

With ChatDRex¹, we present a conversation-based, multi-agent system that facilitates the execution of complex bioinformatic analyses aiming for network-based drug repurposing prediction. It builds on the integrated systems medicine knowledge graph NeDRex. ChatDRex provides natural language access to its extensive biomedical KG and integrates bioinformatics agents for network analysis and drug repurposing, complemented by agents for functional coherence evaluation for *in silico* validation, as well as agents for literature mining and for discussing the obtained results in a scientific context. Its flexible multi-agent design assigns specific tasks to specialized agents, including query routing, data retrieval, algorithm execution, and result visualization. A dedicated reasoning module keeps the user in the loop and allows for hallucination detection.

By enabling physicians and researchers without computer science expertise to control complex analyses in natural language, ChatDRex democratizes access to bioinformatics as an important resource for drug repurposing. It enables clinical experts to generate hypotheses and explore drug repurposing opportunities, ultimately accelerating the discovery of novel therapies and advancing personalized medicine and translational research.

Introduction

The development of novel pharmaceuticals requires substantial time and financial investments. Additionally, it is often accompanied by a high risk of failure in the late stages of clinical trials [1–3]. To address these challenges, there is an increasing emphasis on repurposing already formulated drugs for novel therapeutic applications. This approach utilizes comprehensive pharmacological, clinical, and genomic data to identify potential new

¹ <https://apps.cosy.bio/chatdrex/>

indications for existing drugs [1,2]. This approach not only significantly accelerates the development process but also reduces the risk of clinical failures, as the safety and tolerability of the substances are already established [1,2].

In particular, contemporary computational methodologies, exemplified by systems medicine, have emerged as instrumental in identifying promising candidates, thereby expediting the transition from discovery to clinical application [4]. Networks facilitate the analysis of the interrelationships between genes, drugs, proteins, and diseases, enabling the identification of novel indications for existing pharmaceutical agents [5]. This has already been demonstrated in Alzheimer's disease and cancer [6,7].

A generic workflow for network-driven drug repurposing was established within the NeDRex project [8]. Central to this methodology are concepts such as *seed genes*, which serve as the starting point for drug repurposing queries, typically genes known to be implicated in a specific disease. *Disease modules* are clusters of interconnected genes contributing to the manifestation of a disease phenotype. For example, in Huntington's disease, the *HTT* gene can be regarded as the main disease-causing gene, and the associated network consisting of genes involved in neuronal damage forms the Huntington's disease module. *Disease module identification* algorithms, such as DIAMOnD (DIseAse MOdule Detection), are used to extract these modules from complex biological networks [9]. Once a disease module is identified, *drug prioritization* algorithms rank drugs that may potentially target the identified module, thereby allowing researchers to focus on the most promising candidates for repurposing [10]. These algorithms utilize network topology, often through proximity measures, to determine the association between a drug target and the disease module, providing insights into the drug's potential efficacy [10].

Nevertheless, the field faces considerable challenges due to the substantial and intricate nature of biomedical information that must be examined to identify drug candidates with potential for novel indications. The NeDRex (Network-based Drug Repurposing and Exploration) platform, primarily composed of the NeDRex KG and the NeDRexAPI, was developed to address the identified challenges by providing a comprehensive suite of tools for network-based drug repurposing [8]. Utilizing these advanced tools requires a substantial degree of bioinformatics and programming expertise, which poses a significant hurdle for many clinicians despite their expertise [11]. Consequently, there is a pressing need for more accessible and user-friendly interfaces to bridge the gap between complex bioinformatics tools and the researchers and clinicians who could benefit most from their insights, ultimately accelerating the development of new treatments and personalized medicine approaches [12,13].

Large language models (LLMs) represent a transformative advance in this regard, offering unprecedented capabilities in natural language processing, including question answering and even medical reasoning [14,15]. The success of these models can be attributed to their extensive training on vast quantities of text data, which has enabled them to comprehend and generate text that closely resembles human language [15]. These models have revolutionized biomedical data analysis by providing powerful text-understanding capabilities [16–18]. However, their generalized nature often limits their effectiveness in specialized biomedical domains [19,20]. Additionally, it has been observed that LLMs tend to generate hallucinations, producing plausible yet erroneous or fallacious information [21,22]. This phenomenon poses a significant challenge in high-risk domains such as biomedicine. The unreliability of LLMs underscores the necessity for domain-specific adaptations and rigorous validation when employing LLMs in biomedical research and clinical decision-making processes [21,22]. To overcome this limitation, Retrieval-Augmented Generation (RAG) and in-context learning (ICL) techniques promise to enhance LLMs by incorporating external knowledge retrieval, thereby improving the accuracy and relevance of responses in specialized fields [15,23]. LLMs can further be organized as agents, which are autonomous

entities designed to perform specific tasks. Each agent operates without supervision, allowing them to pursue individual objectives and implement different strategies, including analyzing external data [24]. To execute this task, LLM agents possess a memory that enables them to acquire knowledge from prior interactions and to preserve context over extended periods of time [24]. In particular, in the area of drug repurposing, LLM agents can work towards the goal of providing accurate biomedical insights by autonomously accessing data services, retrieving relevant information, and iteratively refining their responses based on user feedback [25]. Through inter-agent communication, these specialized agents interact with databases, execute algorithms, and generate human-understandable explanations. This collaborative approach bridges the gap between complex computational tools and the needs of researchers and clinicians

Building on these advancements in LLMs and agent technology, we introduce ChatDRex², an intuitive conversational agent designed to assist with identifying disease modules and repurposing drugs. ChatDRex leverages a multi-agent architecture to provide a user-friendly interface to the NeDRex platform, automating complex analyses and enhancing result visualization. The objective of ChatDRex is to democratize access to robust bioinformatics tools and facilitate the identification of potential treatment options for existing diseases by both researchers and clinicians. In addition, ChatDRex uses a novel way of querying a KG (NeDRex) in order to present this knowledge in a simplified manner.

