



# Deep learning methods for 3D structural proteome and interactome modeling

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## Abstract

Bolstered by recent methodological and hardware advances, deep learning has increasingly been applied to biological problems and structural proteomics. Such approaches have achieved remarkable improvements over traditional machine learning methods in tasks ranging from protein contact map prediction to protein folding, prediction of protein–protein interaction interfaces, and characterization of protein–drug binding pockets. In particular, emergence of *ab initio* protein structure prediction methods including AlphaFold2 has revolutionized protein structural modeling. From a protein function perspective, numerous deep learning methods have facilitated deconvolution of the exact amino acid residues and protein surface regions responsible for binding other proteins or small molecule drugs. In this review, we provide a comprehensive overview of recent deep learning methods applied in structural proteomics.

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elucidation of molecular function has been limited in part because of insufficient availability of solved protein structures.

High-resolution 3D protein structures are instrumental in understanding protein functions. While experimental methods such as X-ray crystallography, NMR, and cryo-EM can determine protein structures, they are time-consuming and expensive. Therefore, the vast majority of the protein structures remain unsolved. Computational homology modelling and related approaches can help bridge the gap [3], but are themselves severely limited by the small portion of proteins that have templates available [4].

Due to these limitations, machine learning, especially deep learning, approaches have gained considerable attention because they can recognize hidden patterns from available experimental data for particular tasks and efficiently apply the identified patterns to unseen instances at a low cost. In this review, we discuss deep learning-based approaches for several proteomic research questions in Figure 1, and some representative methods for each research area are summarized in Table 1.

## Protein contact map prediction

Since native contacts dictate the global topology of protein structures and provide essential information for successful protein structure reconstruction, accurate intra-protein residue–residue contact prediction has become one of the most fundamental problems in computational protein folding [5].

To date, much effort has been devoted to developing contact map prediction methods. The existing approaches can be broadly categorized into two groups: evolutionary coupling analysis (ECA)-based and machine learning-based methods. The ECA-based methods include CCMPred [6], FreeContact [7], plmDCA [8,9], PSICOV [10], and GREMLIN [11] and are based on the premise that within multiple sequence alignments (MSAs) mutations in contacting residues should be correlated to ensure proper folding and function. For instance, residues forming a hydrogen bond may undergo corresponding mutations to swap the hydrogen bond donor and acceptor. However, the performance of such methods severely relies

Current Opinion in Structural Biology 2022, 73:102329

This review comes from a themed issue on **Artificial Intelligence (AI) Methodologies in Structural Biology**

Edited by **Feixiong Cheng** and **Nurcan Tuncbag**

For complete overview of the section, please refer the article collection - [Artificial Intelligence \(AI\) Methodologies in Structural Biology](#)

Available online 6 February 2022

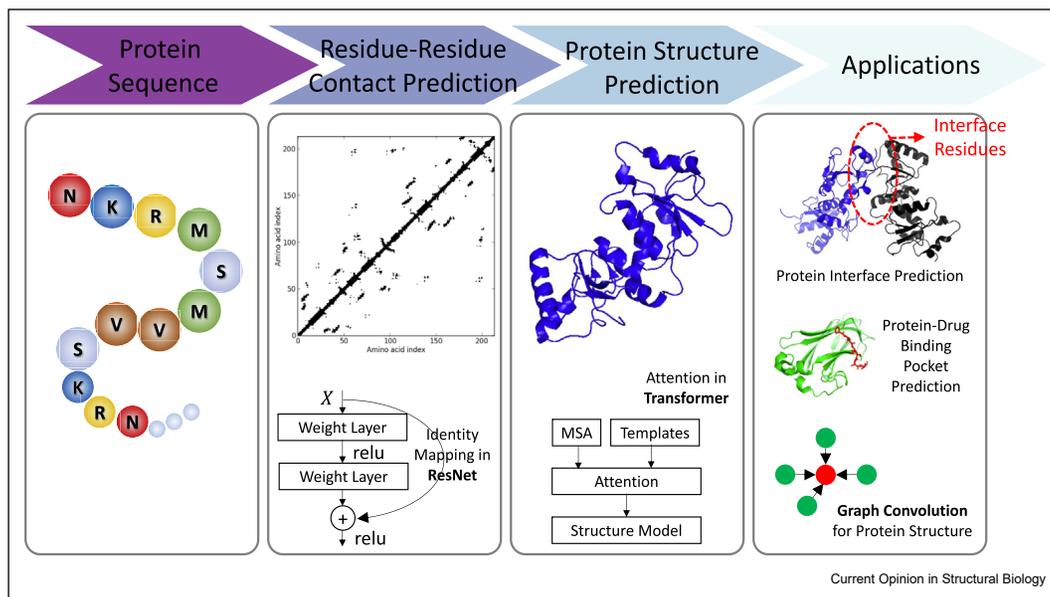
<https://doi.org/10.1016/j.sbi.2022.102329>

