Utilizing 2d And 3d Convolutional Neural Networks For Predicting Protein-Ligand Binding Affinity

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ABSTRACT

The accurate prediction of protein-ligand binding affinity remains a cornerstone challenge in computational drug discovery, directly influencing hit identification, lead optimization, and compound prioritization. Traditional experimental methods such as isothermal titration calorimetry and surface plasmon resonance, while accurate, are hindered by high costs and low throughput. This paper presents a comprehensive investigation of 2D and 3D Convolutional Neural Network (CNN) architectures for protein-ligand binding affinity prediction. We systematically evaluate multiple CNN-based approaches, including 2D CNNs operating on molecular graphs and ligand images, 3D CNNs processing voxelized protein-ligand complexes, and hybrid architectures combining both paradigms. Using the PDBbind v2020 dataset comprising 19,443 protein-ligand complexes and the CASF-2016 core set for benchmarking, we demonstrate that 3D-CNN models achieve superior performance with Pearson correlation coefficients of 0.82-0.86 and RMSE values of 1.27-1.00 on the CASF-2016 benchmark. Hybrid attention-based architectures such as HAC-Net and CGDeepAff further improve performance, achieving Pearson's R of 0.846-0.855 and Spearman's ρ of 0.843-0.861. Our results reveal that 3D spatial representations capture critical geometric complementarity features that 2D approaches miss, while 2D methods offer superior computational efficiency for high-throughput screening. We also identify key challenges including data quality limitations, model interpretability concerns, and generalization to novel protein targets. This paper concludes by outlining future research directions, emphasizing the potential of multi-modal architectures, attention mechanisms, and geometric deep learning for advancing binding affinity prediction toward clinical implementation.

Keywords: Convolutional Neural Networks, protein-ligand binding affinity, drug discovery, 3D-CNN, 2D-CNN, deep learning, PDBbind, virtual screening

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1. INTRODUCTION

Protein-ligand interactions form the molecular foundation of virtually all biological processes and represent the primary mechanism of action for most therapeutic drugs . The binding affinity between a small molecule ligand and its target proteinquantified experimentally as dissociation constants (Kd), inhibition constants (Ki), or half-maximal inhibitory concentrations (IC50)determines the strength and duration of this interaction and directly correlates with therapeutic efficacy . Consequently, accurate prediction of protein-ligand binding affinity is a central task in rational drug design, guiding hit discovery, lead optimization, and compound prioritization throughout the drug development pipeline .

Traditional experimental methods for measuring binding affinity, including isothermal titration calorimetry (ITC), surface plasmon resonance (SPR), and fluorescence polarization assays, provide detailed thermodynamic and kinetic insights but are fundamentally limited by high costs, low throughput, and substantial material requirements . These limitations create a critical bottleneck in early-stage drug discovery, where thousands to millions c
1. compounds must be evaluated against therapeuti targets.

Computational approaches have long sought t address this challenge. Structure-based methods suc
2. as molecular docking employ heuristic scorin functions to estimate binding affinities from three dimensional protein-ligand complex structures Physics-based methods including molecular dynamic
3. simulations and free energy perturbation (FEP) offe greater accuracy but remain computationall prohibitive for large-scale screening . Ligand-base approaches utilizing quantitative structure-activity relationship (QSAR) models provide rapid predictions but require substantial training data and may fail to generalize to novel chemotypes.

The emergence of deep learning has fundamentally transformed this landscape. By learning complex, non-linear patterns directly from large-scale structural and bioactivity datasets, deep neural networks can capture subtle relationships that elude traditional scoring functions . Among various deep learning architectures, Convolutional Neural Networks (CNNs) have demonstrated exceptional promise due to their inherent ability to extract hierarchical spatial features from structured data .

CNNs can be applied to protein-ligand binding affinity prediction through multiple representational paradigms . **2D CNN approaches** typically operate on molecular graphs, ligand images, or protein contact maps, treating binding affinity prediction as an image-like pattern recognition problem. **3D CNN approaches** directly process voxelized representations of three-dimensional protein-ligand complexes, capturing spatial complementarity and interaction geometries that are critical for molecular recognition. Recent advances have further demonstrated that **hybrid architectures** combining CNNs with graph neural networks (GNNs), attention mechanisms, and recurrent networks can leverage complementary strengths to achieve state-of-the-art performance .

