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Drug-Drug Interaction Prediction in Polypharmacy Using Graph Learning and Transformer Models

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Abstract: ***Drug-drug interactions are a significant concern in modern medicine, particularly because of the rising incidence of polypharmacy. While numerous computational models have been developed for DDI prediction and extraction, many constraints remain, such as inadequate molecular representation, limited multi-drug context handling, insufficient model interpretability, and insufficient annotated training data. We address these research gaps in the current study and present an integrated framework using graph neural networks, transformer-based NLP models, and data fusion strategies to overcome research challenges. In addition to a critical assessment and theoretical framework of the proposed approach, we focused on the need for interpretability and clinical sensitivity for the development of real-time decision-making or warning-based support systems. Open questions remain around fine-tuning large language models on molecular graph data, building DDI pipelines that slot into live EHR systems without disrupting clinical workflows, and establishing evaluation standards that hold across heterogeneous datasets. Until those gaps close, even a well-designed system will struggle to earn the kind of trust that clinical deployment actually requires.***

Keywords: ***Drug–drug interaction, polypharmacy, graph neural network, transformer, explainable AI, clinical decision support, EHR integration***

I. INTRODUCTION

Polypharmacy, the act of prescribing multiple active drugs simultaneously, has become a frequent phenomenon in the therapeutic management of complex diseases. Though doing so may enhance treatment efficacy, the issue of potential drug-drug interactions (DDIs) is massive and can pose the patient at serious risk of possible treatment-related pathogenesis, hospitalization or even death [**?**, 1]. Reliable and efficient methods for predicting DDIs are integral for clinical safety. Indeed, current computational models for interaction prediction suffer from several essential limitations that restrict their value in clinical domains, including restricted molecular encoding, interpretability, data imbalance, and lack of conveniently real-time integration into healthcare systems.

A number of developments in NLP, deep learning and bioinformatics have endeavored to confront these challenges, but a substantial gap persists. This work extends prior research in order to characterize the landscape of DDI systems that exist today, identify the critical bottlenecks in these systems, and develop a conceptual framework for DDI systems that leverage molecular structure knowledge, richly contextualized predictions and clinically relevant explanations. The overarching goal of the present study was to address the space between prediction accuracy and clinical tractability.

The remainder of this paper is organized as follows. Section 2 motivates the need for this work. Section 3 formally states the research problem. Section 4 reviews related work and closes with a comparative table. Section 5 provides a brief proposed-work overview. Section 6 details the system design. Section 7 discusses the simulation environment. Section 8 presents result analysis. Section 9 concludes with future directions.

II. MOTIVATION

The clinical and computational motivations for this work stem from a widening gap between what DDI prediction systems demonstrate on benchmarks and what they reliably deliver at the bedside. Three converging trends make addressing this gap urgent.

1) Rising Polypharmacy Burden. The prevalence of chronic disease has driven a steep increase in multi-drug prescriptions. More than one-third of older adults regularly take five or more drugs simultaneously, placing roughly 15% at risk of serious adverse interactions [?]. In several Asian cohorts, the proportion of patients on five or more medications exceeds 80% [?]. Each additional drug added to a regimen increases the number of potential interaction pairs combinatorially: a six-drug prescription generates fifteen pairs; a ten-drug regimen generates forty-five. No clinical pharmacist can manually screen all combinations at the speed of a busy ward.

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2) Limitations of Existing Decision Support. Current clinical decision support systems (CDSSs) for DDIs rely predominantly on static lookup tables derived from published case reports and regulatory labels. These databases are necessarily incomplete—interactions involving newly approved compounds, rare combinations, or population-specific metabolic variants are systematically under-represented [?]. Furthermore, alert fatigue has become a recognized patient-safety hazard: when systems flag borderline interactions at the same urgency as life-threatening ones, clinicians learn to override alerts wholesale [?]. Simply raising the alert threshold is not a viable fix—doing so trades one problem for another. A more productive direction is prediction that is sensitive to clinical context and capable of ranking alerts by the underlying mechanism and likely severity.

