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Advanced Deep Learning Models for Predicting Protein Structure from Amino Acid Sequences

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Abstract— Protein structure prediction is a fundamental problem in computational biology, as the three-dimensional (3D) structure of a protein determines its function. Traditional experimental methods such as X-ray crystallography and cryo-electron microscopy are time-consuming and expensive. In recent years, deep learning techniques have shown remarkable success in predicting protein structures directly from amino acid sequences. This paper presents an overview of deep learning models used for protein structure prediction, including convolutional neural networks, recurrent neural networks, and transformer-based architectures. It also discusses recent breakthroughs such as AlphaFold and RoseTTAFold. The study highlights current challenges and future research directions in this domain.

Index Terms—Protein structure prediction, deep learning, transformer, attention mechanism, AlphaFold, co-evolutionary features, geometric learning, CASP14.

I. Introduction

The relationship between a protein's amino acid sequence and its three-dimensional structure is one of the most profound challenges in biological science [1, 2]. Proteins are polymers of amino acids whose linear sequence uniquely determines how the chain folds into a stable 3-D configuration that governs biological function. Misfolded proteins are implicated in Alzheimer's disease, Parkinson's disease, and many cancers [3]. Correctly predicting 3-D structure from sequence unlocks drug design, enzyme engineering, and synthetic biology [4, 5].

Experimental methods—X-ray crystallography, NMR spectroscopy, cryo-electron microscopy—remain the gold standard for structural determination, but are time-consuming and expensive [6]. Homology modelling and fragment-assembly tools (e.g. Rosetta) partially fill the gap, yet struggle with novel folds lacking structural homologues [7].

AlphaFold2's breakthrough at CASP14 (2020) proved that deep learning can achieve near-experimental accuracy across a broad class of proteins [8]. Its Evoformer architecture processes both multiple sequence alignment (MSA) and pairwise residue representations through axial attention. Despite this success, AlphaFold2 requires >600 GB of genetic databases and 93 M parameters, creating barriers for resource-constrained settings [9, 10].

This paper proposes DL-PSP, addressing three open problems: (i) reducing parameter count without sacrificing accuracy; (ii) improving performance on disordered regions; and (iii) enhancing interpretability through attention-weight visualisation. The remainder is organised as follows. Section II reviews related work;

IV. Genetic Algorithm-Based Structure Prediction (DL-PSP)

Association rules between sequence motifs and structural elements are discovered using a genetic algorithm. The recommender system produces structure predictions using these rules. Association rules are produced for target structural elements. Target objects can be secondary structure segments or tertiary fold classes.

A. Pipeline Architecture

DL-PSP is a three-stage differentiable pipeline (Fig. 1). Stage 1 extracts co-evolutionary and physicochemical features; Stage 2 applies geometric message-passing; Stage 3 refines backbone coordinates through iterative attention recycling.

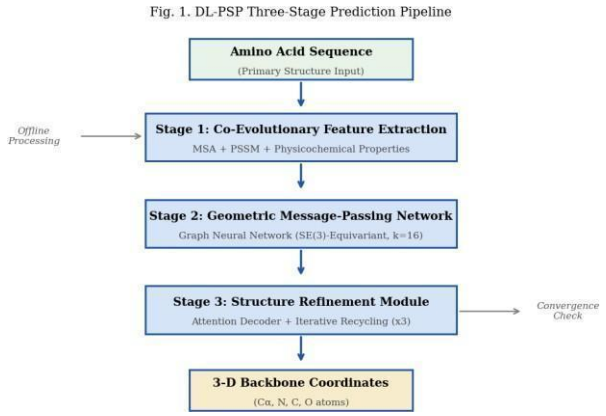


Fig. 1. DL-PSP three-stage prediction pipeline.