ChatDRex: A Multi-Agent System for Drug Repurposing

ChatDRex is built on LangChain4j³ and the Quarkus⁴ Support⁵ to streamline complex, network-based drug repurposing analyses through a conversational interface. This approach is designed to address potential biases and hallucinations in LLMs by integrating directly with validated biomedical databases and specialized bioinformatics tools. This integration ensures data accuracy and enables sophisticated analyses without requiring specialized computational expertise.

The implemented multi-agent architecture is inspired by the chain-of-thought (CoT) paradigm [26], but adapted to the modularity of complex systems. In contrast to the original CoT, in which a single model sequentially externalizes the intermediate steps of reasoning [27]. Our approach delegates reasoning to a set of specialized agents, each of which has a clearly defined role in the drug repurposing workflow (Fig. 1). A central planning agent functions as a meta-controller, breaking down user requests into subtasks, iteratively assigning them to the appropriate expert agents, and merging their results into a coherent outcome. [28]. Consequently, the architecture itself can plan, and each agent can focus on its small subtask using CoT [27].

² Available at: <https://prototypes.cosy.bio/chatdrex/>

³ Available at: <https://docs.langchain4j.dev/>

⁴ Available at: <https://quarkus.io/>

⁵ Available at: <https://docs.quarkiverse.io/quarkus-langchain4j>

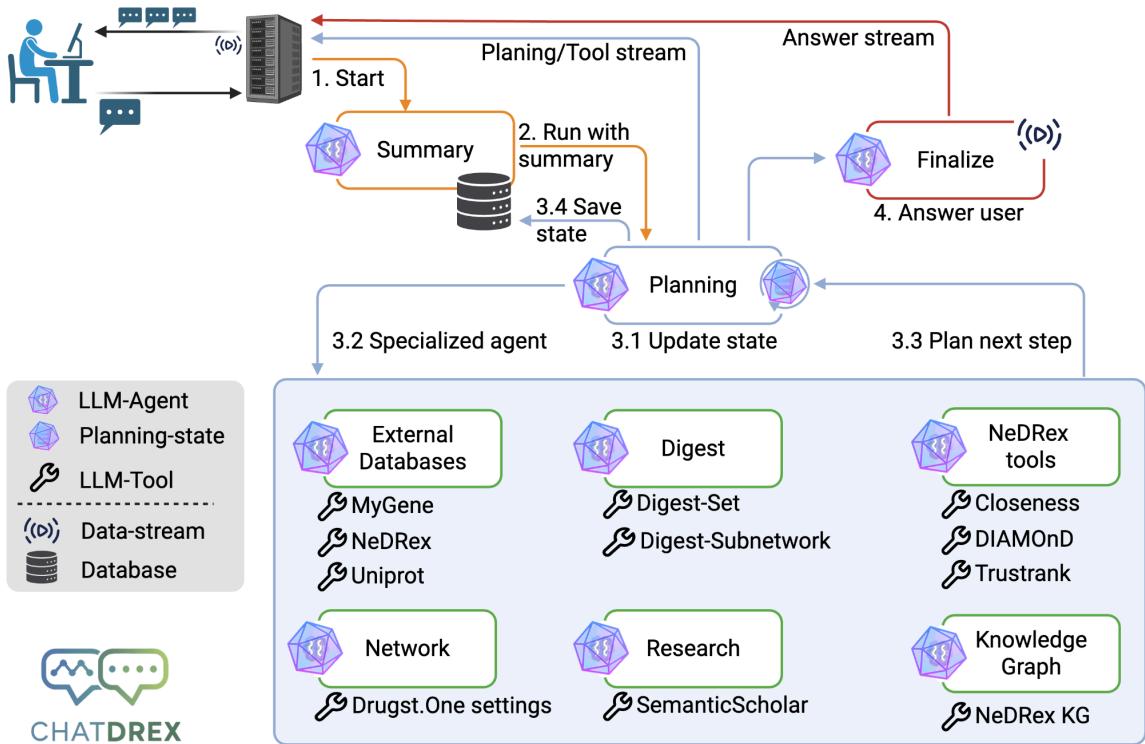


Figure 1: ChatDrex Multi-Agent architecture: The system is orchestrated by a planning agent that directs user queries to specialized agents: DIGEST [29] agent for coherence enrichment analysis, NeDRex [8] agents for accessing NeDRex KG and using network-based drug repurposing tools through NeDRexAPI, and research agent for literature searches. The external database agent for enriching the question with external knowledge. Also, a network agent for adjusting and changing the style of a Drugst.One-powered graph visualization [4]. The Finalize agent synthesizes responses.

ChatDrex agent architecture

ChatDrex comes with multiple agents (Fig. 1). All agents in ChatDrex are constructed based on the same architectural principles (Fig. 2). Each agent integrates a unified control loop consisting of few-shot prompting, short-term and long-term memory access, internal planning routines, and external tool integration. The incoming user messages (1) are enriched by a few-shot system prompt together with relevant memory contents, thereby documenting previous interactions between user, system, and invoked tools in a structured form. This context package is then transmitted to a stateless LLM server (open source hosted, or proprietary, 3), which processes the request independently of prior states. The server’s response is subsequently evaluated by an interpretation module that decides whether immediate feedback can be returned to the user or whether additional tools need to be engaged [30,31] (4-8). When tools are invoked, their outputs are written back into the respective agent’s memory (5-6), thus closing the CoT [27] (Planning). In addition, ChatDrex can incorporate optional safeguard layers. Input guardrails mitigate prompt injection risks before queries reach the LLM (2), while output guardrails constrain generated responses to domain-specific requirements and filter potentially hallucinatory content (7) [32]. These safeguards are not fixed components of every agent but can be activated depending on the task. This selective integration allows the system to balance robustness against computational efficiency in a fine-grained manner.