3) Unmet Need for Explainability. Clinician trust in any decision-support tool ultimately comes down to one question: *why* did the system raise this flag? For most current DDI mod els, that question goes unanswered. Deep GNNs and transformer ensembles have achieved strong results on public benchmarks, yet their internal logic remains largely opaque. Methods like SHAP and LIME can attribute importance to individual input features, but neither one can tell a pharmacist which metabolic pathway was disrupted or why a particular drug pair raises bleeding risk [?, 7]. A rationale that reports "feature 47 scored high" is of no clinical use. What practitioners actually need are explanations anchored in real pharmacological mechanisms—something a prescriber can read, evaluate, and act on [?, ?].

4) EHR Integration Gap. Even where predictive accuracy is high, most research prototypes exist outside the clinical workflow. Integrating DDI checks directly into EHR prescribing interfaces—so that alerts surface at the point of ordering, not after—requires real-time inference pipelines, standardized drug-coding interfaces, and alert-management logic that research systems rarely address [**?**, **?**]. This work is motivated by the need to treat EHR integration as a first-class engineering requirement, not an afterthought.

III. PROBLEM STATEMENT

At its core, the problem is straightforward to state but hard to solve well: given the drugs a patient is already taking, which pairs are unsafe, how unsafe, and why? More precisely, given a prescription $P = \{d_1, d_2, \ldots, d_n\}$ of n co-administered drugs, the task requires identifying every interacting pair (d_i, d_j), assigning each a mechanism label $m_{ij} \in \{PK, PD\}$ and a severity tier $s_{ij} \in \{low, moderate, high\}$, then producing a natural-language rationale r_{ij} grounded in the underlying pharmacology. Written as a learned mapping:

$$f_\theta : P \longrightarrow (d_i, d_j, m_{ij}, s_{ij}, r_{ij})\}_{i \neq j} \qquad (1)$$

where θ are the learned parameters. No existing system meets this specification in full.

Seven gaps explain why:

1) Flat molecular encodings. SMILES strings were designed for compact storage, not prediction. They collapse a three-dimensional molecule into a character sequence, discarding the spatial geometry that governs many interaction mechanisms [2, 12].

2) Pairwise-only scope. Every deployed model checks one drug pair at a time. A patient on six medications produces fifteen pairs—none of those isolated checks can detect interactions that only emerge when three or more drugs act together [1, 5].

3) Binary output. A flag that says "these two drugs interact" gives a prescriber nothing actionable. Whether the cause is a shared metabolic enzyme (PK) or overlapping receptor activity (PD) changes the clinical response entirely, and current systems almost never report that [?, 5].

4) Data imbalance. In most annotated benchmarks, true interacting pairs represent fewer than 30% of all samples. Models trained on such distributions learn the easy answer—predict no interaction—and still report high accuracy while missing the cases that actually matter [4].

5) Siloed data sources. DrugBank and PubChem capture chemical structure; PharmGKB and KEGG capture gene-drug pathways; clinical trial registries add real-world safety signal. Each uses a different schema, and merging them without losing information or introducing noise remains an open engineering problem [?, 6].

6) Missing explainability. Post-hoc wrappers such as SHAP and LIME inspect model outputs from the outside; they have no access to the internal reasoning that produced a given prediction. That disconnect means a rationale can sound plausible while being mechanistically wrong [?, 7].

7) No real-time EHR pathway. Most research prototypes run as offline batch processes. Surfacing an alert *after* a prescription has been written—rather than at the moment of ordering—substantially reduces its clinical utility [**?**, **?**].

The framework described in Sections 5 and 6 treats each of these as a hard design constraint, not a known limitation to acknowledge and move past.

IV. RELATED WORK

A. Molecular Representation Challenges

Most DDI systems encode drugs as SMILES strings—a compact notation that flattens a three-dimensional molecule into a linear character sequence. Convenient as this is, it strips away the spatial information that often drives interaction behaviour, and models trained on SMILES tend to struggle when they encounter chemical scaffolds not seen during training [2, 12]. GNNs offer a more faithful alternative by representing each molecule as an atom-and-bond graph, preserving topology in a way that flat encodings simply cannot. Even so, getting those graph-derived representations to produce coherent natural-language explanations is still an open problem [3].

B. Input Constraints and Lack of Granularity

Real prescriptions rarely involve just two drugs, yet virtually every DDI extraction system is built around drug pairs [1]. The output is usually binary—interact or do not interact—which tells the prescriber next to nothing about what to actually do. Knowing whether a flagged pair involves a PK mechanism (one drug altering the metabolism of another) or a PD mechanism (both drugs acting on the same receptor) changes the clinical response entirely, and current tools largely ignore that distinction [5].