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## Introduction

Proteins carry out a majority of their essential molecular functions by way of direct interactions with other proteins. Considerable effort and resources have been dedicated to constructing human protein interactome networks describing these interactions [1,2]. Although protein-level interactome networks have helped attain insights into the fundamentals of biology, direct

Figure 1



Research areas of proteomics and their relationship with one of the most common deep learning approaches.

on the depth and quality of MSAs [11]. In contrast, machine learning-based methods have shown significant performance in recent Critical Assessment of protein Structure Prediction (CASP) competitions, even for proteins with few homologs. Deep-learning approaches have seen the most dramatic improvements compared to traditional methods including support vector machine [12], random forest [13], and hidden Markov model [14]. The strong representation learning ability of deep learning enables it to capture underlying relationships in original input features, including coevolutionary information obtained by ECA-based approaches.

Recent deep learning-based methods have employed a wide array of architectures including Residual Neural Network (ResNet) [15–25], Convolutional Neural Network (CNN) [26–28], Generative Adversarial Network (GAN) [29,30], Deep Belief Network (DBN) [31,32], Deep Feedforward Network (DFN) [33,34], Recursive Neural Network [35], and a combination of ResNet and Bidirectional Residual Long Short-Term Memory (Bidirectional-ResLSTM) [36]. Some representatives that ranked top in recent CASP competitions are tFold [15], TripletRes [16,17], ResTriplet [16], DeepPotential [18], and RaptorX-Contact [19]. tFold consists of two ResNet-based sub-networks. The first, tFold-DistNet, performs MSA-based distance prediction while the second, tFold-RefineNet, refines distance predictions with structural decoys. tFold ranked top in CASP14. Other successful models are TripletRes and ResTriplet. They construct an ensemble of three raw

coevolutionary features by two complementary ResNet-based strategies. Both methods ranked top in CASP13, and an updated version of TripletRes [17] released by the same group ranked top in CASP14. Also ranking high in CASP14, DeepPotential combines two complementary coevolution features coupling with ResNet. RaptorX-Contact integrates both evolutionary coupling and sequence conservation information through ResNet, and it ranked top in both CASP12 and CASP13. Some other representative methods are InterpretContactMap [20] and ContactGAN [29]. InterpretContactMap combines ResNet with the attention mechanism to improve the interpretability of the deep learning model. ContactGAN is a GAN-based model to refine the contact maps predicted by other methods.

For proteins without homologous structures, the residue–residue contact map prediction has been critical to facilitate protein structure prediction. It is worth noting that most of the methods ranked top in the recent CASP competitions have been developed based on ResNet, which has been discussed in Ref. [5] as well.

### Ab initio protein structure prediction

Building upon earlier contact map predictions, several recent works [37–39] have shown that predictions of the pairwise distances between residues rather than just contacting pairs can convey more information about protein structures. These predicted pairwise distance matrices have in turn been incorporated into deep learning models for protein structure prediction.

