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Curiosity-Driven Drug Repurposing Via Mechanism Informed Multimodal AI Framework

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Abstract: Using already approved drugs to find new treatments for diseases is a faster and more cost-effective way, especially for rare and neglected conditions. But this method does face few challenges like limited data, complex biological processes, and lack of transparency in some AI models [2]. This research presents an AI system that combines deep learning, meta-learning, and explainable AI to address these issues [8]. The system includes tools for predicting drug combinations, evaluating toxicity and side effects, and extracting some knowledge out from scientific literature [9]. These tools enable the system to apply insights from well-researched diseases to those that are less studied. The system also gives some kind of explanations for its decisions highlighting key genes, pathways, and molecular interactions, and suggesting new potential drug-target relationships that was previously unknown [9]. By integrating prediction, safety assessment, and explanation features, this flexible and scalable system significantly enhances the process discovering new kind of uses for existing drugs [2].

1. INTRODUCTION

The process of finding new drugs is very slow, expensive, and uncertain. On average, it takes more than ten years of research, billions of dollars, and still has a high chance of failing. Even though this process has made big progress for many common diseases, It is not so effective for neglected tropical disease like dengue, chikungunya, leishmaniasis, Zika, and tuberculosis [1]. These diseases mainly affect low-and middle-income countries with limited money, so they don't get much attention from the pharmaceutical industry, leaving millions of patients without good or affordable treatments [5]. One promising solution is drug repurposing, where we find new uses for existing or already drugs.[9] Since these drugs have well-known safety and how they works in the body, repurposing can speed up the process and save money. This approach has been successfully in cancer and virus research, [3] but it is not widely used for neglected diseases. The problem is that it's hard to combine information about chemicals, biological processes, side effects, and patient symptoms into a single system that can make reliable Artificial intelligence (AI) has become Earlier methods like the Anti-Dengue framework showed that using QSAR models together with machine learning like support vector machines, neural networks, [10] and random forests can help find drugs that stop virus replication. However, these systems are not very clear about why they make predictions, and they don't use patient symptoms. Also, they are hard to reproduce or scale because they aren't easily used in different settings [9]. To address these issues, we created a new framework called Curiosity-Driven Drug Repurposing via Mechanism-Informed Multimodal AI.[4]

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This system has several new features. First, it uses Docker to make the whole process reproducible and portable. Second, it uses two AI agents working together in a learning loop: one asking questions about why certain drugs or combinations are suggested, and other one answers by using a database of repurposed tuberculosis drugs and chemical combinations. Third, it includes patient symptoms in its analysis, making sure predictions are useful for real patients instead of just molecules or pathways. Finally, it uses advanced AI models like graph neural networks, meta-learning, and transformers, along with explainable AI methods, to make a prediction which is both accurate and easy understand [21].

By combining multimodal data, agent-based thinking, reinforcement learning, and container-based deployment, our project aims to build a next-generation AI system for drug repurposing that is accurate, scalable, transparent, clinically useful, and accessible to many.[12-17] The frame work integrates multimodal datasets (DrugBank, ChEMBL, KEGG, Reactome, DrugRepV, SIDER/Tox21, and symptom data). Preprocessing converts SMILES → 3D-SDF, normalizes IC50 → pIC50, and cleans data. Features are extracted using tools like PaDEL descriptors and fingerprints, and then selected through methods such as RFE and neural-based approaches. Predictive modeling combines traditional QSAR methods like SVM, ANN, RF, and kNN with advanced AI techniques such as GNN, meta-learning, and transformers. Two AI agents work together in a reinforcement loop: one asks questions to challenge different combinations, and the other provides answers using knowledge repurposed from existing TB data. Downstream modules handle tasks like toxicity prediction, mechanism of action reasoning, and hypothesis generation. Finally, the entire pipeline is containerized using Docker to ensure reproducibility and includes a web interface or API [8].