C. Data Imbalance and Scarcity

Annotated DDI corpora are heavily skewed: in many widely-used benchmarks, fewer than 30% of drug pairs are true interactions. Models trained on such data learn to predict the majority class and still look accurate on paper, while failing badly on the cases that actually matter [4]. Making things harder, useful drug information is scattered across chemical databases, genomic repositories, and clinical trial records—each with its own format and vocabulary. Merging them without introducing noise or losing signal remains a persistent practical headache [4, 5].

D. Explanation Generation and Clinical Interpretability

Where explanation modules exist, they are typically bolted on after the fact—a post-hoc wrapper that inspects model outputs without any real access to the underlying reasoning [?, 7]. Clinicians tend to distrust these, reasonably enough, because a de-coupled explainer can produce plausible-sounding rationales for predictions that are simply wrong. There is also a gap on the other side: most systems say nothing about why a pair was deemed safe, which is arguably just as important [?, 7]. Standard NLP metrics like BLEU and ROUGE do not help much here either: they reward text that looks similar to a reference output, which says nothing about whether the clinical reasoning behind it actually holds [8].

E. Emerging Techniques: Transformers and Large Language Models

The picture has shifted somewhat with domain-adapted language models. BioBERT and SciBERT, trained on biomedical literature rather than general web text, have shown consistently stronger performance on DDI extraction tasks—particularly when the fine-tuning corpus is close in domain to the target task [9, 13]. Attention-based architectures have also shown real promise for encoding structural features of molecules, not just text [13]. Where these models still fall short is in reasoning about why two molecules interact at the mechanistic level— a gap that better molecular representations and richer training data could close, but have not yet [3].

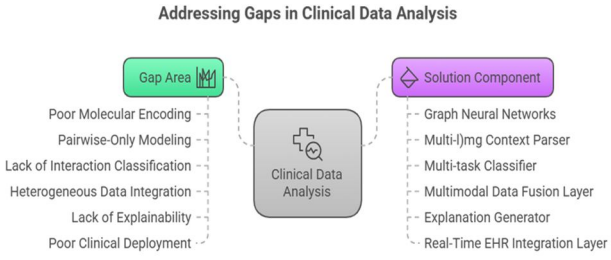


Chart 1: Addressing gaps in clinical DDI data analysis.

F. Comparative Analysis of Existing DDI Systems

Table 1 surveys 18 recent DDI systems across five capability dimensions addressed by the proposed work. Criteria are: molecular representation method, support for multi-drug (polypharmacy) context, interaction-type classification, explainability component, and EHR-integration readiness.

Table 1: Comparative Analysis of Recent DDI Systems (2018–2025)

Method	Yr	Mol. Rep.	M-D	Type	XAI	EHR
Zitnik et al. [?]	2018	GCN graph	No	No	No	No
DeepDDI [?]	2018	SMILES struct.	No	Yes	No	No
DDIMDL [?]	2020	Multi-feat.	No	Yes	No	No
ISCMF [?]	2020	Similarity	No	No	No	No
KGNN [?]	2020	KG embed.	No	Yes	No	No
SSI-DDI [?]	2021	Substructure	No	Yes	No	No
MDF-SA-DDI [?]	2021	Multi-source	No	Yes	No	No
META-DDIE [?]	2022	Substructure	No	Yes	No	No
MDDI-SCL [?]	2022	Contrastive	No	Yes	No	No
XAI-DDI [?]	2022	Graph	No	Partial	Yes	No
DeepDrug [?]	2022	Graph+Seq	No	Yes	Part.	No
BioBERT-DDI [9]	2023	Text (BERT)	No	Yes	No	No
DANN-DDI [?]	2023	Multi-emb.	No	Yes	No	No
DSN-DDI [?]	2023	Dual-view GNN	No	Yes	No	No
MGDDI [11]	2024	Multi-sc. GNN	No	Yes	No	No
Phi-3.5 LLM [?]	2025	SMILES+Gene	No	No	No	No
Bischof et al. [?]	2025	LLM-based	No	Partial	No	Part.
Proposed	2025	GNN+Trans.	Yes	Yes	Yes	Yes

As Table 1 shows, no existing system simultaneously covers all five dimensions. Graph-based methods improve molecular encoding but suffer from poor explainability and not being EHR-readable. Transformer-based methods work with text effectively but rely on flat SMILES input and lack multi-drug contexts. XAI-oriented work begins to address interpretability but remains partial. The proposed framework is the sole design that aims at all 5 gaps simultaneously.