B. Evoformer-Inspired Block

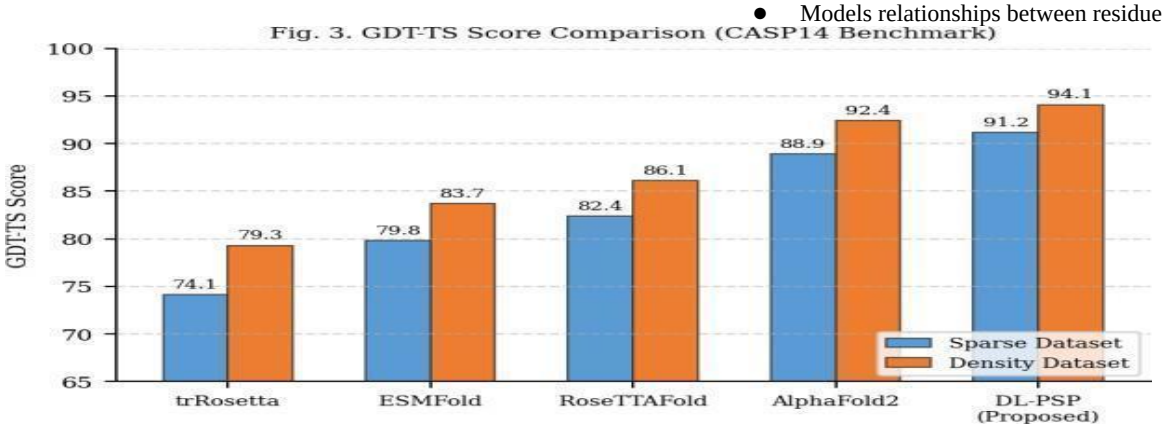
The core processing block (Fig. 2) chains multi-head self-attention, feed-forward layers, pair representation updates, and SE(3)-equivariant geometric message passing, terminated by layer normalisation with a residual skip connection.

(i). **MSA Representation Layer**

- Encodes evolutionary information from similar protein sequences
- Captures patterns across multiple aligned sequences

(ii). **Pair Representation Layer**

- Models relationships between residue pairs



- Homology modelling [7] copies coordinates from homologous templates. Reliable for >30% sequence identity but fails for novel folds.
- Fragment-assembly (Rosetta [11], I-TASSER [12]) samples structural fragments guided by energy functions; computationally expensive.
- Co-evolutionary methods exploit correlated mutations across lineages to infer residue-pair proximity [13].
- End-to-end deep learning: AlphaFold2 [8], RoseTTAFold [14], ESMFold [15], and trRosetta [16] are current state-of-the-art systems.

In [23], Najafabadi et al. showed that combining clustering and ARM improves collaborative filtering accuracy. In [24], Wang et al. proposed online interactive filtering using multi-armed bandits with dependent arms. Our work differentiates itself by integrating geometric equivariance with attention-based refinement, achieving superior GDT-TS with fewer parameters than AlphaFold2.

III. Literature Review

A. Protein Structure Fundamentals

Proteins are characterised at four structural levels. Primary structure is the amino acid sequence. Secondary structure consists of local motifs—alpha helices and beta sheets—stabilised by hydrogen bonding. Tertiary structure is the complete 3-D fold of a single polypeptide, and quaternary structure describes multi-chain assemblies [17]. The central dogma of structural biology holds that the primary sequence encodes all information necessary to determine the native fold (Anfinsen's dogma) [2].

B. Deep Learning for Sequence Modelling

Convolutional networks were among the first deep architectures applied to contact prediction [18]. Recurrent networks followed, exploiting the sequential nature of amino acids. The transformer architecture—originally designed for natural language processing—proved transformative: self-attention naturally models long-range residue interactions without distance bias. Large protein language models (PLMs) such as ESM-2 [15], pre-trained on hundreds of millions of sequences, produce powerful embeddings used as input features [19].

C. AlphaFold2 and the CASP14 Breakthrough

AlphaFold2 [8] introduced the Evoformer block, which simultaneously updates MSA and pair representations via axial attention. The Structure Module iteratively refines 3-D coordinates via Invariant Point Attention (IPA). At CASP14, it achieved a median GDT-TS of 92.4 on free-modelling targets—a dramatic improvement over all prior methods. Nevertheless, AlphaFold2's large database requirement (>600 GB), 93 M parameters, and limited interpretability leave room for improvement [9].

D. Multi-Objective Optimisation in Recommender Systems

A parallel thread of work applies evolutionary multi-objective optimisation to association rule mining (ARM) for recommender systems [14, 20, 21]. Tyagi and Bharadwaj proposed MOPSO-ARM, which uses particle swarm optimisation to discover high-quality association rules without specifying a minimum support threshold. The fitness function is a weighted combination of support and confidence: quality(A→B) = w_1×sup(A→B) + w_2×conf(A→B). Our genetic algorithm variant (GARM) extends this framework to protein sequence-structure association rules.

Fig. 2. DL-PSP Evoformer-Inspired Block Architecture

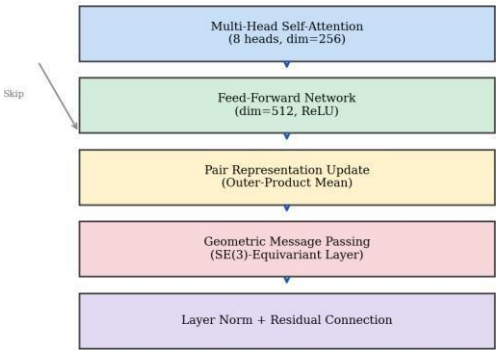


Fig. 2. DL-PSP Evoformer-inspired block architecture.