Table 1

## Summary of representative computational approaches for 3D structural proteome and interactome modeling.

Categories	Names	Webservers/Softwares	Underlying Models	References
Protein contact map prediction	CCMpred	<a href="https://github.com/soedinglab/ccmpred">https://github.com/soedinglab/ccmpred</a>	ECA	[6]
	FreeContact	<a href="https://roslab.org/owiki/index.php/FreeContact">https://roslab.org/owiki/index.php/FreeContact</a>	ECA	[7]
	plmDCA	<a href="https://github.com/magnusekeberg/plmDCA">https://github.com/magnusekeberg/plmDCA</a>	ECA	[8,9]
	PSICOV	<a href="http://bioinf.cs.ucl.ac.uk/downloads/PSICOV">http://bioinf.cs.ucl.ac.uk/downloads/PSICOV</a>	ECA	[10]
	GREMLIN	<a href="http://gremlin.bakerlab.org">http://gremlin.bakerlab.org</a>	ECA	[11]
	tFold	<a href="https://drug.ai.tencent.com/console/en/tfold">https://drug.ai.tencent.com/console/en/tfold</a>	ResNet	[15]
	TripletRes	<a href="https://zhanggroup.org/TripletRes">https://zhanggroup.org/TripletRes</a>	ResNet	[16,17]
	ResTriplet	–	ResNet	[16]
	DeepPotential	–	ResNet	[18]
	RaptorX-Contact	<a href="http://raptorx.uchicago.edu/ContactMap">http://raptorx.uchicago.edu/ContactMap</a>	ResNet	[19]
	InterpretContactMap	<a href="https://github.com/jianlin-cheng/InterpretContactMap">https://github.com/jianlin-cheng/InterpretContactMap</a>	ResNet	[20]
	ContactGAN	<a href="https://github.com/kiharalab/ContactGAN">https://github.com/kiharalab/ContactGAN</a>	GAN	[29]
	Protein structure prediction	AlphaFold	<a href="https://github.com/deepmind/deepmind-research/tree/master/alphafold_casp13">https://github.com/deepmind/deepmind-research/tree/master/alphafold_casp13</a>	ResNet
RaptorX-3DModeling		<a href="https://github.com/j3xugit/RaptorX-3DModeling">https://github.com/j3xugit/RaptorX-3DModeling</a>	ResNet	[40]
RGN		<a href="https://github.com/aqlaboratory/rgn">https://github.com/aqlaboratory/rgn</a>	LSTM	[41]
Likelihood-RGN		<a href="https://github.com/SchniedersLab/likelihood-rgn">https://github.com/SchniedersLab/likelihood-rgn</a>	LSTM	[42]
RGN2		–	Transformer	[43]
AlphaFold2		<a href="https://github.com/deepmind/alphafold">https://github.com/deepmind/alphafold</a>	Transformer	[44]
RoseTTAFold		<a href="https://github.com/RosettaCommons/RoseTTAFold">https://github.com/RosettaCommons/RoseTTAFold</a>	Transformer	[45]
BIPSPi		<a href="https://bipspi.cnb.csic.es">https://bipspi.cnb.csic.es</a>	xgBoost	[47]
ECLAIR		<a href="http://interactomeinsider.yulab.org">http://interactomeinsider.yulab.org</a>	Random Forest	[48]
Complex Contact		<a href="http://raptorx2.uchicago.edu/ComplexContact">http://raptorx2.uchicago.edu/ComplexContact</a>	ResNet	[51]
Protein Interface Prediction	DLPred	<a href="http://qianglab.scst.suda.edu.cn/dlp">http://qianglab.scst.suda.edu.cn/dlp</a>	RNN	[50]
	DELPHI	<a href="http://github.com/lucian-ilie/DELPHI">http://github.com/lucian-ilie/DELPHI</a>	RNN and CNN	[49]
	Fout. et al.	<a href="https://github.com/fouticus/pipgcn">https://github.com/fouticus/pipgcn</a>	GCN	[52]
	Liu. et al.	–	GCN and CNN	[54]
	SASNet	<a href="https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/H93ZKK">https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/H93ZKK</a>	3D CNN	[53]
	PINet	<a href="https://github.com/FTD007/PInet">https://github.com/FTD007/PInet</a>	PointNet	[55]
	UniRep	<a href="https://github.com/churchlab/UniRep">https://github.com/churchlab/UniRep</a>	mLSTM	[58]
	MaSIF	<a href="https://github.com/LPDI-EPFL/masif">https://github.com/LPDI-EPFL/masif</a>	Geodesic CNN	[59]
	dMaSIF	<a href="https://github.com/FreyrS/dMaSIF">https://github.com/FreyrS/dMaSIF</a>	Geodesic CNN	[60]
	DeepDrug3D	<a href="https://github.com/pulimeng/DeepDrug3D">https://github.com/pulimeng/DeepDrug3D</a>	3D CNN	[61]
LigVoxel	–	CNN	[62]	