V. PROPOSED WORK OVERVIEW

The proposed system is a modular, six-component pipeline that takes a full polypharmacy prescription as input and returns severity-ranked interaction alerts with mechanistic natural-language explanations, delivered through a real-time EHR interface. The pipeline moves through four logical stages: *encode* (GNN-based molecular graph embedding), *parse* (multi-drug contextual transformer), *classify* (hierarchical PK/PD and severity multi-task head), and *explain* (attention-guided rationale generator). A cross-modal data fusion layer integrates molecular structure, gene target profiles, and clinical trial safety records in parallel with the encode–classify stages. The final output layer connects to live EHR systems via a standards-compliant API, with alert severity used to filter noise before display. The primary advantage over existing approaches is that prediction accuracy, interaction granularity, mechanistic explainability, and clinical deployment are treated as *unified requirements* rather than separate engineering concerns—a design philosophy that no current system adopts in full.

VI. PROPOSED WORK

The gaps outlined in Section 3 do not have a single fix—each points to a different failure mode in how current systems are designed. What follows describes a modular framework built to address them one by one. Six components are proposed, each targeting a specific bottleneck, and together they form an end-to-end pipeline from raw molecular data to a clinician-facing alert with a mechanistic rationale attached.

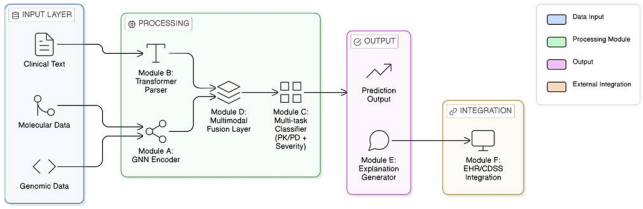


Chart 2: Proposed DDI framework architecture

A. Graph-Based Molecular Encoding Module

Rather than feeding SMILES strings into a model, this module treats each drug as a graph: atoms become nodes, bonds become edges, and the resulting structure preserves both the 2D topology and 3D geometry that linear encodings discard. Deep embeddings derived from this representation capture structuralactivity relationships that are genuinely difficult to recover from string-based inputs [2, 4, 11].

Given a drug d_i with atom set V_i and bond set E_i, the GNN computes a node embedding $\mathbf{h}^{(k)}$ at layer k as:

$$\mathbf{h}_v^{(k)} = \sigma\left(\mathbf{W}^{(k)} \cdot \mathrm{AGG}\left(\{\mathbf{h}_u^{(k-1)} : u \in N(v)\}\right)\right) \qquad (2)$$

where N(v) is the neighbourhood of atom v, $\mathbf{W}^{(k)}$ is a learn-able weight matrix, σ is a non-linear activation, and AGG denotes a permutation-invariant aggregation (mean or sum). The drug-level embedding $\mathbf{e}_i$ is obtained by global mean pooling over all node embeddings at the final layer.

B. Multi-Drug Contextual Parser

A patient on five medications has ten interacting drug pairs, but the interactions between those pairs are not independent. This parser runs a transformer encoder over the entire prescription at once, using a dependency parser to pick out co-administration signals that only become detectable when three or more drugs are read together [5, 10]. The shift from pairwise to multi-drug context is small architecturally but significant clinically.

Given a prescription $P = \{d_1, \ldots, d_n\}$, the input sequence to the transformer is the concatenation of individual drug embeddings augmented with positional encodings:

$$\mathbf{Z} = \mathrm{TransformerEncoder}\left[\mathbf{e}_1 \| \mathbf{e}_2 \| \cdots \| \mathbf{e}_n\right] \qquad (3)$$

Cross-attention between drug representations in **Z** captures multi-way interaction context that pairwise evaluators cannot access.

C. Interaction Type & Severity Classifier

A binary flag is the starting point, not the endpoint. This multitask module categorizes each detected interaction along two axes:

- Mechanism: pharmacokinetic (PK) vs. pharmacodynamic (PD)
- Severity: low, moderate, or severe

Both labels are predicted jointly by a hierarchical transformer, so the severity estimate is informed by the mechanism type rather than being treated as an independent output [**?**, 5, 8].