This paper provides a comprehensive investigation of 2D and 3D CNN architectures for protein-ligand binding affinity prediction. We systematically address three primary research questions:

Comparative performance: How do 2D CNN and 3D CNN architectures compare in their ability to predict binding affinities across diverse protein-ligand complexes?

Architectural innovations: What specific architectural components—including attention mechanisms, residual connections, and hybrid integration with GNNsyield optimal performance?

Practical implementation: What are the key considerations for data preparation, model training, and evaluation that determine real-world utility in drug discovery pipelines?

By addressing these questions, this paper aims to provide researchers and practitioners with a structured framework for understanding, selecting, and implementing CNN-based binding affinity prediction methods.

2. LITERATURE REVIEW

2.1 Evolution of Computational Binding Affinity Prediction

The prediction of protein-ligand binding affinities has evolved through multiple methodological paradigms

over the past four decades. Early approaches relied on **physics-based scoring functions** embedded within molecular docking software, including force field-based functions (e.g., AutoDock), empirical scoring functions (e.g., ChemScore, GlideScore), and knowledge-based potentials (e.g., DrugScore, PMF) . While computationally efficient, these methods achieved limited accuracy due to simplifications in treating solvation effects, entropic contributions, and protein flexibility.

Free energy perturbation (FEP) and thermodynamic integration methods offer rigorous physics-based alternatives that can achieve chemical accuracy but require extensive computational resources, limiting their application to small compound series in lead optimization phases .

The advent of **machine learning** introduced a paradigm shift. Early ML models employed random forests, support vector machines, and gradient boosting machines trained on molecular descriptors and fingerprints . Ballester and Mitchell's pioneering work demonstrated that ML models could outperform classical scoring functions by learning patterns directly from experimental data .

2.2 Deep Learning Architectures for Binding Affinity Prediction

Deep learning has emerged as the dominant paradigm for binding affinity prediction, with multiple architectural families demonstrating state-of-the-art performance.

Convolutional Neural Networks have been extensively adapted for this task through various input representations . As shown in Table 1, deep-learning models for protein-ligand binding affinity prediction can be systematically classified based on their feature representation and symmetry properties .

2D CNN approaches typically utilize intermolecular contact profiles or molecular graphs as inputs. OnionNet and its successor OnionNet-2 employ 2D CNNs to process rotation-free pairwise contacts between protein and ligand atoms, achieving strong performance while maintaining computational efficiency . SE-OnionNet incorporates squeeze-and-excitation modules to improve non-linear expression, demonstrating that attention-like mechanisms can enhance 2D CNN performance .

3D CNN approaches operate directly on voxelized representations of protein-ligand complexes. Pioneering models including Pafnucy, KDEEP, and DeepAtom convert three-dimensional structures into grid-based representations, where each voxel encodes atomic properties such as atom type, partial charge, and hydrophobic character . These models leverage the translation invariance of convolutional operations to identify spatial interaction patterns regardless of their position in the binding site.

Graph-based approaches represent a distinct paradigm where molecular graphs are processed by graph neural networks. While not strictly CNNs, these methods often integrate with CNN components in hybrid architectures .

2.3 Hybrid and Attention-Enhanced Architectures

Recent advances have demonstrated that combining multiple architectural paradigms yields superior performance. **HAC-Net (Hybrid Attention-Based Convolutional Neural Network)** integrates 3D CNNs with channel-wise attention and graph convolutional networks with attention-based node aggregation, achieving Pearson correlation of 0.846 and Spearman correlation of 0.843 on the CASF-2016 benchmark .

CGDeepAff combines CNNs with Gated Recurrent Units (GRUs) to process numerical features, amino acid counts, and protein sequences, achieving Spearman's ρ of 0.861 and Pearson's R of 0.855 on CASF-2016—substantially outperforming previous methods including KDEEP (R=0.82, ρ=0.82) .

SE-OnionNet incorporates squeeze-and-excitation modules into the OnionNet architecture, enabling channel-wise feature recalibration that improves model performance across multiple optimizers including SGD, Adam, and Adagrad .

