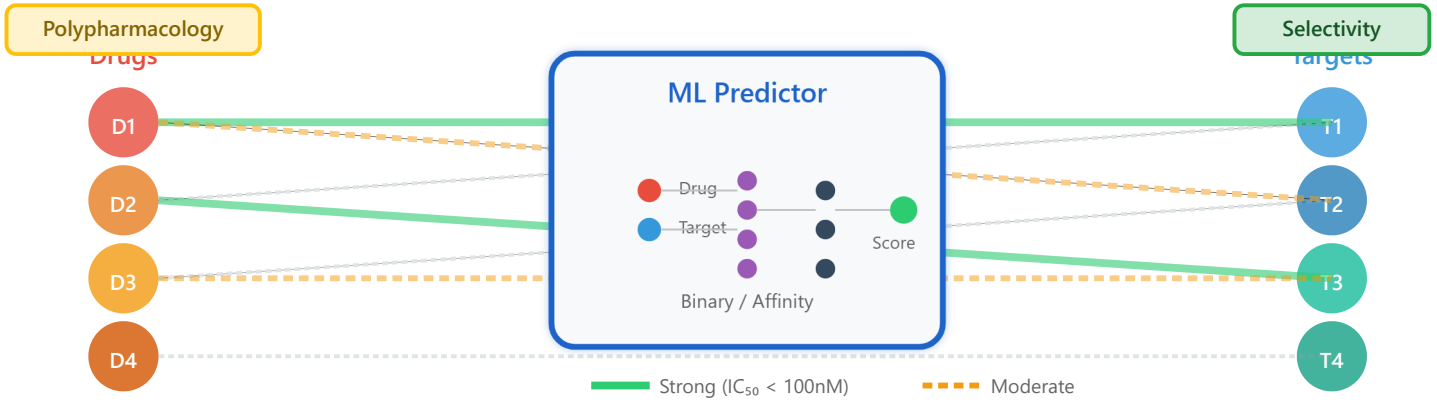
Drug-Target Interaction



Binary classification

Predicting interaction likelihood

Binding affinity

Quantitative affinity prediction

Kinome profiling

Kinase selectivity analysis

Polypharmacology

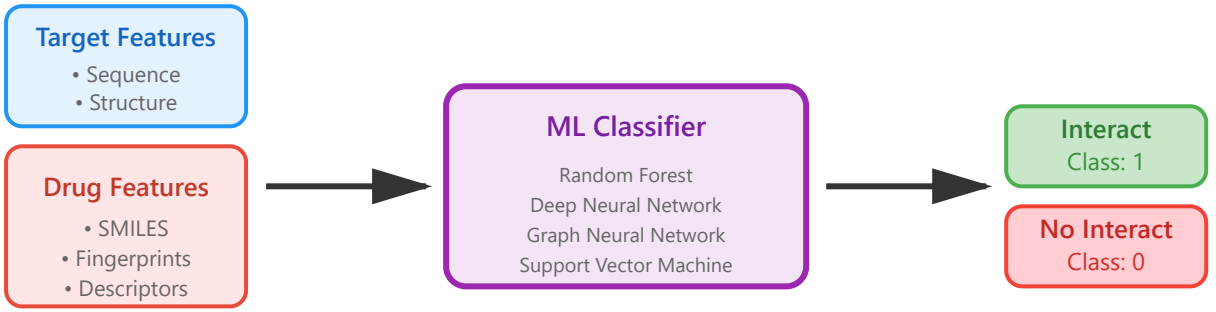
Multi-target interactions

Off-target prediction

Safety profiling

1. Binary Classification

Binary classification predicts whether a drug-target pair will interact or not, producing a yes/no or 0/1 output. This is the fundamental task in drug-target interaction prediction and serves as the foundation for drug discovery pipelines.