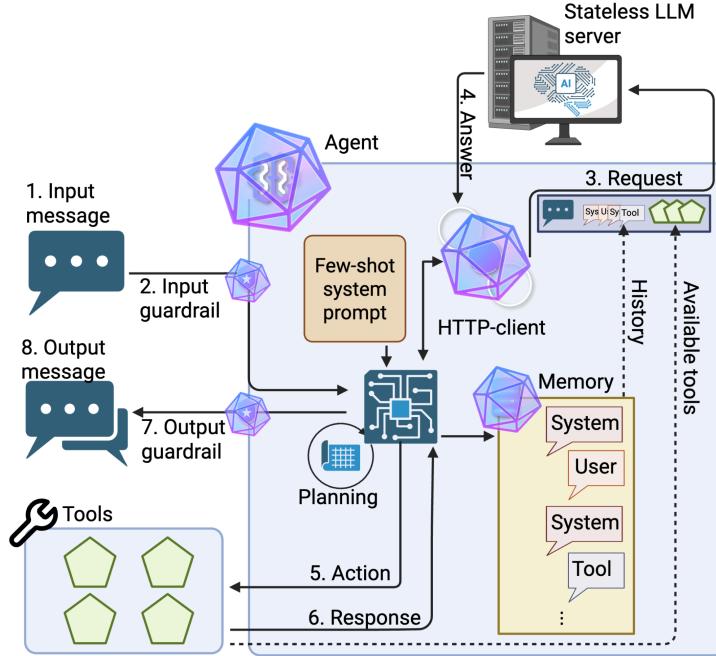


Figure 2: ChatDREx agent architecture: In ChatDREx, the selected agent architecture receives a user message as input (1). This message is sent to a stateless LLM server via a few-shot system prompt and tools, along with memory (3). The response is then forwarded (4-8).

ChatDREx agents

The **Summary agent's** function is to summarize previous steps based on the current input, with the objective of saving tokens and improving the ability to respond to previous questions and answers [33]. This allows the reset of all agents' memory to zero and the reinitialization of the summary. The agent uses an input guardrail to check for prompt injection and returns an error message if it is present.

The **Planning agent** functions as an orchestration agent to our multi-agent system, forwarding human input to the appropriate agent depending on the agent type [34]. The system utilizes an LLM to analyze requests and determine the appropriate agent to which they should be directed. The solution to this problem is achieved through the completion of N (in our case N=6) steps. To identify the most suitable agent, the LLM is provided with the number of remaining steps and the current state each time it is invoked. The state contains the responses from the previously contacted agents. This approach enhances efficiency and accuracy by ensuring that each request is handled by the most suitable specialized agent, thereby optimizing system performance through task specialization [25].

The **DIGEST node** performs functional coherence analysis on a set of genes, here used to evaluate disease modules. In contrast to conventional enrichment approaches, DIGEST quantifies the coherence of the functional annotations of each gene within this gene set, by comparing it to functional coherence observed in comparable but random gene sets. Thereby, an empirical p-value is derived, denoting the statistical significance of functional coherences within the disease module rather than merely listing enriched terms [29]. Through the employment of LLMs, the agent is able to interface with the DIGEST tool [29] via API calls, enabling assessment of the relevance and statistical significance of identified disease modules and disease-associated genes, based on functional annotation from Gene Ontology (GO) and KEGG. The LLM-based agent processes user queries and presents both graphical and textual results in an accessible manner. Through its chatbot-like interface, the

agent not only delivers a seamless integration of this in silico validation of disease modules but also facilitates a more accessible interpretation of the functional coherence analysis and individual functional or pathway enrichment results.

The **NeDRex agent** is responsible for queries pertaining to the analysis of genes, their interactions, and the exploration of biological networks. Proteins and genes are internally translated between, but for simplicity, they will be used interchangeably in the following. The network agent employs several tools, DIAMOnD for disease module identification and TrustRank and Closeness Centrality for drug ranking:

- The **DIAMOnD tool** identifies disease-relevant protein clusters, known as disease modules, by expanding a biological network around a group of known disease-associated genes, referred to as seed genes[10]. It iteratively adds proteins based on their connectivity significance to seed proteins in the protein-protein interaction network (PPI), uncovering potential genetic contributors to the disease mechanism.
- The **TrustRank tool** assesses the reliability of gene associations within a biological network by scoring nodes based on their connection to trusted seed nodes[35]. It is used to identify relevant drugs, targeting given seeds by propagating trust scores, prioritizing drugs close to and strongly connected with the given set of proteins or the disease module, the trusted seeds.
- The **Closeness tool** determines the closeness centrality within biological networks and prioritizes drug nodes based on the length of their shortest paths to all other nodes.

The **Knowledge Graph agent** (Fig. 3) is a strictly structured, knowledge graph (KG) centered question answering chain. Based on user input, the question is first mapped semantically to the fixed structure of the NeDRex KG and broken down into a question list. In this case, the edges are explicitly disregarded, which distinguishes this method significantly from other graph-spanning approaches that continue to use edges [36]. Each element in the list is communicated by an LLM call, indicating the type of node in the KG. The LLM is responsible for creating both the value and the subquery. Furthermore, a Boolean value is assigned to indicate whether this node requires filtering at a later stage.