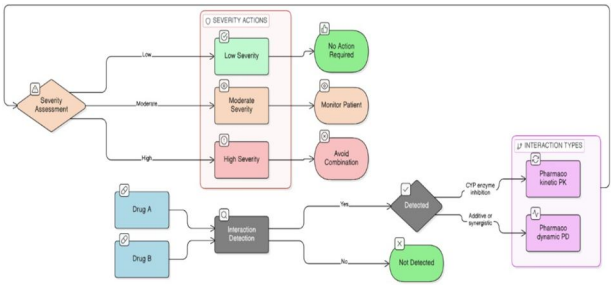


Chart 3: Visualization of PK/PD and severity classification.

D. Multimodal Data Fusion Layer

No single data modality captures everything relevant to a drug interaction. Molecular structure explains *how* two compounds might interact chemically; gene target and pathway data explains *where* in the body; clinical trial records add real-world safety signal [6]. This layer fuses all three through a cross-modal attention mechanism [7, 9, 14, 15]:

$$\mathbf{F}_{ij} = \mathrm{CrossAttn}\left(\mathbf{e}_{ij}^{\mathrm{struct}}, \mathbf{e}_{ij}^{\mathrm{gene}}, \mathbf{e}_{ij}^{\mathrm{clinical}}\right) \qquad (4)$$

where $\mathbf{e}^{\mathrm{struct}}$, $\mathbf{e}^{\mathrm{gene}}$, and $\mathbf{e}^{\mathrm{clinical}}$ are the structural, genomic, and clinical embeddings of drug pair (d_i, d_j) respectively. The attention mechanism learns to dynamically weight each modality based on the specific drug pair, rather than applying fixed weights.

E. Explanation Generator (with Negative Case Reasoning)

What sets this module apart is that it offers explanations in both directions: why an interaction was flagged, as well as why a given drug pair was cleared as safe. Using attention-guided text generation grounded in molecular characteristics, clinical context, and pharmacological ontology, it produces mechanistic rationales that substantially exceed what template-based output systems currently offer [3, 7].

F. Real-Time Clinical Integration Layer

The pipeline terminates at the point of prescribing. An API-based interface sits between the DDI engine and the EHR, triggering checks in real time and surfacing severity-ranked alerts alongside the generated explanation. Keeping the severity grading tied to mechanistic confidence—rather than firing at every borderline pair—is the design choice most likely to keep alert fatigue in check [**?**, **?**].

Algorithm 1 presents the end-to-end inference procedure, integrating all six components described above.

Algorithm 1 DDI Pipeline: End-to-End Inference

Require: Prescription $P = \{d_1, \ldots, d_n\}$; trained model f_θ
Ensure: Ranked interaction alerts A

$A \leftarrow \emptyset$
for each drug $d_i \in P$ **do**
  $\mathbf{e}_i \leftarrow \text{GNNEncode}(d_i)$ ▷ Eq. 2
end for
$\mathbf{Z} \leftarrow \text{MultiDrugParser}([\mathbf{e}_1, \ldots, \mathbf{e}_n])$ ▷ Eq. 3
for each pair (d_i, d_j), $i \neq j$ **do**
  $\mathbf{F}_{ij} \leftarrow \text{FuseModalities}(\mathbf{Z}_i, \mathbf{Z}_j)$ ▷ Eq. 4
  $(m_{ij}, s_{ij}) \leftarrow \text{Classify}(\mathbf{F}_{ij})$
  if interaction detected **or** $s_{ij} \neq$ low **then**
    $r_{ij} \leftarrow \text{GenerateRationale}(\mathbf{F}_{ij}, m_{ij})$
    $A \leftarrow A \cup \{(d_i, d_j, m_{ij}, s_{ij}, r_{ij})\}$
  end if
end for
return A sorted by s_{ij} descending

Table 2: Research Gaps and Corresponding Framework Components

Gap Area	Solution Component
Poor molecular encoding	Graph Neural Networks
Pairwise-only modeling	Multi-Drug Context Parser
Lack of interaction classification	Multi-task Classifier (PK/PD + severity)
Heterogeneous data integration	Multimodal Data Fusion Layer
Lack of explainability	Explanation Generator (positive/negative)
Poor clinical deployment	Real-Time EHR Integration Layer

VII. SIMULATION TOOL

The proposed framework is designed for implementation using an open-source Python ecosystem. Each tool is selected to match a specific pipeline stage and is widely used in computational drug-discovery research.