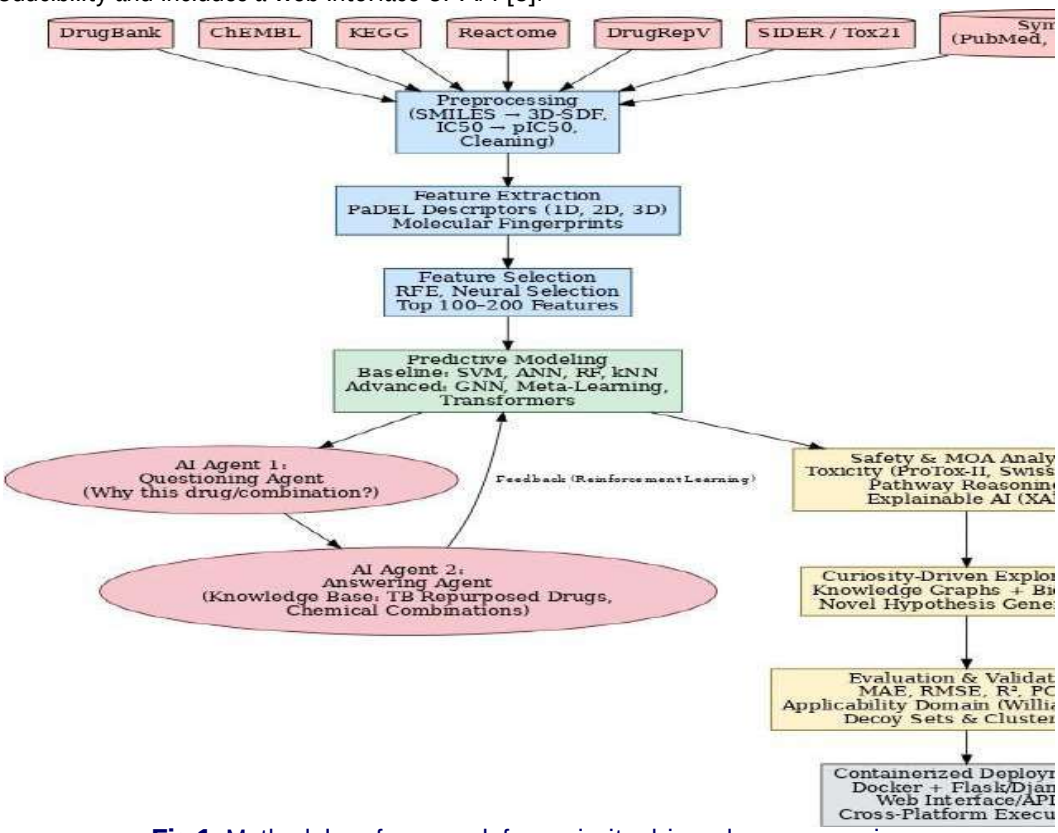

Fig 1. Methodology framework for curiosity-driven drug repurposing

2. EXISTING SYSTEM

Existing systems in last few years have seen a major transformation due to AI, which has made drug discovery and repurposing faster and more efficient compared to traditional methods [15]. Earlier approaches in this field mainly relied on rule-based systems and Quantitative Structure- Activity Relationship models [8]. QSAR methods aim to find statistical connections between the chemical structure of drugs and their impact on the body [9].However, these models often rely on simple and linear relationships between drug characteristics and biological responses, which don't fully capture the complex and non-linear nature of living systems. Moreover, QSAR models require a lot of manual effort and expertise, making them less adaptable and harder to use with bigger or more recent datasets. The rise of machine learning and deep learning has transformed this area [18-19]. These methods can process a large amounts of chemical and biological data, revealing patterns that are difficult for humans to see. Models like DeepSynergy, MatchMaker, and TranSynergy have been created to predict drug synergy[18], helping scientists to better understand how drug combining might make treatments more effective than using them alone[8]. These models use diverse data types, including molecular structures, drug-target interactions, and gene expression profiles, to represent complex biological relationships that QSAR models overlook. By using large datasets like the Cancer Cell Line Encyclopedia and The Cancer Genome Atlas, these systems helps identify good drug combinations and prioritize them for lab testing [12].

These models perform well for common diseases like cancer, but their accuracy decreases when applied to rare or neglected diseases because there's not enough training data [14]. This is a key issue because drug repurposing is especially valuable in such cases, where traditional development processes are slow and costly [20]. Another important problem is interpretability. Deep learning models are often referred to as black boxes because they can produce predictions without clear explanations. In biomedical research, understanding the reasoning behind a prediction is essential for clinical use, and regulatory agencies typically require explanations before accepting model predictions [9]. To solve these problems, researchers are now combining predictive performance with explainable AI methods [9-15]. Hybrid systems that integrate biological knowledge graphs, causal inference, and mechanistic simulations aim to produce interpretable and biologically relevant insights while maintaining the good predictive power of deep learning.