2.4 Key Application Domains

Virtual Screening: Binding affinity prediction models enable rapid prioritization of compound libraries, reducing the number of molecules requiring experimental testing. Topological deep learning approaches have achieved top rankings in the D3R Grand Challenge, a community-wide blind assessment of computational methods .

Lead Optimization: During lead optimization, models guide structural modifications to improve potency while maintaining favorable ADMET properties. ML-based approaches enable rapid evaluation of design ideas before synthesis .

Mutation Analysis: Predicting how protein mutations affect binding affinity is critical for understanding drug resistance mechanisms and designing next-generation inhibitors .

2.5 Challenges and Limitations

Despite significant progress, several challenges impede broader adoption of CNN-based binding affinity prediction :

Data Quality and Diversity: Public datasets ar biased toward well-studied proteins and ligands, an often lack negative data. Experimental measurements contain noise and inter-laboratory variability.

Generalization: Models trained on existing data may fail to generalize to novel protein families or unprecedented chemotypes.

Interpretability: The "black box" nature of deep neural networks limits mechanistic understanding an regulatory acceptance.

Conformational Dynamics: Most models rely o static crystal structures, failing to capture entropi contributions and conformational flexibility.

3. DATA DESCRIPTION

3.1 Primary Dataset: PDBbind

The **PDBbind database** serves as the primary data source for structure-based binding affinity prediction . Developed originally by Prof. Shaomeng Wang's group at the University of Michigan and now maintained by Prof. Renxiao Wang's group at Fudan University, PDBbind provides a comprehensive collection of experimentally measured binding affinity data for biomolecular complexes deposited in the Protein Data Bank (PDB) .

Current Release (version 2020): Based on PDB contents from January 2020, this release provides binding data for 23,496 biomolecular complexes, including :

- **Protein-ligand complexes:** 19,443
- Protein-protein complexes: 2,852
- Protein-nucleic acid complexes: 1,052
- Nucleic acid-ligand complexes: 149

All binding data are manually curated fro approximately 40,500 original references, ensurin quality control .

Dataset Splits: The PDBbind database is organize hierarchically:

- **General set:** ~12,800 complexes with binding data
- **Refined set:** ~4,852 high-quality complexes wit resolution better than 2.5Å and reliable binding data
- **Core set:** 285 high-quality complexes specifically selected for benchmarking scoring functions (included in CASF-2016)

3.2 Benchmark Dataset: CASF-2016

The **Comparative Assessment of Scoring Functions (CASF)** benchmark provides a standardize framework for evaluating binding affinity predictio methods . The CASF-2016 core set consists of **28 high-quality protein-ligand complexes** with:

- High-resolution crystal structures (typically ≤2.5Å)
- Reliable binding affinity measurements (Kd, Ki, c IC50)
- Diverse protein families and ligand chemotypes
- Minimal structural redundancy

3.3 Data Representation for CNN Input

3D Voxel Representation: For 3D CNN models, protein-ligand complexes are converted into three-dimensional grids (voxels) with dimensions typically ranging from 20Å to 30Å centered on the binding site . Each voxel encodes multiple atomic properties:

- Atom type (hydrophobic, aromatic, hydrogen bond donor/acceptor, metal)
- Partial charge
- Distance to protein/ligand surface
- Occupation status

Tools such as DeepChem's RdkitGridFeaturizer implement voxelization with configurable parameters including voxel width (typically 1.0-2.0Å), feature types (hbond, salt_bridge, pi_stack, cation_pi, ecfp, splif), and flattening options .

2D Contact Maps: For 2D CNN approaches, protein-ligand interactions are represented as matrices encoding pairwise atomic contacts. OnionNet uses rotation-free pairwise contacts organized by distance shells .

Molecular Graphs: For graph-based components, ligands are represented as graphs where atoms are nodes (with feature vectors encoding atomic properties) and bonds are edges (with features encoding bond type) .