AlphaFold [38] is one of the most successful and famous models that relies on coevolutionary information. It consists of hundreds of convolutional neural network layers. AlphaFold first predicts the distances and torsions between  $C_{\beta}$  atoms of residue pairs. Then, the distribution of predicted distances is engaged to construct a protein-specific statistical potential function, i.e., potential of mean force, from which the gradient is calculated to optimize the model to approach the native structure. In CASP13, AlphaFold achieved the best performance.

However, one of the most telling indicators of the strength of deep-learning approaches in protein folding is their success in directly inferring sequence to structure relationships in the absence of higher order features such as coevolution. Xu *et al.* [40] showed that ResNet-based models can predict structures of correct folds from primary sequences without coevolution. Another method is

Recurrent Geometric Network (RGN) [41] that incorporates local and global protein structure with subtly designed geometric units and folds protein sequences by a joint optimization function from input to output. Ongoing augmentations to the base RGN model are in development to improve the rate of convergence in model training [42] and to remove the dependency of MSAs [43] when preparing sequence protein features. While these coevolution-irrespective deep learning methods are not fully competitive with the best coevolution-based approaches, the direct sequence to structure learning may better conceptually represent the biological problem of protein folding. Moreover, they provide important complementary approaches that may perform best for protein design applications or folding orphan proteins where homologous sequences are not available.

Although Coevolution-dependent approaches may outperform the coevolution-irrespective deep learning

methods, they heavily rely on homologous structures. For example, AlphaFold has low atomic accuracy when no homologous structures are available. To overcome this limitation, DeepMind, the developer of AlphaFold, presented AlphaFold2 [44], which is a Transformer-like deep learning network. AlphaFold2 not only jointly embeds MSAs and pairwise features with a trunk of networks but also incorporates physical and geometric constraints into the learning process with a structure module that allows more flexible refinement of the entire structure simultaneously. Using this approach, AlphaFold2 combines the innovations of both coevolution-dependent and coevolution-irrespective approaches, and won CASP14. Motivated by AlphaFold2, Baek et al. [45] extended the AlphaFold2 framework and proposed a three-track model, RoseTTAFold, which transforms and integrates protein sequences (1D), residue pairing distances (2D), and structure coordinates of residues (3D) to provide better predictions. In addition to protein structure prediction, RoseTTAFold can also solve the challenges of x-ray crystallography and cryo-electron microscopy modeling and has shown some promise in transferability to protein-protein complex structures.

Accurate prediction of protein structure is crucial to understand fundamental protein functions as the predictions can be used for some downstream tasks such as protein-protein docking and protein interface prediction.

### Protein interface prediction

Accurate annotation of protein interfaces can provide insights into molecular functions. For example, mapping disease mutations onto known protein interfaces can help dissect the molecular mechanisms underlying disease. However, experimental determination of 3D complex structures is resource-intensive and time-consuming. Although some computational methods such as protein-protein docking [46] and homology modeling [3] can predict protein interfaces, they suffer from the limitations of available structures and cannot be applied to full-interactome scales. Various machine learning models—such as XGBoost [47] and Random Forests [48]—have previously been developed to overcome these shortcomings. Moreover, several recently proposed deep learning-based methods have been shown to achieve greater success. These deep learning approaches can roughly be split based on features used: sequence-based [49–51] and structure-based models [52–55].

Sequence-based models solely rely on the protein sequence information. Specifically, they use sequence-based features such as hydrophathy and evolutionary conservation to represent each amino acid. With these sequence features, various deep learning architectures

have been employed. ComplexContact [51] is built on RaptorX-Contact [19], which is a ResNet-based contact map prediction model. ComplexContact accepts the concatenated MSAs of two interacting proteins as input to identify interfaces. Their test result shows that ComplexContact outperforms existing pure coevolution methods such as Gremlin-Complex [56]. Recurrent Neural Networks (RNNs) have also been used with sequence-based features. DLPred [50] is a bidirectional RNN model with a novel RNN cell, simplified LSTM (SLSTM). The authors removed and simplified particular processes in the LSTM cell. As SLSTM cell has fewer parameters than the LSTM cell, DLPred could avoid overfitting with better computational efficiency. DELPH [49] is another RNN-based model where RNN is combined with CNN. Although both deep learning models accept the same sequence input, each architecture produces its own feature embeddings which when integrated together achieve more comprehensive representations for prediction.