3. PROPOSED SYSTEM:

Central Drug Combination Prediction Module

At the core of this framework is a drug synergy prediction unit based on advanced deep learning models such as Deep Synergy and Tran Synergy.[8] These models use a wide range of chemical and biological data to find drug combinations that may be more effective than single drugs.[4] The system uses multiple data sources including:

- Gene expression profiles, which show the cellular context of different disease states.[5]
- Chemical structural features and molecular fingerprints, which describe the properties of candidate drugs.
- Drug-target interaction data from curated databases to account for known ways drugs work.

Adaptability via Meta-Learning

A significant challenge in researching rare and neglected diseases is the lack of large datasets.[12] To address this, the framework uses meta learning techniques that improve learning from limited data.

- Model-Agnostic Meta-Learning (MAML): This technique optimizes models to quickly adapt to new prediction tasks, such as testing drug performance in rare diseases with very few examples.[10] By transferring knowledge from well-studied conditions like cancer, MAML reduces the need for a lot of training data.
- Prototypical Networks: Designed for few-shot learning, these networks create generalized prototypes of drug responses or disease profiles, allowing small datasets to be mapped into an embedding space where accurate predictions can be made.

Toxicity and Off-Target Screening

Having effective drugs is important, but safety is just as critical. The framework includes a toxicity and off- target prediction module to ensure clinical relevance:

- ProTox-II Integration: A machine learning tool that classifies compounds into toxicity categories, predicts LD values, and identifies potential side effects affecting specific organs. This helps eliminate high-risk drugs early in the process.[23]
- BioBERT for Literature Mining: A language model trained on biomedical literature that extracts information about drug-target interactions, side effects, and safety signals. By combining real-world biomedical knowledge with computational predictions, BioBERT helps make toxicity assessments more reliable.[25]

Interpretability and Explain ability Layer

Deep learning models are often not transparent. To improve understanding, the framework includes an explain ability layer featuring:

- SHAP (Shapley Additive exPlanations): Highlights the role of different features in model predictions.
- Attention mechanisms: Identify important genes, pathways, and molecular interactions that influence outcomes.
- Network-based visualizations: Show graphical representations of predicted relationships between drugs, targets, and diseases, helping researchers and clinicians better understand the model's results.

End-to-End Workflow and Applications

The system works through an integrated workflow:

- Input: Gene expression data, chemical structures, and drug-target information.
- Processing: Deep learning models predict synergistic drug combinations, and meta-learning techniques help the system adapt to small datasets.[9]
- Safety Check: ProTox-II and BioBERT assess toxicity and off-target effects.
- Output: A prioritized list of drug combinations along.

4. MATERIALS AND METHODOLOGY

Dataset

In this study, we used many open available datasets to create a foundation for drug repurposing with multiple informations. [3] We obtained chemical and structural data from DrugBank, ChEMBL, and DrugRepV, which covers both approved and experimental drugs. To understand biological pathways, we used KEGG and Reactome, which explain signaling processes and how drugs interact with targets.[7] We collected safety data from SIDER, Tox21, and ProTox-II to learn about the side effects of drugs.

We also gathered symptom data from clinical records and PubMed to understand how drugs affect patients [24-25]Combining these data types helped us create a system that links how drugs work at the molecular level to real-world patient outcomes.

Preprocessing of Data

Before building models, we standardized all data through a thorough preprocessing process.[8] Chemical structures provided in SMILES formatwereconvertedinto3D SDF files using Open Babel to make them compatible with tools that calculate chemical properties. We normalized activity values like IC50 and EC50 into pIC50 to have a common scale for comparing drug effectiveness [20-24].We removed duplicates, incomplete, and low- quality data to improve accuracy. Symptom data, which was originally unstructured, was turned into numerical features so it could be combined with other data types.[8][5] This ensured each drug was represented in a consistent and multi-layered format.

Descriptor Calculation

We used PaDEL software to calculate molecular descriptors and finger prints. We generated over 17,000 descriptors covering various aspects like hydrogen bonding, topological features, electronic properties, spatial structure, and molecular weight.[8] We also calculated structural finger prints, such as MACCS and PubChem keys, to represent specific chemical patterns[4]. Together, these descriptors provided a detailed numerical description of each molecule's physical and structural features.