Key Characteristics

- **Output:** Binary label (interact/non-interact) or probability score (0-1)
- **Threshold:** Typically IC_{50} < 10μM or Kd < 10μM defines positive interactions
- **Evaluation metrics:** Accuracy, Precision, Recall, F1-score, AUROC, AUPRC
- **Class imbalance:** Negative samples often far outnumber positive samples

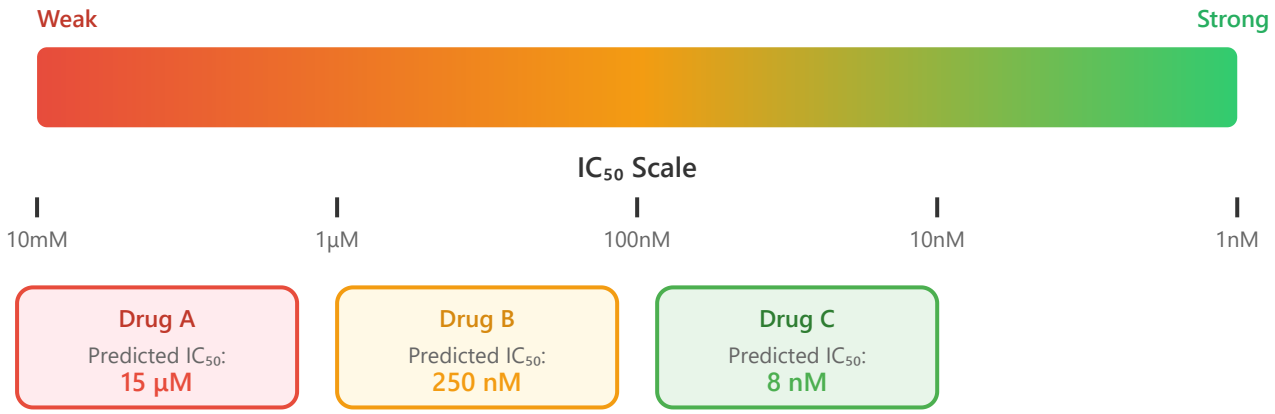
Common Approaches

1. **Feature-based methods:** Extract molecular fingerprints and protein descriptors
2. **Similarity-based methods:** Leverage chemical and genomic similarities
3. **Network-based methods:** Use known DTI networks for prediction
4. **Deep learning:** End-to-end learning from raw sequences and structures

Clinical Example: Predicting whether a new kinase inhibitor will bind to EGFR receptor. The model outputs probability = 0.92, indicating high likelihood of interaction, warranting further experimental validation.

2. Binding Affinity Prediction

Binding affinity prediction provides quantitative measurements of how strongly a drug binds to its target protein. This is crucial for lead optimization and understanding drug efficacy, typically measured as IC_{50}, Kd, Ki, or ΔG values.



Affinity Metrics

- **IC_{50}:** Concentration causing 50% inhibition (most common in screening)
- **Kd (Dissociation constant):** Equilibrium binding constant
- **Ki (Inhibition constant):** Affinity of inhibitor binding
- **ΔG (Binding free energy):** Thermodynamic measure of binding strength

Computational Approaches

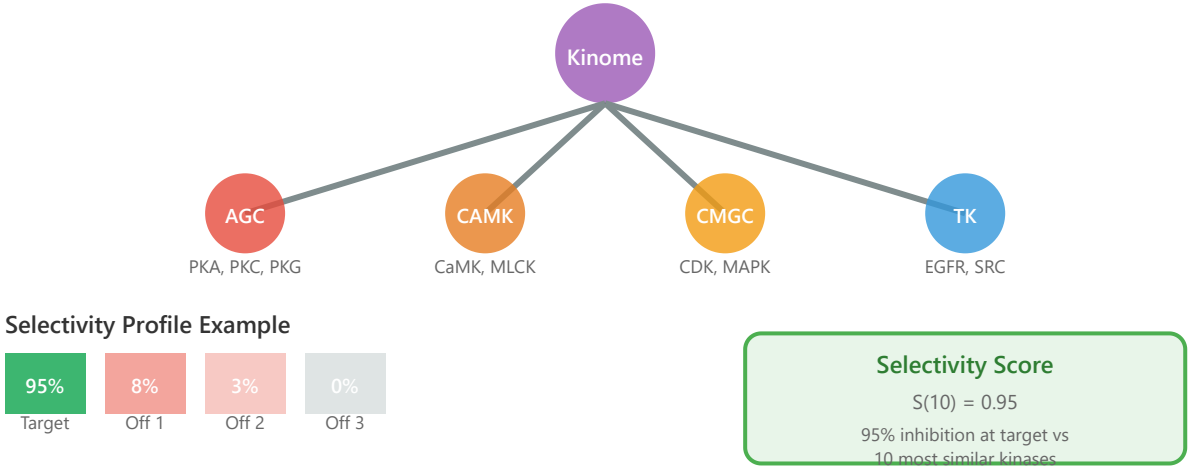
Structure-based: Molecular docking, MD simulations, free energy calculations
Ligand-based: QSAR models, 3D-QSAR, pharmacophore modeling
Machine Learning: Regression models (RF, SVM, DNN) trained on bioactivity databases
Deep Learning: Graph networks, attention mechanisms, transformer models