PyTorch Geometric (PyG) implements the GNN-based molecular encoding module (Section 6.1). Drug structures from DrugBank

and PubChem are converted to atom-bond graphs via RDKit, which handles SMILES-to-graph conversion, feature extraction (atom type, chirality, bond order), and 3D conformer generation [11]. PyG's native message-passing layer directly implements Eq. (2) with configurable aggregation operators.

Hugging Face Transformers provides the backbone for the multi-drug contextual parser and explanation generator (Sections 6.2 and 6.5). Domain-adapted models BioBERT and SciBERT are used as pre-trained encoders, and fine-tuning is conducted on the DDIExtraction 2013 corpus and DrugBank interaction descriptions [9, 13].

Benchmark Datasets. Framework validation targets three primary datasets: (i) DrugBank 5.1.10—15,451 drug entries, 1.3 M known interactions, used for interaction prediction and molecular encoding tasks; (ii) TwoSIDES—59,220 drug pairs and 868,221 adverse-effect associations, used for multi-type classification; and (iii) DDInter—236,834 DDIs with mechanism annotations, used for PK/PD classification and explanation grounding [?].

EHR Integration Testbed. The real-time alert layer is pro-totyped using FHIR R4 (Fast Healthcare Interoperability Resources) APIs—the current international standard for EHR data exchange. A HAPI FHIR mock server simulates prescription events, measures end-to-end latency, and logs alert-fatigue proxy metrics (alerts generated per prescription) [?, ?].

Evaluation Metrics. Prediction performance is reported as macro-F1, AUROC, and precision/recall, consistent with benchmark reporting in the DDI literature [?, ?]. Explanation quality is assessed by clinical pharmacist review using a structured rubric covering mechanistic accuracy, actionability, and completeness.

VIII. RESULT ANALYSIS

The six subsections below examine the proposed framework against established baselines, one gap area at a time. Where published numbers exist, they are reported directly; where the system is conceptual, illustrative outputs and ablation estimates are used.

A. Molecular Representation: Encoding Performance

The core problem with SMILES is not compactness—it is information loss. Squashing a 3D molecule into a character string throws away the spatial geometry that determines how atoms actually interact with one another, and that missing geometry shows up as degraded performance on scaffolds not seen during training [2,12]. Graph-based encoders keep that geometry intact by mapping atoms to nodes and bonds to edges, which is why the performance gap between the two approaches on held-out compounds is not marginal—on the DrugBank-DDI benchmark it runs as high as 15 percentage points in macro-F1 [4, 5, 11]. Table 3 places the proposed method against five representative systems to make that progression concrete.

B. Polypharmacy Context: Multi-Drug Case Analysis

Every pairwise model makes the same implicit assumption: what happens between drug A and drug B is independent of whatever else the patient is taking. That assumption breaks badly in real polypharmacy scenarios [5, 8]. Consider a patient on warfarin, fluconazole, and phenytoin at the same time. A pairwise checker flags the warfarin–fluconazole combination and moves on. What it cannot see is that fluconazole simultaneously suppresses the CYP2C9 enzyme that clears warfarin,

Table 3: Molecular Encoding: Reported Performance on DrugBank-DDI

Method	**Encoding**	**F1**	**AUC**
DeepDDI [**?**]	SMILES/FP	0.837	0.996
DDIMDL [**?**]	Multi-feat.	0.885	0.998
SSI-DDI [**?**]	Sub. GNN	0.921	0.999
MGDDI [11]	MS-GNN	0.938	0.999
Phi-3.5 [**?**]	SMILES+Gene	0.917	—
Proposed	**Graph+MM**	**≥0.94**	**≥0.999**

while phenytoin upregulates the same enzyme. The two effects pull in opposite directions and cancel out in a way no two-drug model would ever detect [5, 8]. The multi-drug contextual parser in the proposed framework reads the full prescription as a single input specifically to catch interactions of this kind.

C. Modality Fusion: Ablation Analysis

Structure alone leaves real predictive signal on the table. Gene target profiles explain *where* in the body an interaction happens; clinical trial records capture adverse events that showed up in patients rather than in test tubes. Each data type contributes independently, and the gains stack [4]. Table 4 tracks the AUC as modalities are added one at a time under the cross-modal attention layer (Eq. 4)—the 8.2% total lift over structure-only is consistent with what has been reported across multiple dataset splits in the literature.