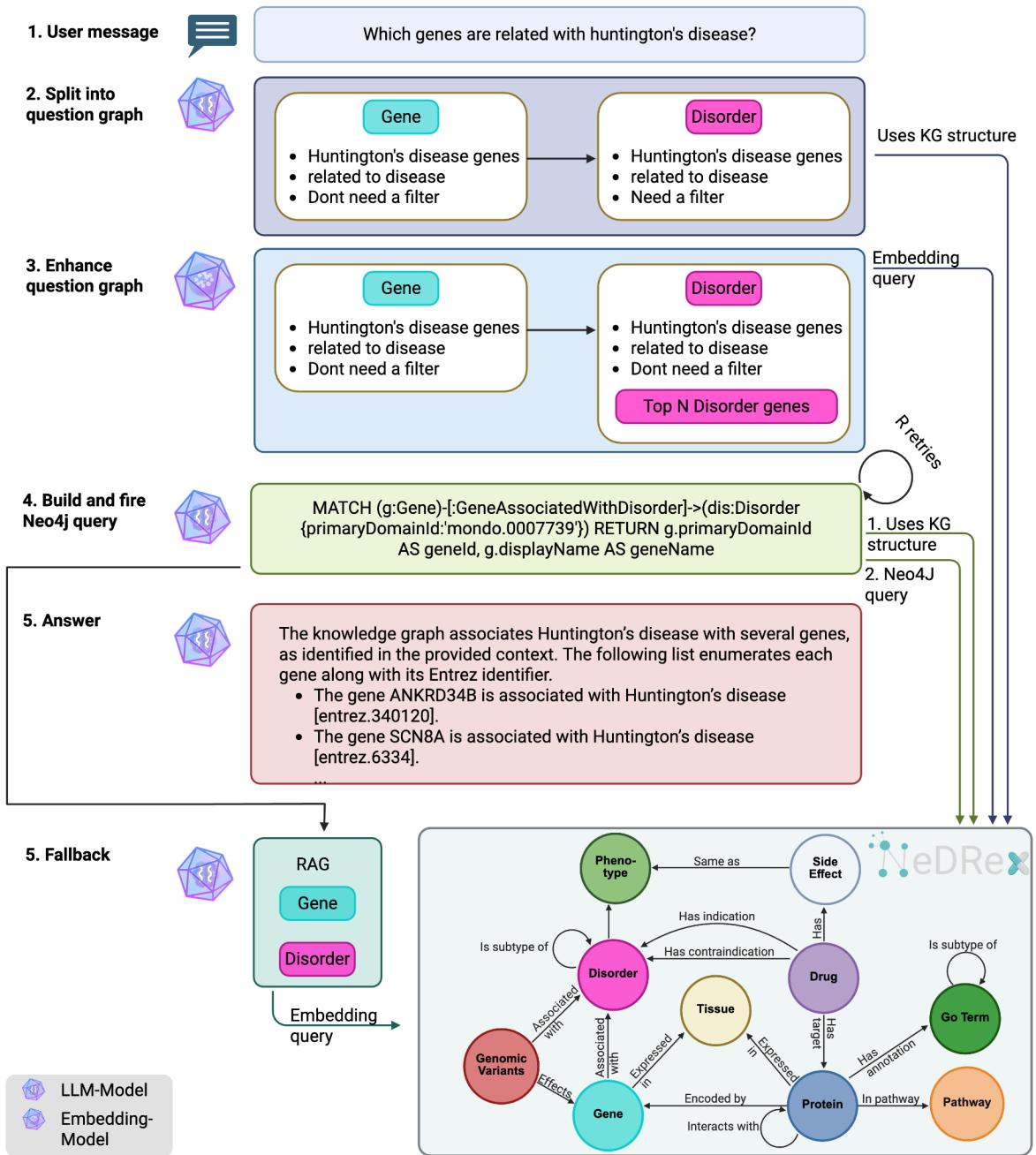


Figure 3: ChatDrex NeDRex-KG-Agent architecture: The process begins with the user query (step 1), which is broken down into a structured query graph (step 2) (e.g., "gene" and "disorder") and then expanded with embeddings and KG structure (step 3). Subsequently, a Cypher query is formulated and executed in Neo4j (step 4). The results are returned as a response (step 5). In the event of query failure, a fallback step to RAG is initiated.

Subsequently, each element in the question list that requires filtering is enriched with the top N nodes that are most similar to it. To accomplish this objective, the KG is searched using an embedding-based similarity query option, with the value and the subquestion as inputs. In the next step, the agent generates deterministic Cypher queries against Neo4j. The known KG schema, in conjunction with the type and edge restrictions embedded within the question graph, serves as the guiding principle for the creation process. This approach has been demonstrated to reduce the occurrence of hallucinations and enhance traceability [37,38].

Due to the prior enrichment, the LLM is capable of utilizing the user's value for filtering purposes and has access to the relevant IDs obtained from the previous embedding-based nodes matching. This reduction in error rate is a key benefit of the proposed approach. If only the value used by the user is employed, the Cypher query itself may be accurate; however, it may not yield any results due to variations in spelling across the database, despite the inclusion of nodes and connections. By categorizing the elements in advance as to whether they require filtering, it is ensured that the LLM does not add filters that degrade the results. The agent has a fixed number of retries for the Cypher query creation, denoted as R. If the creation fails R times, the agent uses a fallback based on the GraphRAG principle [39]. In this case, the graph-guided retrieval steps are summarized and only the condensed passages relevant to the graph structure are submitted to the LLM for generation.

The **Research agent** is used in cases where NeDRex has limited or no information. We use human-like input to query scientific information, leveraging the Semantic Scholar tool to identify relevant literature [40]. To enhance the precision and reliability of the search, an LLM is employed to parse the query into three distinct, more targeted inquiries. This approach of task decomposition not only improves the efficiency of the search process but also enhances the relevance of the retrieved results by encompassing a diverse range of queries [28].