Challenge: Affinity prediction requires continuous value regression, which is more complex than binary classification. Data sparsity across the full affinity range poses challenges.

Application: Lead optimization - comparing analogs to identify compounds with improved binding affinity while maintaining drug-like properties.

3. Kinome Profiling

Kinome profiling assesses how a compound interacts with the entire kinase family (~518 human kinases). This is critical for understanding selectivity profiles, predicting efficacy, and identifying potential off-target effects of kinase inhibitors.



Key Aspects

- **Selectivity index:** Ratio of activity against target vs off-targets
- **Panel screening:** Testing against representative kinase panels (e.g., 50-400 kinases)
- **Kinase phylogenetic tree:** Understanding relationships helps predict cross-reactivity
- **Binding mode analysis:** Type I, II, III, IV inhibitors show different selectivity patterns

Profiling Technologies

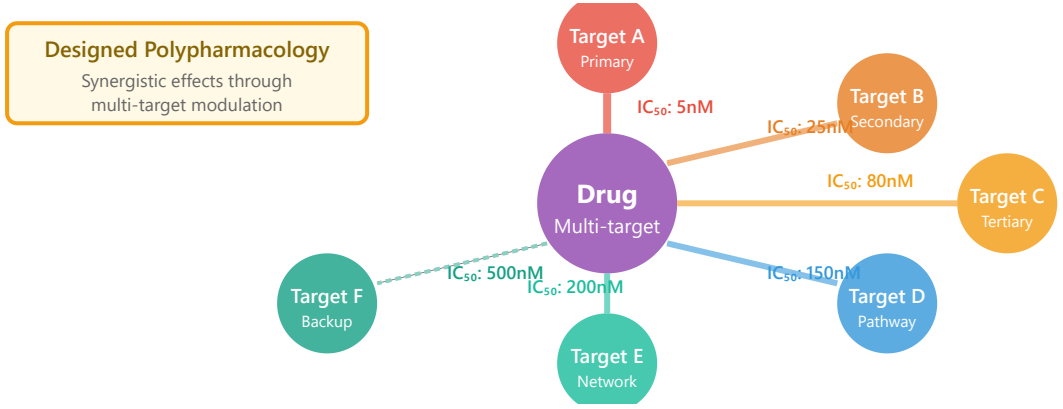
Experimental: KINOMEscan, Reaction Biology panels, NanoBRET
Computational: Structure-based virtual screening across kinome

ML approaches: Multi-task learning, transfer learning, proteochemometric modeling
Visualization: Kinome tree diagrams, phylogenetic heat maps

Clinical Relevance: Imatinib (Gleevec) was designed to inhibit BCR-ABL but also shows activity against c-KIT and PDGFR. This off-target profile contributes to its efficacy in GIST (gastrointestinal stromal tumors) but also causes side effects.

4. Polypharmacology

Polypharmacology refers to the intentional or unintentional binding of a drug to multiple therapeutic targets. Modern drug discovery increasingly embraces designed polypharmacology to achieve enhanced efficacy through multi-target modulation.