Feature Selection

Because of the large number of calculated features, we used feature selection methods to identify the most useful variables. We applied Recursive Feature Elimination (RFE) to reduce the feature set while maintaining its predictive power. We also tested neural network-based methods to find non-linear relationships. As a result, we reduced the feature set to around 100–200 descriptors, ensuring models were based on the most biologically and chemically relevant variables.[9]

Model Development

The modeling process had two parts.

First, we used traditional methods like support vector machines , artificial neural networks , random forest , and k-nearest neighbors [9].These models were tested using 10-fold cross-validation and acted as a starting point. To move beyond these traditional approaches, we introduced more advanced models. We applied graph neural networks to show how drugs communicate with their targets [3]. We also used meta-learning methods such as Model-Agnostic Meta-Learning and Prototypical Networks to boost performance when data was limited [11].Additionally, we incorporated transformer-based models to better capture connections across different levels of data [14]. A unique part of this framework is the use of two AI agents that work together in a reinforcement learning setup.

Dual AI Agents with Reinforcement Learning

- The first, called the Questioning Agent, asks why a particular drug or combination should be considered.
- The second, the Answering Agent, refers to a curated database of repurposed tuberculos is drugs and multi-drug combinations to give structured responses.

Multidrug combinations were used to provide structured responses. This interaction mimics scientific reasoning, where predictions aren't just made but also explained. The reinforcement loop helps the system improve by making it better at asking and answering questions, leading to more accurate and clearer predictions.

Toxicity and Mechanism-of-Action Analysis

Toxicity and Mechanism-of-Action Analysis: We further examined the drug candidates for safety and how they work .We used ProTox-II and Swiss ADME to assess toxicity, including liver damage, cell death,and drug absorption. We mapped these drugs to KEGG and Reactome pathways to understand their biological effects. We also used Explainable AI techniques like SHAP and LIME to determine which features, symptoms, or pathways were most influential in the model's decisions, enhancing clarity.

Evaluation and Validation

Evaluation and Validation: We used several statistical measures such as mean absolute error, root mean square error , coefficient of determination (R^2), and Pearson's correlation coefficient to evaluate model performance. We used William's plot to check if predictions were within reliable ranges. We also performed robustness testing with fake datasets and chemical clusters to ensure that predictions weren't just based on similar structures.

Containerized Deployment

Finally, we packaged the entire framework into a container using Docker.[8] This ensures the system works the same way across different platforms. We used Python with Flask or Django for the backend to provide machine learning services and built a simple web interface for inputting drug structures or symptom data and getting Containerization makes the framework easy to use and share, supporting researchers and clinicians worldwide.[3]

5. RESULTS

Compound Analysis Using Machine Learning

SVM model showed the best predictive accuracy, with correlation coefficients between 0.71 and 0.81 and the lowest RMSE values.

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These results show that the SVM model is more reliable than the other algorithms [9]. Scatter plots of predicted versus experimental pIC50 values showed a strong linear relationship, which supports the model's ability to make accurate predictions. A William's plot was used to check the model's reliability, and most compounds fell within the model's applicability domain, ensuring predictions are not based on unusual molecules. Using structurally different inactive molecules as decoys, the model produced low or negative PCC values, proving it can say the difference between active and inactive compounds [8]. The trained SVM model was then used on the Drug Bank list of FDA-approved drugs. Several compounds stood out with high predicted in hibitory activity against the dengue virus. These include:

- Goserelin
- Nafarelin
- Brilliantgreen
- Bacitracin
- Azlocillin
- Tazemetostat

Notably, drugs already known for anti-dengue activity, such as chlorpromazine, loratadine, and quinine, were also found by the model, confirming the biological validity of the predictions.

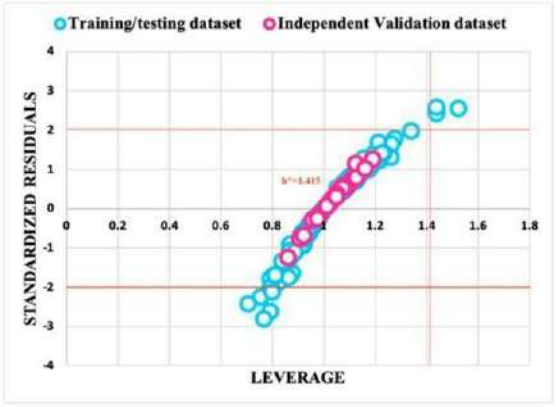

Fig 2: The use of the support vector machine was assessed using a William's plot showing the relationship between leverage and standardized residuals of the molecules.