The **Finalize agent** synthesizes responses from the processing agents to generate, given the initial user query, a coherent final response in Markdown format, as commonly used in other popular solutions like ChatGPT. Based on the question and the information provided by the latest state, the agent will create a comprehensive answer. This answer maintains academic accuracy by citing sources and adhering to structured formats [41,42]. This systematic approach ensures that the synthesized answers are both informative and methodologically sound, thus supporting the node's goal of providing high-quality, well-structured results in the context of various fields [41]. A specialized output guardrail has been developed to address the prevalent issue of hallucinations in LLMs by employing hallucination verification [43,44]. To this end, the streamed response from the Finalize agent is reviewed paragraph-wise by another LLM to ensure consistency with the previous context and to eliminate incorrect content. This approach effectively overcomes the common limitations of fluent but factually inaccurate formulations [43,44].

ChatDRex utilizes gpt-oss-20b [45], a highly capable LLM developed by OpenAI and optimized for helpful responses. It is hosted through a self-hosted Ollama [46]. We use Ollama behind a self-hosted OpenWebUI⁶. Furthermore, ChatDRex's multi-agent architecture is designed to be flexible, allowing the integration of new and improved LLMs at the individual agent level as they become available. This modularity ensures the system remains at the forefront of AI advancements.

Result

ChatDRex provides end-to-end conversational analysis for network-based drug repurposing. It accomplishes this by following a workflow proposed, amongst others, in NeDRex [8], but within a chatbot-like environment. ChatDRex combines schema-constrained knowledge graph (KG) querying, network module expansion (DIAMOnD), drug prioritization (TrustRank or Closeness Centrality), and *in silico* validation based on functional coherence (DIGEST). Further, literature grounding is added as part of a single workflow, mimicking usual human behaviour when assessing the validity of results. Results are rendered in-chat as interactive networks with a consistent visual legend across analyses using Drugst.One [4] for visualization.

⁶ <https://github.com/open-webui/open-webui>

Through all the previously presented steps, ChatDRex provides researchers with an interface to access and analyze biomedical data while maintaining conversation coherence and system reliability. The system implicitly translates between gene and protein identifiers and efficiently handles secure connections to the NeDRex database through a custom API client, facilitating the comprehensive exploration of genomic data relationships.

To demonstrate the platform's capabilities, we present several use cases that align with common workflows in drug repurposing research (Fig. 4). The platform integrates NeDRex, which enables schema-constrained Cypher queries to retrieve disease indications and related associations directly from the knowledge graph. It also incorporates DIAMOnD for disease module detection and DIGEST to estimate these modules' functional coherence based on enriched pathways and functional annotations. TrustRank is applied to prioritize proteins and drugs for assessing network reliability. Finally, ChatDRex uses Semantic Scholar's research agent to facilitate targeted literature searches and summarize relevant findings about drugs and diseases. Supplementary Material 1 provides step-by-step workflows, intermediate outputs, and UI snapshots for each use case.

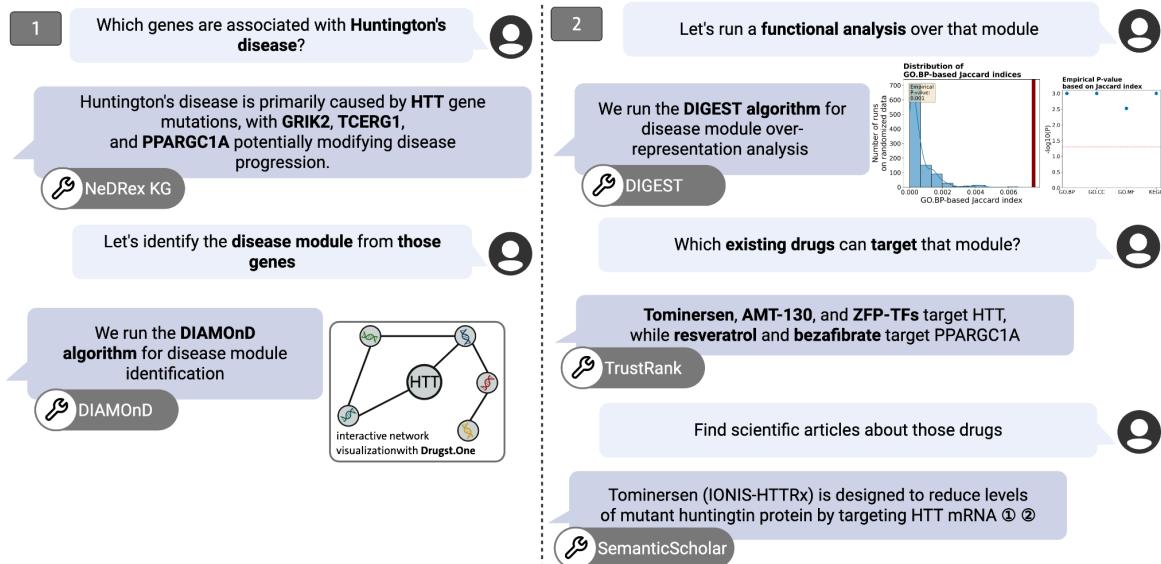


Figure 4: Example Workflow for Huntington's Disease: A user initiates a query about Huntington's disease. ChatDRex identifies relevant genes, constructs a disease module using DIAMOnD, visualizes it with Drugst.One, performs a function-based module coherence analysis via DIGEST, identifies potential drug targets with TrustRank, and retrieves supporting literature through Semantic Scholar, ultimately providing a comprehensive, conversational analysis of potential drug repurposing opportunities.