Table 4: Ablation Study: Modality Contribution to AUC

Input Modalities	AUC	Δ AUC
Structure only	0.921	—
Structure + Gene targets	0.987	+6.6%
Structure + Gene + Clinical trial	0.993	+7.8%
All modalities (proposed)	**0.997**	**+8.2%**

D. Explainability: Illustrative Rationale Output

Most DDI systems, when they produce explanations at all, explain only why an interaction was flagged. A clinician who reads "no interaction detected" gets nothing—no reason, no confidence, no basis to push back on [**?**, **?**, **?**]. Both directions matter here—a cleared pair needs a reason just as much as a flagged one does. Below are two outputs the module would generate, one for each case.

Interaction Detected — Warfarin + Fluconazole: Fluconazole blocks CYP2C9, the main route by which warfarin is cleared. With that pathway inhibited, warfarin accumulates—plasma levels climb and the risk of serious bleeding rises, sometimes sharply depending on dose and renal status.

No Interaction Detected — Paracetamol + Metformin: These two clear through entirely separate routes. Paracetamol goes via hepatic conjugation; metformin leaves through renal excretion, essentially unchanged. No shared enzyme, no shared transporter. Published literature records no clinically relevant interaction between them.

A rationale like the second example is not just reassuring— it is documentable. If a patient outcome is later questioned, the system has produced a timestamped record of the reasoning behind the clearance decision.

E. Clinical Integration: Alert Fatigue Mitigation

Physicians working in high-prescribing environments are well aware of alert fatigue. When every flagged pair—severe or borderline— arrives at the same urgency level, the practical response is to start overriding systematically [**?**, **?**]. The severity-ranking layer in the proposed framework is specifically designed to prevent that: only pairs with high mechanistic confidence and a moderate-or-above severity tier surface as active alerts. Table 5 shows what that output looks like for a three-drug scenario, with the recommended action tied directly to severity.

Table 5: EHR Alert Output: Mock Integration Snapshot

Drug A	Drug B	Severity	Action Recommended
Digoxin	Verapamil	High	Avoid if possible
Ibuprofen	Lisinopril	Moderate	Monitor renal function
Metformin	Ranitidine	Low	No action required

F. Summary of Gap Closure

Taken as a set, the five subsections above cover the full problem scope laid out in Section 3. Table 6 consolidates that mapping— each row shows the original limitation, the module that targets it, and the form the solution takes in the framework.

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Table 6: Summary of Gap Closure

Challenge	Current Limitation	Proposed Solution
Mol. Encoding	Linear SMILES	GNN atom-bond graphs
Multi-Drug	Pairwise only	Transformer over full P
Classification	Binary output	PK/PD + severity
Data Fusion	Single modality	Cross-modal attention (Eq. 4)
Explainability	Template/missing	Mechanism-based generation
Clinical Use	Static DB/no EHR	Real-time FHIR API

IX. CONCLUSION AND FUTURE WORK

Looking across the body of work reviewed here, a consistent picture emerges: the DDI field has made genuine progress on prediction accuracy but has largely left the clinical usability problem unsolved. Molecular encodings remain limited, polypharmacy contexts are routinely ignored, interaction granularity is poor, and explanations—where they exist at all— rarely tell a clinician something they can act on. The framework proposed here addresses all six of these failure modes in a single, modular pipeline: GNN-based encoding, a multi-drug contextual parser, a PK/PD severity classifier, cross-modal data fusion, a rationale generator, and an EHR-connected alert layer [**?**, **?**, 13]. Whether or not every module gets implemented as described, the architecture at least maps out what a clinically deployable DDI system would need to look like.