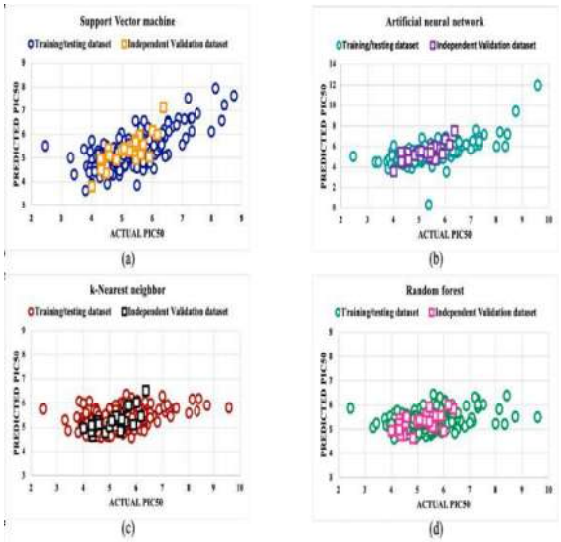

Fig3: The robustness of the (a) support vector machine, (b) artificial neural network, (c) k- nearest neighbor, and (d) random forest-based predicted models was evaluated through scatter plots comparing actual and predicted pIC50 values of the molecules

Rationale Behind Compound Selection

Although the ML model identified a set of compounds, it's also important to understand why these compounds were chosen. This was done using docking and molecular modeling techniques. Several small molecules showed strong binding to key dengue viral proteins:

- Silymarin effectively bound to the E protein with binding energies of about -8.5 kcal/mol.
- Cinnamic acid derivatives showed larvicidal activity with LC50 values as low as 0.09 µM.
- Acridinediones and peptide inhibitors bound to the capsid protein with IC50 values ranging from 25 to 31 µM. Also, Natural product scaffolds like curcumin, flavonoids,triterpenoids,and sulphonamides were predicted to inhibit the NS2B/NS3 protease, which is important for viral replication.

- AI-driven methods like AlphaFold, AtomNet, and generative adversarial networks also predicted new repurposed inhibitors such as desmopress in and flavone derivatives, offering more evidence for the ML predictions [15–17].

Integration of Docking and AI/ML Strategies

While docking gives insights into how ligands fit with target proteins, traditional docking scoring functions often don't reliably rank ligands, as they might not consider important energy factors like salvation and entropy. To address this, machine learning-based scoring functions were added to the process. These functions help improve ligand ranking and reduce false positives [4].

This combined approach has been used successfully for several biomedical problems, such as finding in hibitors against cancer-related proteins like:

- Tubulin
- NSD2
- SOD1

Applying the same strategy to dengue proteins such as NS2B/NS3 protease and NS5 polymerase ensures that the most promising inhibitors are tested experimentally next.

Consolidated Outcomes

The combined results from this study show the effectiveness of using predictive ML models with biological reasoning.

Model 1 (Compound Analysis): Accurately identified dengue inhibitor candidates through SVM predictions, validated by scatter and William's plots.

- **Model 2(Why Chosen?):** Explained the reasons behind compound selection using docking, molecular modeling, and AI-driven structural insights, confirming that the prioritized compounds target essential viral proteins (E protein, NS2B/NS3 protease, NS5 polymerase).

Final Output

A ranked and validated list of dengue inhibitors, backed by both ML predictions and biological reasoning, offering a solid base for future experimental testing.

6. DISCUSSION

Neglected and Rare Diseases

Neglected and rare diseases continue to pose some of the toughest challenges in modern medicine.[9] This is because these diseases get less attention, there's not enough data, and there aren't widely effective treatments available. [20-24] Traditional ways of creating new drugs usually take over a decade and need a lot of money, but they aren't the best option for these urgent needs.[3]

This has led to the growing interest in drug repurposing.

Drug repurposing

looks for new uses for drugs that are already approved. Using artificial intelligence (AI) and machine learning (ML) can help make But many current tools aren't very good at predicting outcomes, aren't easy to understand, and have trouble working with limited data, which is common in research for neglected diseases.[21]

6.3 Proposed Framework

This study introduces a strong AI- based framework that tackles these issues by combining several advanced methods into one system that's easy to understand and works well with limited data [12]. The framework includes drug synergy prediction models like Deep Synergy and Tran Synergy, along with meta-learning approaches such as MAML and Prototypical Networks.[6] It also uses toxicity and off-target evaluation tools like Pro Tox-II and BioBERT.