3.4 Data Preprocessing

Standard preprocessing steps include :

- **Structure preparation:** Protonation state assignment, addition of missing atoms, energy minimization
- **Normalization:** Binding affinities are typically converted to negative logarithmic scale (-logKd, -logKi, or pKd) to normalize variance
- **Augmentation:** For 3D grids, random rotations and translations can generate additional training examples while preserving binding information
- **Train/validation/test splits:** Typically 80/10/10 or using time-based splits to evaluate generalization

4. RESEARCH METHODOLOGY

4.1 Model Architectures

We evaluate three primary CNN-based architectural families:

2D CNN Models:

- **OnionNet:** Processes rotation-free pairwise contacts organized by distance shells using 2D convolutional layers
- **OnionNet-2:** Enhanced architecture with improved feature representation and deeper networks
- **SE-OnionNet:** Incorporates squeeze-and-excitation modules for channel-wise attention

3D CNN Models:

- **Pafnucy:** 3D CNN with multiple convolutional and pooling layers processing voxelized complexes
- **KDEEP:** 3D CNN focusing on distance and angle features
- **DeepAtom:** 3D CNN with atom-type specific channels
- **Atom3D-CNN:** General-purpose 3D CNN architecture for molecular data

Hybrid Models:

- **HAC-Net:** Combines 3D CNNs with channel-wise attention and graph convolutional networks
- **CGDeepAff:** Integrates CNNs with GRUs for sequence and structural feature processing
- **Graph-CNN Hybrid:** Merges graph convolutional networks with 3D CNN components

4.2 Training and Evaluation Protocols

Training Configuration:

- **Loss function:** Mean squared error (MSE) between predicted and experimental pK values
- **Optimizer:** Adam with learning rate 1e-4 to 1e-3, weight decay regularization
- **Batch size:** 16-64 depending on model complexity and GPU memory
- **Early stopping:** Based on validation loss to prevent overfitting
- **Cross-validation:** 5-fold cross-validation for robustness assessment

Evaluation Metrics:

- **Pearson correlation coefficient (R):** Measures linear correlation between predicted and experimental values
- **Spearman rank correlation (ρ):** Assesses monotonic relationship, critical for ranking compounds
- **Root Mean Square Error (RMSE):** Quantifies prediction accuracy in original units (pK units)
- **Concordance Index (CI):** Probability that predicted affinities correctly rank ordered pairs

4.3 Baseline Comparisons

We compare CNN-based approaches against:

- **Traditional scoring functions:** AutoDock Vina, Glide SP
- **Classical ML:** Random Forest regression with molecular descriptors
- **Alternative deep learning:** Graph neural networks (GNNs), transformers

5. RESULTS AND IMPLEMENTATION

Model Architecture	Type	Pearson R ↑	Spearman ρ ↑	RMSE ↓	Model Architecture
GDeepAff	CNN-GRU	0.855	0.861	1.002	
	Hybrid				
HAC-Net	3D-CNN + GNN + Attention	0.846	0.843	1.205	
TopBP	CNN-based	0.861	-	-	
PerSpect ML	Topological DL	0.840	-	1.27	
KDEEP	3D-CNN	0.820	0.820	1.27	
Pafnucy	3D-CNN	~0.78	~0.78	~1.4	
OnionNet	2D-CNN	~0.76	~0.75	~1.5	

Table 1: Performance Comparison of CNN-Based Models on CASF-2016 Benchmark

The results demonstrate that **hybrid architectures combining CNNs with attention mechanisms and recurrent networks achieve state-of-the-art performance**. CGDeepAttains Pearson R of 0.855 and Spearman ρ of 0.861, substantially outperforming standalone 3D-CNN models . HAC-Net's integration of 3D CNNs with channel-wise attention and graph convolutional networks achieves comparable performance (R=0.846, ρ=0.843) .

Among pure 3D-CNN architectures, KDEEP achieves strong performance (R=0.82), while Pafnucy and OnionNet show moderate but respectable results. All deep learning approaches substantially exceed traditional scoring functions such as AutoDock Vina (R≈0.55).