Evaluation

Evaluating agent systems based on LLMs is challenging because their performance cannot be reduced solely to classic output accuracy. Unlike deterministic systems, LLMs generate responses that encompass generation processes, complex interpretation, and decision-making mechanisms [47]. This leads to a multidimensional evaluation problem [48]. First, it must be verified whether the model uses external tools correctly and appropriately. The next step is to check whether the resulting information is processed and communicated correctly wrt. the actual content. Additionally, LLMs can generate statements that sound plausible yet are factually incorrect, meaning traditional accuracy measures such as accuracy or the F₁-score are only of limited help [49]. A robust evaluation, therefore, requires a combined approach of automated metrics and manual validation [47].

Table 1 Agent evaluation: Overview of the evaluated agent-tool combinations with associated metrics (*Tool-Accuracy*, *Call-Accuracy*, *Answer-Accuracy*) for evaluating correct tool usage, result interpretation, and answer generation. The NeDRex KG tool uses F_1 -score.

Agent	Tool	Tool-Accuracy	Call-Accuracy	Answer-Accuracy
NeDRex	Closeness Centrality	1	0.95	0.95
NeDRex	TrustRank	0.61	0.74	0.44
NeDRex	DIAMOnD	0.89	0.89	0.89
DIGEST	DIGEST-Set	0.92	0.92	0.45
DIGEST	DIGEST-Subnet work	0.76	0.76	0.32
Knowledge Graph	NeDRex KG	-	0.74 (F_1 -score)	0.83

With the *Tool-Accuracy*, agents are evaluated, if they can call up the right tool based on the question. The Closeness Centrality, TrustRank, DIAMOnD, and DIGEST tools were tested in a two-stage evaluation process. For each tool, 100 = specific questions were manually curated, for which both an API call and the generated result were available. In the first stage, it was checked whether the LLM called the respective API correctly and optimally so that accuracy could be determined on this basis (*Call-Accuracy*). In the second stage, a manual validation was performed to assess whether the agent correctly interpreted and processed the returned results in terms of content (*Answer-Accuracy*). To evaluate the NeDRex KG tool, we checked for 174 questions to determine whether the result set returned by the agent represents a superset of the silver standard annotations created by human experts. The rule is that each returned element must include all the properties contained in the gold standard, but may contain additional attributes. However, no expected elements may be missing, nor may additional, semantically inappropriate entries be introduced. A matching procedure was implemented to calculate this score. This procedure identifies a possible hit in the AI result for each manually created silver result standard. Such hit is only counted if all values of the silver standard result are contained in the corresponding AI entry. Based on the correctly assigned entries (hits), F_1 -score (*Call-Accuracy*) are calculated according to classic information retrieval metrics. In a second step, the natural answer generated by the agent was manually checked for content correctness and coherence. This evaluation is referred to as *Answer-Accuracy*. The other tools are implicitly evaluated using these methods. This demonstrates an average *Tool-Accuracy* of 0.86, a *Call-Accuracy* of 0.852, and an *Answer-Accuracy* of 0.61 (Table 1).

Discussion and outlook

Although ChatDRex has the potential to significantly simplify drug discovery, particularly network-based drug repurposing, it has notable limitations. First, the system's performance depends significantly on the quality of the input. Incomplete or inconsistent inputs can lead to distortions and limit the reliability of the generated hypotheses. Another limitation is the interpretability of the results. While ChatDRex automates complex analyses, users without bioinformatic knowledge may have difficulty interpreting the results. This raises questions about explainability, which are particularly crucial in a clinical context. Furthermore, using

LLM-based methods can increase the risk of identifying seemingly plausible yet biologically irrelevant correlations (hallucinations). Additional experiments and guardrails are necessary to provide a more guided, interpretable, and assisted experience.

Although standardizing workflows improves reproducibility, long-term maintenance and updating of the system are also necessary. Changes in databases, algorithms, or interfaces can hinder usability. Finally, while ChatDRex facilitates access to bioinformatics expertise, it does not replace the critical scientific evaluation of results.

Nevertheless, ChatDRex shows promise for the future. Through the continuous expansion of data sources, the implementation of robust validation mechanisms, and the integration of more transparent explanatory models, ChatDRex could become more reliable. In addition, transparent and standardized benchmarking can improve confidence in the system. Further, with the rise of smaller and smaller high-quality LLMs for agentic use cases, the use of these models in our multi-agent framework will improve the general speed and accuracy of ChatDRex.

Conclusion

ChatDRex has the potential to accelerate drug discovery and enhance network-based drug repurposing research workflows by addressing several key challenges in the field. ChatDRex democratizes access to data (Semantic Scholar, NeDRex KG) and drug repurposing tools (DIGEST, Closeness Centrality, DIAMOnD, DIGEST) to enable researchers without specialized computer skills to effectively analyze and interpret complex biomedical data. Its integration of various specialized tools streamlines data analysis workflows and enhances data integration, potentially leading to more holistic insights into disease mechanisms and drug targets. The system's literature-based discovery capabilities and support for network-based approaches facilitate rapid hypothesis generation and testing. By providing a standardized, co-pilot approach, ChatDRex will also improve reproducibility in drug repurposing studies. The natural language interface lowers barriers to entry, enabling a broader range of researchers to contribute to drug discovery efforts. Through automation of data analysis and literature review, ChatDRex has the potential to significantly reduce the time required to move from initial hypothesis to experimental validation, thereby accelerating the overall drug discovery and repurposing process. In addition, the expandable planning approach allows for the quick addition of further tools in the future, so that users can always be offered new tools.