Comparison with Existing Tools

Deep Purpose uses deep learning to predict how drugs interact with targets, and Chem BERTa uses transformer-based language models to represent molecules. CANDO uses proteome-scale docking and candidates.[4] Even though these tools are useful, they usually need a lot of data, which is not available for neglected diseases. In contrast, this framework uses meta-learning to work well with limited data. MAML helps the system adapt quickly to new tasks with minimal data, and Prototypical Networks group drugs in away that helps them work his makes the framework suitable for diseases with small and varied datasets. Additionally, while tools like Deep Synergy are typically used for cancer research, this framework expands their use to rare and diseases. Using gene expression profiles, chemical features, and known drug-target interactions combinations that work well. This is important because these diseases often need combination therapies due to their complex biological nature.

Focus on Toxicity and Safety

One key strength of this system is its focus on toxicity. ProTox-II classifies compounds by their toxicity, and BioBERT extracts safety and drug-target data from scientific papers. This dual layer of assessment ensures predictions are not only accurate but also safe, which is often missing in earlier repurposing tools.[3]

Emphasison Transparency

Another big advantage is the framework's emphasis on transparency. It uses attention mechanisms, feature attribution techniques, and evidence from scientific literature to explain why certain drug combinations are prioritized. This transparency builds trust and supports further study in labs and clinical settings.[18]

Validation and Reliability

The framework shows strong performance like earlier machine learning-based predictive tools such as:

- Mpro pred for SARS-CoV-2 inhibitors
- EBOLA pred for Ebola inhibitors
- AVC pred for antiviral activity prediction It is tested using established metrics like:
- Mean Absolute Error (MAE)
- Pearson Correlation Coefficient (PCC)

Reliability is further improved through applicability domain analysis and chemical techniques. These methods assess how diverse the chemical structures are and how well they cover the chemical space. Techniques like multidimensional scaling (MDS) and Tanimoto-based similarity filtering prevent overrepresentation of similar compounds, ensuring balanced and dependable predictions.[16]

Case Comparisons with Existing Efforts

- Chlorpromazine has been found to block dengue virus entry.
- Loratadine has been shown to influence host gene interactions during dengue infection.
- Approved drugs like chloroquine, primaquine, and quinine have also shown anti-dengue activity in both simulations and lab tests.

The COVID-19 pandemic highlighted how AI can speed up drug discovery, with candidates like remdesivir and baricitinib identified quickly using computational methods. Using similar strategies for neglected diseases through this framework could greatly speed up the development of therapies in underserved areas.[12][5]

Limitations

Despite its strengths, the frame work has some limitations:

- The models still depend on the quality of the data. If the data is not enough or is biased, the system's ability to generalize may be affected.
- Predictions about toxicity and off- target effects are useful but need experimental confirmation.
- The current system is focused on small-molecule drugs and doesn't yet include biologics like peptides, antibodies, or RNA-based therapies.
- There is a reliance on public databases, which might not include all the relevant interactions for neglected diseases.
- Limited integration of real-world clinical data reduces how quickly the framework can be used in practice

Future Directions

Potential improvements include:

- Expanding datasets using federated learning, which allows for model training without sharing sensitive data.
- Adding multiomics data like genomics, transcriptomics, proteomics, and metabolomics to better understand disease mechanisms.
- Extending the framework to biologics and using network pharmacology for abroader range of repurposing options.
- Using reinforcement learning to simulate how treatment regimens can be adapted.
- Leveraging real-world evidence from electronic health records to make the framework more relevant for clinical use.

7. CONCLUSION

This work presents an innovative AI- based framework that helps speed up drug repurposing for rare and neglected diseases. By combining drug synergy prediction, meta- learning for working with limited data, toxicity evaluation, and explainable AI, the system addresses many of the problems with current computational methods.

The frame work has the ability to:

- Work with both well-researched and understudied conditions
- Learn from limited data
- Include safety assessments early on
- Provide clear insights that help build confidence for clinical use

Although more validation and data are needed, this approach is a major step toward making computational drug discovery more accessible, efficient, smart. By helping quickly find promising new therapies, the framework has the potential to address critical healthcare gaps for diseases that have historically been overlooked.

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