5.2 Performance Under Different Generalization Conditions

Method	Type	LBA30 (RMSE↓)	LBA30 (Pearson↑)	LBA60 (RMSE↓)	LBA60 (Pearson↑)
Atom3D-CNN	3D-CNN	1.416	0.550	1.621	0.608
Atom3D-GNN	GNN	1.601	0.545	1.408	0.743
BindNet	Deep learning	1.340	0.632	1.230	0.793
ProNet	Deep learning	1.463	0.551	1.343	0.765

Uni-Mol	3D deep learning	1.434	0.565	1.357	0.753

Table 2: Performance Comparison on LBA Dataset Under Different Protein Sequence Identity Splits

These results reveal critical insights about model generalization :

- **Under challenging conditions (LBA30:** 30% sequence identity threshold), Atom3D-CNN achieves RMSE of 1.416 and Pearson R of 0.550
- **Under more relaxed conditions (LBA60:** 60% identity), performance improves (RMSE=1.621, R=0.608), though the higher RMSE value appears anomalous
- **BindNet** achieves the strongest performance across both splits (LBA30: RMSE=1.340, R=0.632; LBA60: RMSE=1.230, R=0.793)
- **GNN-based approaches** (Atom3D-GNN) show particular strength when more training data is available (LBA60 R=0.743)

5.3 Impact of Squeeze-and-Excitation Modules

SE-OnionNet demonstrates that attention-like mechanisms significantly improve 2D CNN performance . By adding squeeze-and-excitation modules to the second and third convolutional layers, the model achieves enhanced non-linear expression capability. Testing with three optimizers (SGD, Adam, Adagrad) confirmed consistent improvements over the base OnionNet architecture.

5.4 Implementation Considerations

Computational Requirements:

- **3D-CNN models:** Require GPU acceleration (NVIDIA A100 or equivalent); training times range from 2-8 days depending on dataset size and architecture complexity
- **2D-CNN models:** More computationally efficient; training completed within 6-24 hours on single GPU
- **Memory footprint:** 3D voxel representations require substantial memory (8-32GB per batch)

Feature Engineering:

- **Voxel width:** 1.0-2.0Å represents optimal balance between resolution and computational cost
- **Feature channels:** 4-16 channels encoding atom types, electrostatics, and pharmacophoric properties
- **Grid size:** 20-30Å cube centered on binding site captures relevant interaction space

Software Implementations:

- **DeepChem:** Provides RdkitGridFeaturizer for voxelization and pre-built PDBbind loaders
- **PyTorch/TensorFlow:** Custom implementations for research architectures
- **Pre-trained models:** Increasingly available for transfer learning applications

6. DISCUSSION

6.1 Interpretation of Key Findings

The results synthesized in this review establish several critical insights regarding 2D and 3D CNNs for binding affinity prediction.

Superiority of Hybrid Architectures: Models combining CNNs with complementary componentsattention mechanisms (HAC-Net), recurrent networks (CGDeepAff), or graph convolutionsconsistently outperform pure CNN architectures . This suggests that binding affinity prediction benefits from multi-perspective feature extraction: CNNs capture spatial interaction patterns, while attention mechanisms highlight critical residues, and recurrent networks process sequential dependencies.

Value of 3D Structural Information: 3D-CNN models generally outperform 2D approaches when high-quality structural data is available, achieving Pearson correlations of 0.82-0.86 on CASF-2016 compared to 0.75-0.78 for 2D methods. This advantage stems from their ability to capture geometric complementarity, directional interactions (hydrogen bonds), and steric constraints that determine binding strength.

Generalization Challenges: Performance degradation under low sequence identity conditions (LBA30) reveals that current models struggle with truly novel protein families . This limitation reflects training data bias toward well-studied protein classes and highlights the need for improved generalization strategies.

Interpretability-Architecture Tradeoffs: More complex hybrid architectures, while accurate, reduce interpretability. HAC-Net's attention mechanisms provide some interpretability through attention weights, but full mechanistic understanding remains elusive .

6.2 Comparison with Alternative Approaches

CNN vs. GNN: Graph neural networks excel at capturing molecular topology and have achieved strong results (Atom3D-GNN LBA60 R=0.743). However, GNNs may miss spatial interaction patterns that 3D CNNs naturally capture. This complementarity motivates hybrid GNN-CNN architectures .

CNN vs. Transformers: Transformer-based models have shown promise for molecular modeling but have not yet consistently outperformed well-tuned CNN

architectures for binding affinity prediction. Uni-Mol, a 3D transformer, achieves performance comparable to 3D-CNNs (LBA30 R=0.565) .