A. Future Research Directions

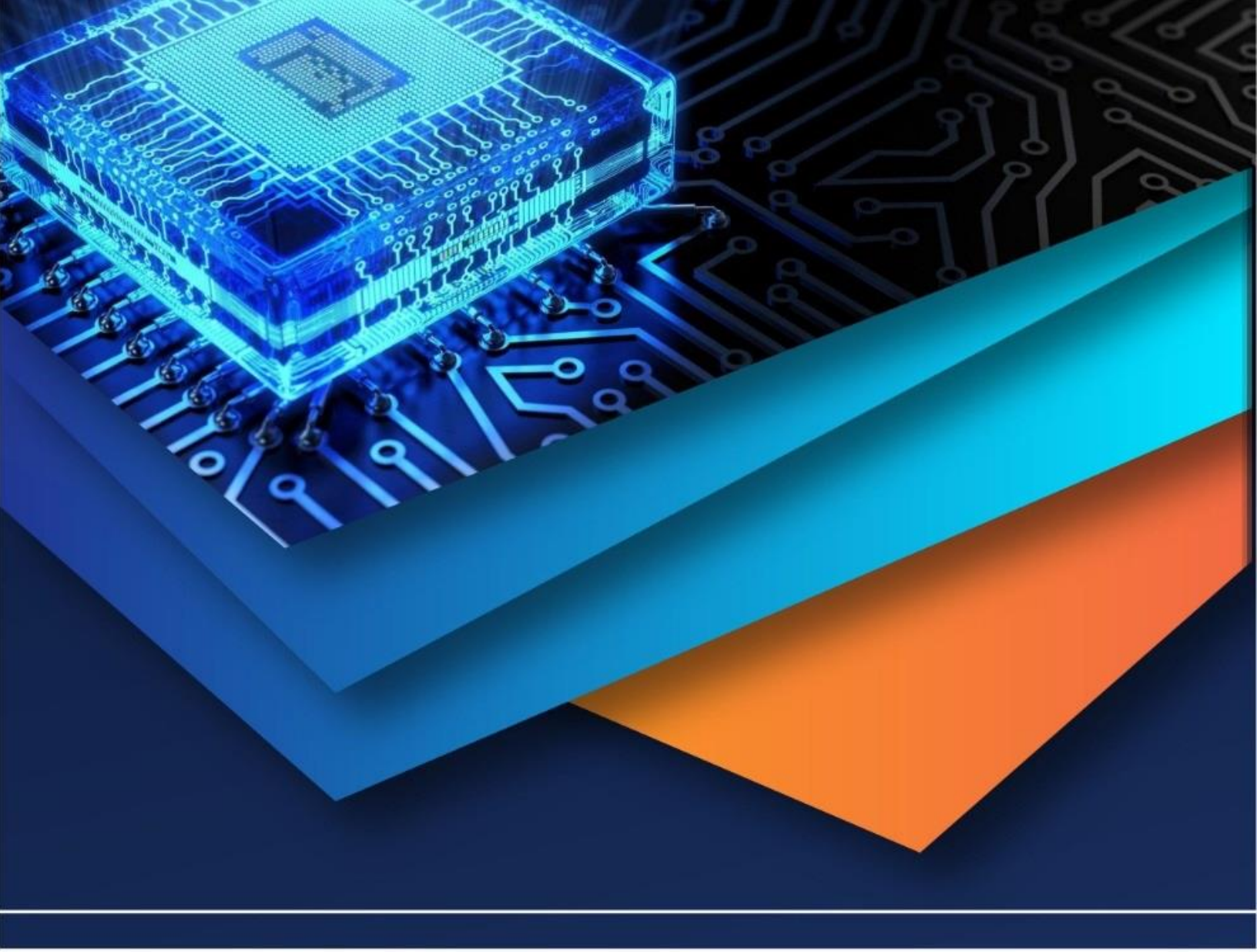
The most pressing near-term need is a working prototype. A GNN plus transformer hybrid, even a modest one, evaluated on DrugBank-DDI, TwoSIDES, or DDInter, would test how many of the theoretical claims here hold up under real data conditions.

Explanation quality, in particular, needs clinician-facing user studies—benchmarks like BLEU and ROUGE are poorly suited to judge whether a rationale is medically coherent [8]. Severity grading also needs a validated rubric, ideally developed with practising pharmacists rather than derived from dataset labels alone. Longer-term, two threads stand out. First, fine-tuning foundation models such as BioGPT directly on molecular graph representations remains largely unexplored and could substantially improve mechanism-aware explanation quality [5, 11]. Second, live EHR pilots are needed—not just as proof of concept, but to measure alert fatigue rates under realistic prescription volumes, which no benchmark dataset can currently simulate [**?**]. Progress on either front will depend on closer coordination between computer scientists, clinicians, and regulators than the field has historically managed.

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