Code availability

The code for ChatDRex is publicly available at the following GitHub repository: <https://github.com/SimonSuewerUHH/ChatDRexAPI4J> and <https://github.com/SimonSuewerUHH/ChatDrexUI>. The front end (Angular⁷) connects to Quarkus servers, which communicate via WebSocket. In addition to the WebSocket server, the back end offers a REST API and an MCP server⁸. These provide the most important tools for external integration. These features make the front end interchangeable and integrable into other LLM workflows [50]. This repository contains the source code, documentation, and instructions for setting up and running ChatDRex locally. For users who prefer not to set up a local environment, a web-based interface for ChatDRex is available at: <https://apps.cosy.bio/chatdrex/>. The ChatDRex software is free for academic and non-profit use under the BSD 3-Clause License (<https://opensource.org/license/BSD-3-Clause>). Commercial users must contact the Cosy.Bio laboratory at University of Hamburg (<https://cosy.bio>) to obtain a commercial license.

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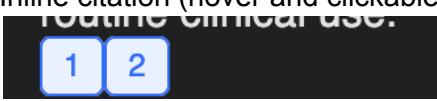
Supplementary material 1: Use cases

Table 1: Functional Enrichment Analysis Workflow and User View in ChatDRex. This table illustrates the key agent Workflow Steps involved in performing a functional enrichment analysis using ChatDRex, alongside corresponding snippets of the user interface. The user initiates the analysis by providing a set of genes, and ChatDRex handles the routing of the query, interaction with the DIGEST tool, and generation of a human-readable summary of the results, including a visualization of enriched pathways.

Agent Workflow Step	Description														
User Input	<i>"Can you tell me which pathways or functions are enriched for the genes APOE, APP, PSEN1, PSEN2, and SORL1?"</i>														
Decisions	Start planning ... CALL_DIGEST_TOOL-> User requests pathway/function enrichment for specified genes; DIGEST tool will perform the enrichment analysis. FINALIZE-> Enrichment results obtained; ready to present summary to user.														
Tool Interaction	<table border="1"> <thead> <tr> <th>Tool</th><th>Input</th><th>Result</th></tr> </thead> <tbody> <tr> <td>Summary</td><td><User Input></td><td><First question, no result></td></tr> <tr> <td>NeDRex KG</td><td>APOE, APP, <i>PSEN1</i>, <i>PSEN2</i>, SORL1</td><td><Different Hits></td></tr> <tr> <td>DIGEST</td><td>320, 5664, 322, 10307, 23621</td><td><Received 4 enrichment results from DIGEST-Set.></td></tr> </tbody> </table>			Tool	Input	Result	Summary	<User Input>	<First question, no result>	NeDRex KG	APOE, APP, <i>PSEN1</i> , <i>PSEN2</i> , SORL1	<Different Hits>	DIGEST	320, 5664, 322, 10307, 23621	<Received 4 enrichment results from DIGEST-Set.>
Tool	Input	Result													
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DIGEST	320, 5664, 322, 10307, 23621	<Received 4 enrichment results from DIGEST-Set.>													
Response	The Finalize agent (LLM) generates a human-readable summary of the results, highlighting key enriched terms and pathways related to Alzheimer's disease, amyloid metabolism, and cholesterol regulation. ChatDRex: Enriched pathways and functions for APOE, APP, PSEN1, PSEN2, and SORL1 KEGG pathways Alzheimer's disease (hsa05010) – 3 out of 5 genes participate in this pathway, indicating a strong association with AD pathology. Neuroactive ligand-receptor interaction (hsa04722) – 1 gene is involved, reflecting neuronal signaling roles. Wnt signaling pathway (hsa04330) – 1 gene participates, implicating developmental and cell-proliferation processes. Huntington's disease (hsa05022) – 1 gene is linked, suggesting shared neurodegenerative mechanisms.														

	... (<i>truncated</i>)
Visualization	<p>The DIGEST (Enrichment Analysis) node provides the user with a plot of the results.</p> <p style="text-align: center;">DIGEST Functional Enrichment Analysis Results</p> <p style="text-align: center;">Legend: GO.BP (Blue), GO.CC (Green), GO.MF (Yellow), KEGG (Red)</p> <p style="text-align: center;">Term Sco</p> <ul style="list-style-type: none"> GO:0050714 GO:0050714 GO:0006355 GO:0006355 GO:0006508 GO:1904646 GO:1904646 GO:0016485 GO:0016485 GO:0016604 GO:0016604 GO:0016020 GO:0016020 GO:0005737 GO:0005829 GO:0005829 GO:0015629 GO:0015629 GO:0050750 GO:0050750 GO:0008134 GO:0008134 GO:0005515 GO:0001540 GO:0001540 GO:0004175 GO:0004175 hsa05010 hsa04722 hsa04330 hsa05022

Table 2: Literature Search Workflow and User View in ChatDRex - An example with limitations. This table illustrates the agent workflow steps involved in a literature search using ChatDRex, alongside snippets of the user interface. While the system attempts to answer the user's query about new drugs for Alzheimer's disease, the initial response contains a large amount of data from Semantic Scholar. The final summary also exhibits some inaccuracies. This example highlights some of the current limitations of the system.