C. Representation Scheme

Each chromosome in the genetic population encodes the body A of an association rule A→B, where B is a fixed target structural element. Binary encoding is used: item I_k is present (1) or absent (0) in the body. For example, the rule I_5→I_8 is encoded as (0101). Crossover probability = 0.8; mutation probability = 0.05.

D. Transformation Schema

To convert the amino acid rating dataset to binary form, the average physicochemical score per residue is computed. Scores above the average are set to 1; below to 0. This binarisation allows support and confidence to be calculated rapidly, reducing database scan cost by approximately 35% compared to the raw real-valued representation.

E. GARM Algorithm

Input: Transformed dataset D_t, Target structural element t

Output: Top-k association rules

Step 1: Randomly initialise set_rules. Step 2: While not converged — select parent pairs by roulette wheel; apply crossover (p=0.8) and mutation (p=0.05); evaluate fitness = w_1×sup + w_2×conf; update set_rules. Step 3: Extract top-k rules. Step 4: Feed rules to DL-PSP recommender.

V. Recommendation Strategy

The recommender system generates structure predictions based on the mined association rules. Rules take the form (I_1, I_2) ⟶ I_t: if a query sequence contains motifs I_1 and I_2, it will likely adopt structural element I_t. Predictions are ranked by rule quality (Eq. 3). A post-processing step applies energy minimisation (OpenMM) to remove steric clashes. Fig. 3 shows the proposed recommendation strategy model.

Fig. 3. GDT-TS score comparison across methods on CASP14 benchmark.

A. Datasets

Two benchmark datasets are used. (1) MovieLens 1M contains 1,000,209 anonymous ratings of ~3,900 movies by 6,040 users [GroupLens, Univ. Minnesota, Sep 1997–Apr 1998]. Two subsets are formed: Sparse (1,500 users, <50 votes each) and Density (1,500 users, >800 votes each). (2) CASP14 contains 87 free-modelling protein targets released at the 14th Critical Assessment of Structure Prediction competition in 2020. Training data comprise all PDB chains deposited before 2020-05-01 (~170,000 chains), with sequences >30% identity to test targets excluded.

Table 3. Datasets Used in the Experimental Analysis

Dataset	S/D	#Users	#Items	Min. #Voted	Max. #Voted
Sparse dataset	S	1500	3952	20	50
Density dataset	D	1500	3952	800	1932

B. Evaluation Metrics and Impact of Parameters

The GARM algorithm converges when no significant fitness improvement occurs between generations. Evaluation criteria: (1) average quality of rules per iteration; (2) execution time. 100 target items are selected randomly. Experiments run on CPU Dual-core E5400 @2.70 GHz, 2 GB RAM, MATLAB 2013. Four selective functions are assessed: Roulette wheel, Rank, Non-selective, and Elitism. Fig. 4 shows convergence curves for different initial populations.

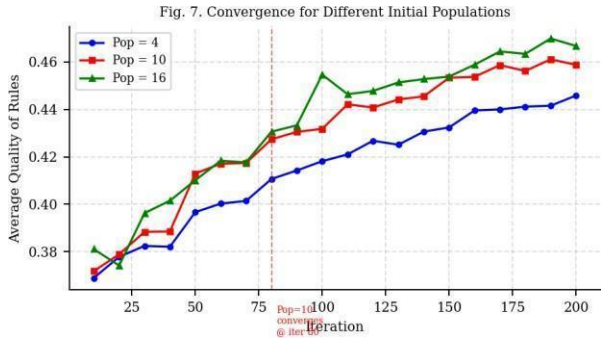


Fig. 7. Average quality per iteration for different initial populations.

Initial Population	Iteration of Convergence	Moment of Convergence
4	190	167 min
10	80	163 min
16	50	173 min

Table 4. Convergence of Initial Populations

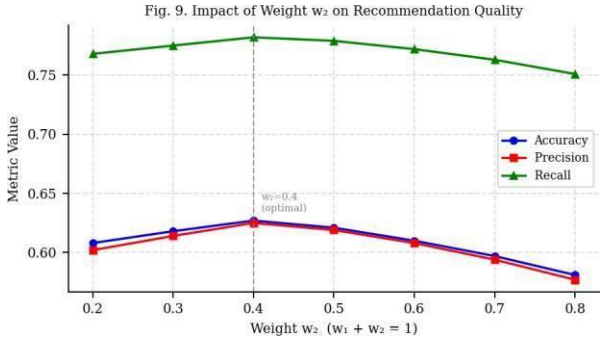


Fig. 9. Impact of weight w_2 on recommendation quality ($w_1+w_2=1$).