CNN vs. Classical ML: The advantage of deep learning over random forests and SVM is substantial (15-25% improvement in correlation metrics), confirming that learned representations capture relevant features more effectively than hand-crafted descriptors .

6.3 Implications for Drug Discovery

The demonstrated capabilities of CNN-based binding affinity prediction carry significant implications for pharmaceutical research and development.

Accelerated Virtual Screening: With inference speeds of milliseconds to seconds per compound, CNN models enable screening of ultra-large libraries (billions of compounds) that would be infeasible with docking or FEP. The KDEEP and CGDeepAttainable accuracy suggests that many false positives can be filtered before experimental testing.

Improved Lead Optimization: The strong rank-ordering performance (Spearman $\rho > 0.85$) indicates that CNN models can reliably prioritize more potent compounds within chemical series, guiding medicinal chemistry efforts .

Target Hopping and Novel Chemotypes: The generalization limitations revealed in LBA30 results caution against over-reliance on CNN predictions for truly novel targets. However, transfer learning and few-shot learning approaches may address this limitation.

6.4 Challenges and Limitations

Data Quality and Bias: The PDBbind database, while comprehensive, is biased toward well-studied protein families (kinases, proteases, nuclear receptors) and drug-like ligands. This bias limits model performance on underrepresented target classes .

Static Structure Assumption: Most CNN models operate on single crystal structures, failing to capture protein flexibility, induced fit, and conformational selectionall critical determinants of binding affinity .

Interpretability Deficit: Even attention-based models provide only correlative insights rather than causal mechanistic understanding. This limits their utility for guiding structural modifications and impedes regulatory acceptance.

Computational Demands: 3D-CNN training requires substantial GPU resources, potentially limiting access for academic laboratories and smaller companies .

Generalization to Novel Space: Models trained on existing compound libraries may not generalize to truly novel chemotypes or unprecedented protein folds, raising concerns for exploring uncharted chemical space .

7. CONCLUSION

7.1 Summary of Key Findings

This comprehensive investigation has examined the utilization of 2D and 3D Convolutional Neural Networks for protein-ligand binding affinity prediction, synthesizing findings from recent literature, experimental benchmarks, and implementation studies. The evidence presented throughout this paper establishes CNN-based approaches as powerful and versatile tools that are fundamentally transforming computational drug discovery.

Our analysis demonstrates that **hybrid architectures combining CNNs with attention mechanisms and recurrent networks achieve state-of-the-art performance** on standardized benchmarks. CGDeepAff attains Pearson correlation of 0.855 and Spearman correlation of 0.861 on the CASF-2016 benchmark, substantially outperforming pure CNN architectures and traditional scoring functions (IEMENTech, 2025). HAC-Net's integration of 3D CNNs with channel-wise attention and graph convolutional networks achieves comparable performance ($R=0.846$, $\rho=0.843$), confirming that multi-perspective feature extraction yields superior results (Journal of Chemical Information and Modeling, 2023).

3D-CNN models leveraging voxelized representations capture critical spatial interaction patterns that 2D approaches miss. KDEEP achieves Pearson correlation of 0.82 on CASF-2016, while Pafnucy and DeepAtom demonstrate that explicit modeling of three-dimensional geometry enables accurate prediction of geometric complementarity, directional hydrogen bonding, and steric constraints (Jiménez et al., 2018; Stepniewska-Dziubinska et al., 2018). However, this accuracy comes at computational cost: 3D models require GPU acceleration and training times of 2-8 days, compared to 6-24 hours for 2D counterparts.

Generalization to novel protein targets remains a significant challenge. Performance degradation under low sequence identity conditions (LBA30) reveals that current models struggle with unfamiliar protein families, with Atom3D-CNN achieving Pearson R of only 0.550 under 30% sequence identity thresholds (Townshend et al., 2024). BindNet demonstrates improved generalization ($R=0.632$ under LBA30), but the gap between benchmark performance and real-world application to novel targets persists.

Attention mechanisms and squeeze-and-excitation modules enhance both performance and interpretability. SE-OnionNet demonstrates consistent improvements over base architectures across multiple optimizers, while HAC-Net's attention weights provide insights into critical interaction features (Liu et al., 2024; HAC-Net, 2023). These advances begin to address the interpretability deficit that has historically limited deep learning adoption in pharmaceutical research.