Agent Workflow Step	Description											
User Input	<i>"Can we search scientific literature about new drugs for Alzheimer's disease?"</i>											
Decisions	Start planning ... FETCH_RESEARCH-> User requests literature search on new drugs for Alzheimer's disease FETCH_RESEARCH-> User wants more literature on new drugs for Alzheimer's disease FINALIZE-> Literature search completed; no further actions needed											
Tool Interaction	<table border="1"> <thead> <tr> <th>Tool</th><th>Input</th><th>Result</th></tr> </thead> <tbody> <tr> <td>SemanticScholar</td><td>Alzheimer's disease new drug development 2023</td><td><Paper></td></tr> <tr> <td>SemanticScholar</td><td>new drugs for Alzheimer's disease clinical trials 2023</td><td><Paper></td></tr> </tbody> </table>			Tool	Input	Result	SemanticScholar	Alzheimer's disease new drug development 2023	<Paper>	SemanticScholar	new drugs for Alzheimer's disease clinical trials 2023	<Paper>
Tool	Input	Result										
SemanticScholar	Alzheimer's disease new drug development 2023	<Paper>										
SemanticScholar	new drugs for Alzheimer's disease clinical trials 2023	<Paper>										
Response	<i>The context includes a recent phase 2 investigation of a novel third-generation anti-amyloid antibody, Abx-123. The study demonstrates a design focused on early-stage Alzheimer's disease, with a rigorous safety and biomarker evaluation that could inform future drug development. The report pro...</i>											
Visualization	Inline citation (hover and clickable/Black mode) 											

Paper List (2 out of many - white UI mode)

REVIEW 2024
Counseling and disclosure practices
in predictive Alzheimer's disease
diagnostics: A scoping review

 Alzheimer's & Dementia - 2024

DOENÇA DE ALZHEIMER:
DIAGNÓSTICO PRECOCE E ACESSO
AO TRATAMENTO – REVISÃO DE
LITERATURA

 Revista ft - 2025

Table 3: Network Analysis Workflow and User View in ChatDRex. This table outlines key agent workflow steps in ChatDRex for network-based biomedical analysis, demonstrating its ability to integrate multiple algorithms and tools. The process begins by identifying key Alzheimer's disease related genes using the NeDRex KG tool, followed by detecting a disease module using DIAMOnD. The TrustRank tool then ranks candidate drugs and the Semantic Scholar tool retrieves relevant information about the identified compounds. ChatDRex streamlines complex network-based analyses through its multi-agent system, enabling researchers to explore disease-gene-drug relationships efficiently.

Agent Workflow Step	Description																														
NeDRex KG tool: Finding Key Genes																															
User Input	"Which genes are related to alzheimer?"																														
Decisions	Start planning ... FETCH_KG-> Need gene-disease associations for Alzheimer from the knowledge graph FINALIZE-> KG returned gene list; no further steps needed																														
Tools	<table border="1"> <thead> <tr> <th>Tool</th> <th>Input</th> <th>Result</th> </tr> </thead> <tbody> <tr> <td>NEDREX</td> <td>alzheimer</td> <td><Hit></td> </tr> <tr> <td>NEDREX_KG</td> <td>Which genes are related to alzheimer</td> <td><List of Genes></td> </tr> </tbody> </table>	Tool	Input	Result	NEDREX	alzheimer	<Hit>	NEDREX_KG	Which genes are related to alzheimer	<List of Genes>																					
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NEDREX_KG	Which genes are related to alzheimer	<List of Genes>																													
Response	<p><i>Genes related to Alzheimer's disease</i></p> <p><i>The NeDRex Knowledge Graph identifies the apolipoprotein E (APOE) gene as the most prominent Alzheimer-related gene in the query result. In addition, the graph lists a number of other genes, many of whose names could not be resolved but whose Entrez identifiers are present. The resolved genes include NPBWR1, OR4C16, GOLGA6L10, PKD1L3, PCDHGA4, and MIA. The list also c</i></p>																														
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	<p>Detail Dialog with more information for individual node results</p> <ul style="list-style-type: none"> • <i>OR4C16</i> (Entrez ID 219428) – gene name resolved. • <i>G</i> • <i>P</i> • <i>P</i> • <i>M</i> <p>entrez.128092252</p> <p>Type: Gene</p> <p>Other uncharacterized LOC128092252</p> <table border="1"> <thead> <tr> <th>Gene</th><th>Primary Domain ID</th><th>entrez.128092252</th></tr> </thead> <tbody> <tr> <td><i>OR4C16</i></td><td>Created</td><td>Sep 4, 2025</td></tr> <tr> <td><i>PMF1</i></td><td>Updated</td><td>Sep 4, 2025</td></tr> <tr> <td><i>BLID</i></td><td>Data Sources</td><td>ncbi</td></tr> <tr> <td><i>NPIP8</i></td><td>Domain IDs</td><td>entrez.128092252 ensembl.ENS00000288645</td></tr> <tr> <td><i>PCDH</i></td><td>Synonyms</td><td>uncharacterized LOC128092252</td></tr> <tr> <td><i>PCDH</i></td><td></td><td>entrez.403253</td></tr> <tr> <td><i>CCDC</i></td><td></td><td>entrez.389690</td></tr> <tr> <td><i>RGS2</i></td><td></td><td></td></tr> <tr> <td><i>PSG11</i></td><td></td><td></td></tr> <tr> <td><i>OR5G3</i></td><td></td><td></td></tr> <tr> <td><i>OR4A47</i></td><td></td><td></td></tr> <tr> <td><i>MROH5</i></td><td></td><td></td></tr> </tbody> </table>	Gene	Primary Domain ID	entrez.128092252	<i>OR4C16</i>	Created	Sep 4, 2025	<i>PMF1</i>	Updated	Sep 4, 2025	<i>BLID</i>	Data Sources	ncbi	<i>NPIP8</i>	Domain IDs	entrez.128092252 ensembl.ENS00000288645	<i>PCDH</i>	Synonyms	uncharacterized LOC128092252	<i>PCDH</i>		entrez.403253	<i>CCDC</i>		entrez.389690	<i>RGS2</i>			<i>PSG11</i>			<i>OR5G3</i>			<i>OR4A47</i>			<i>MROH5</i>		
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