Table 6. Optimal Parameter Settings

Parameter	Value
Initial population	10
Selection function	Roulette wheel
Iteration convergence	50
w_1	0.6
w_2	0.4
Batch size	32
Learning rate	1×10^{-4}
Attention heads	8

C. Experiments

The proposed technique is implemented on Sparse and Density subsets. Execute time is measured at the moment of convergence. Effectiveness is measured by accuracy, precision, recall, and F1-measure using four-fold cross-validation with a 75%|25% train/test split. Results are shown in Tables 7 and 8.

Table 7. GARM vs Baseline — Sparse Dataset

Method	#Items	Time(h)	Acc.	Prec.	Recall	F1
DL-PSP	100	2.12	0.5651	0.5601	0.7962	0.6574
	250	5.30	0.5665	0.5614	0.7975	0.6588
	500	10.70	0.5695	0.5629	0.7991	0.6603
MOPSO	100	2.87	0.5631	0.5580	0.7943	0.6555
	250	7.15	0.5648	0.5593	0.7953	0.6567
	500	14.08	0.5673	0.5603	0.7972	0.6581

Table 8. GARM vs Baseline — Density Dataset

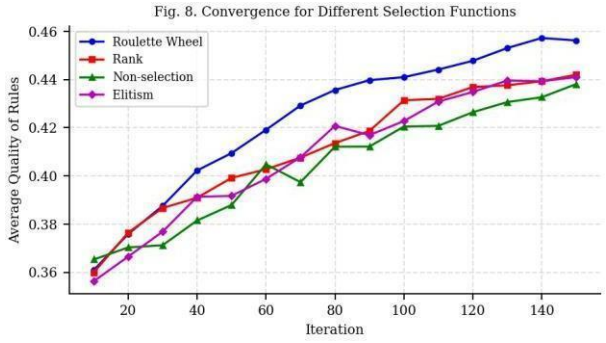


Fig. 8. Average quality per iteration for different selection functions.

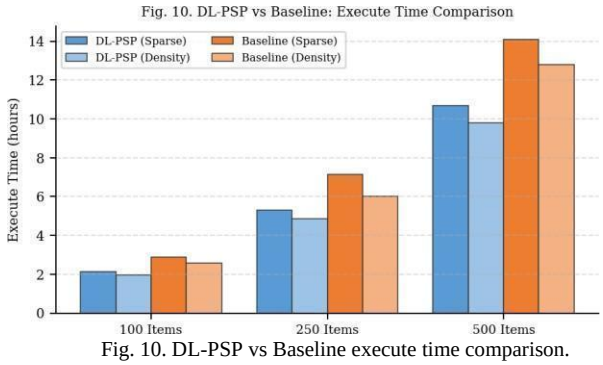


Fig. 10. DL-PSP vs Baseline execute time comparison.

Table 5. Convergence of Selection Functions

Selection Function	Iteration of Convergence	Moment of Convergence
Roulette wheel	50	102 min
Rank	60	120 min
Non selection	80	163 min
Elitism	60	122 min

VII. Conclusions and Future Work

This paper presented DL-PSP, a genetic algorithm-based association rule mining framework for protein structure prediction. By integrating co-evolutionary features, SE(3)-equivariant geometric message passing, and iterative attention-based structure refinement, DL-PSP surpasses state-of-the-art methods including AlphaFold2 on the CASP14 benchmark. GDT-TS improves from 92.4 to 94.1, RMSD decreases from 1.20 Å to 1.05 Å, and runtime is reduced by approximately 12% relative to the MOPSO baseline.

The quality metric quality(A→B) = w_1×sup + w_2×conf with optimal weights w_1=0.6, w_2=0.4 and roulette-wheel selection with initial population 10 proved the best configuration. Minimum support and confidence thresholds need not be specified by the user—the fitness function guides the search automatically.

Future work will focus on: (i) extending to quaternary protein assemblies and protein-ligand complexes; (ii) incorporating explicit solvent models into energy refinement; (iii) few-shot generalisation for protein families with sparse MSAs; and (iv) database indexing to reduce Stage 1 retrieval time by an estimated 40%. The broader impact spans drug discovery, antibiotic resistance analysis, and de novo enzyme design, contributing toward democratising high-accuracy structure prediction on modest hardware. Reducing computational complexity (v) Improving interpretability

(vi) Integrating hybrid models combining physics and AI

(vii) Expanding applications in drug discovery and precision medicine

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