Types and Strategies

- **Designed polypharmacology:** Intentional multi-target binding for synergistic effects
- **Network pharmacology:** Targeting multiple nodes in disease pathways
- **Activity cliff analysis:** Small structural changes causing dramatic activity shifts
- **Scaffold hopping:** Finding chemotypes that maintain multi-target profiles

Computational Prediction

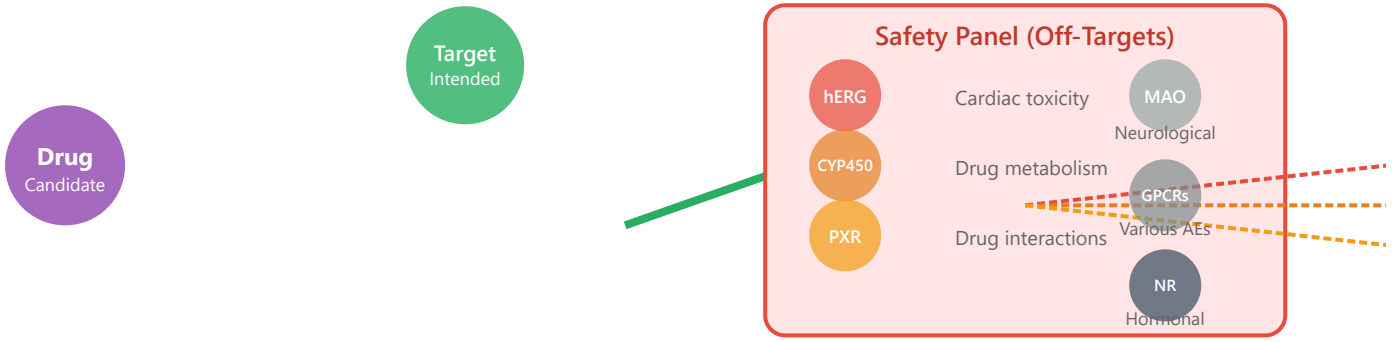
Multi-task learning: Simultaneous prediction across multiple targets
Network analysis: Protein-protein interaction networks and pathway modeling
Similarity-based: Chemical similarity to known polypharmacological agents
De novo design: Generative models for multi-target optimization

Success Story: Sunitinib inhibits multiple RTKs (VEGFR, PDGFR, c-KIT, FLT3) providing broad anti-angiogenic and anti-tumor activity in renal cell carcinoma.

Challenge: Balancing desired polypharmacology with unwanted promiscuity. Requires careful optimization of the activity profile across the target panel.

5. Off-Target Prediction

Off-target prediction identifies unintended drug-protein interactions that may cause adverse effects or toxicity. This is critical for safety assessment and early identification of potential liabilities in drug development.



Critical Safety Targets

- **hERG channel:** Cardiac toxicity (QT prolongation) - most common cause of drug withdrawal
- **CYP450 enzymes:** Drug-drug interactions and altered metabolism
- **Nuclear receptors:** PXR, CAR - hepatotoxicity and drug interactions
- **Neurotransmitter receptors:** 5-HT, dopamine, histamine - CNS side effects
- **Ion channels:** Nav, Cav - cardiac and neurological toxicity

Prediction Strategies

Target-based screening: Virtual screening against safety panels
Ligand-based models: QSAR for specific off-targets (e.g., hERG prediction)
Similarity searching: Structural alerts and known toxicophores

AI/ML approaches: Multi-task deep learning, graph neural networks
Inverse docking: Screening compound against protein structure library

Risk Assessment: Early off-target prediction can save millions in development costs. A compound with predicted strong hERG binding (IC_{50} < 1μM) should be deprioritized or modified before expensive in vivo studies.

Regulatory Impact: FDA and EMA require comprehensive off-target assessment. Computational predictions complement experimental safety pharmacology panels (e.g., SafetyScreen44).

Integrated Approach: Modern drug discovery combines all five DTI prediction approaches - starting with binary classification and affinity prediction for hit identification, followed by kinome profiling and polypharmacology assessment for optimization, and rigorous off-target prediction for safety evaluation throughout the pipeline.