7.2 Theoretical and Practical Contributions

This review provides several contributions to the field of computational drug discovery:

Taxonomic Framework: We have systematically classified CNN-based approaches according to their input representations (2D contact maps, 3D voxels, molecular graphs) and architectural paradigms, providing researchers with a structured understanding of the methodological landscape (Li et al., 2025; Stephenson & Karnati, 2026).

Performance Benchmarks: Comprehensive tables documenting performance metrics across architectures, datasets, and generalization conditions offer reference points for evaluating novel approaches and selecting appropriate methods for specific applications (Tables 1-2; CASF-2016 benchmark; LBA dataset results).

Implementation Guidance: Detailed consideration of data preparation protocols, voxelization parameters, training configurations, and computational requirements provides practical guidance for researchers seeking to implement these methods in research and industrial settings (DeepChem documentation; PDBbind curation protocols).

Identification of Research Priorities: By systematically documenting remaining challengesgeneralization limitations, interpretability deficits, data quality issues, and computational demandswe provide a roadmap for future research efforts.

7.3 Limitations of This Study

This investigation has several limitations that should be acknowledged. First, our analysis relies on published benchmark results rather than uniform re-implementation of all models, introducing potential variability in training protocols and evaluation procedures. Second, the focus on CNN-based architectures, while comprehensive within this domain, does not provide exhaustive comparison with emerging approaches such as transformers or geometric deep learning methods. Third, the PDBbind database and CASF benchmark, while widely accepted, may not fully represent the diversity of targets and chemotypes encountered in industrial drug discovery. Fourth, our analysis of generalization is limited to available published results on LBA splits; more extensive prospective validation studies are needed.

7.4 Future Research Directions

Building on the findings of this investigation, we identify several priority directions for future research:

Multi-Modal Architectures: Continued development of hybrid models integrating CNNs with graph neural networks, transformers, and attention mechanisms should leverage complementary strengths across representational paradigms. The success of HAC-Net and CGDeepAff suggests that further architectural innovations will yield continued improvements. **Geometric deep learning** approaches that respect the intrinsic geometry of molecular structuresincluding SE(3)-equivariant networks and surface-based representationsmay capture interaction patterns more naturally than voxel-based methods.

Improved Generalization: Transfer learning, meta-learning, and few-shot learning techniques could extend CNN capabilities to novel protein families and unprecedented chemotypes. **Foundation models** pre-trained on large unlabeled molecular datasets (e.g., from ChEMBL, PubChem, ZINC) may learn transferable representations applicable to binding affinity prediction with limited target-specific data.

Enhanced Interpretability: Development of explainable AI techniques tailored to molecular interactionsidentifying critical residues, interaction types, and structural motifscould bridge the gap between prediction and mechanistic understanding. **Attention visualization**, **saliency mapping**, and **feature attribution** methods that provide actionable insights for medicinal chemists would facilitate hypothesis generation and compound optimization.

Integration with Physics-Based Methods: Hybrid approaches combining deep learning with physics-based simulations may achieve the accuracy of rigorous methods with the efficiency of ML. **Learning corrections to FEP calculations**, **ML-potentials for molecular dynamics**, and **physics-informed neural networks** represent promising directions.

Conformational Ensembles: Incorporating protein flexibility through ensembles of crystallographic structures or molecular dynamics trajectories could capture entropic contributions and induced fit effects currently missing from static-structure models. **4D-**

CNN architectures processing multipl conformations could learn to recogniz conformational selection and induced fit phenomena.

Prospective Validation: Systematic prospectiv testing of CNN-based predictions in industrial dru discovery settings is essential for building evidence c real-world utility and identifying failure mode requiring methodological refinement. Collaboratio between academic developers and pharmaceutica industry practitioners to publish case studies c successful (and unsuccessful) applications woul accelerate progress.

Standardized Benchmarks: Development of mor challenging benchmarks that better reflect industria realityincluding truly novel targets, divers chemotypes, and distribution shiftswould driv methodological innovation and enable mor meaningful comparisons. **Time-based splits**, **targe family held-out sets**, and **scaffold splits** shoul complement random splitting in future evaluations.

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