Structure-based models utilize structure information in addition to sequence-based features. In interface prediction, structural information is critical as by most definitions, buried residues inherently cannot be part of the interface. BIPSPI [47] and ECLAIR [48] empirically showed the importance of structural features based primarily on solvent accessibility. Some deep learning models are capable of retaining protein shape information in their structural features. For example, GCN and 3D CNN take as input graph and voxel representations of protein structures, respectively. Fout et al. [52] proposed Graph Convolutional Network (GCN)-based methods. The authors represented a protein structure as a graph where each node indicates a residue with features and an edge denotes an adjacent neighbor. This GCN was also integrated with 2D CNN [54]. The integrated model extracts residue features from both structures and sequences of two interacting proteins. Another deep learning architecture for 3-dimensional protein structures is 3D CNN. Townshend et al. [53] proposed SASNet which treats voxelized protein structures as 3-dimensional images. Point cloud is another way to represent 3-dimensional protein structures. Dai et al. [55] developed PInet that is rooted in the framework of PointNet [57]. PointNet is a deep learning model for shape classification and segmentation that takes point clouds as input.

Although protein-protein interactions from the network studies have provided valuable information for understanding the molecular functions of proteins, accurate prediction of protein interface made possible by advances in deep learning will help achieve key functional insights.

## Molecular characterization and protein–drug binding pocket prediction

Protein sequence and structure can provide a rich vein of information. While it is often difficult to construct meaningful hand-crafted features, deep learning automatically transforms raw data such as protein sequences and structures into numerical features that preserve important information in the original data. UniRep [58] is a Multiplicative LSTM (mLSTM)-based model that takes in unlabeled protein sequences and distills the fundamental features of the input into statistical representations. MaSIF [59] uses a geometric deep learning approach to extract features from protein surfaces. These learned protein features can be meaningfully applied to downstream prediction tasks for predictions of ligand or protein binding surfaces. Sverrisson *et al.* [60] further developed the geometric deep learning approach by taking raw 3D atomic coordinates with a novel geometric convolutional layer and presented dMaSIF.

Similarly, several applications such as DeepDrug3D [61] and LigVoxel [62] have been applied to extract features from protein pockets. DeepDrug3D employs a 3D voxel-based CNN to classify known binding pockets based on the type of ligand that binds them. LigVoxel presents a CNN-based end-to-end framework for the generation of ligand property fields given the structure of a protein binding site. One important benefit of these methods is that the meaningful information being learned from the deep models can be readily visualized.

## Conclusion

The advancement of deep learning has led to substantial progress in various proteomic research areas. In most applications, deep learning-based methods have outperformed other traditional machine learning models. The most noticeable achievement could be found in protein structure prediction because the advent of AlphaFold2 was glorified as the solution to the protein folding problem, a 50-year-old challenge in biology.

Despite the remarkable success of deep learning, some limitations still make it less accessible and narrow its scope of application. Specifically, training deep learning models requires optimization of up to millions of parameters, and therefore requires a massive amount of data. Sufficiently large training datasets may not be readily available in general, making overfitting a long-standing concern for deep learning. As a result, deep learning is considered the most expensive machine learning approach. In the context of biological applications, problems in which acquisition of training data is dependent on extensive experiments are likely to remain intractable for deep learning models. Moreover, deep learning models usually do not allow easy interpretation of their architectures and individual model parameters. Thus, alternative methods may be preferable in

applications where understanding the relationship between input and output is of scientific interest more than simply producing a working model. However, in light of the growth in experimental data and computing technology, machine learning, especially deep learning, approaches are still expected to play a crucial role in structural proteomics.

## Conflict of interest statement

Nothing declared.

## Acknowledgements

This work was supported by grants from The National Institute of General Medical Sciences (R01 GM124559, R01 GM125639, R01 GM130885, RM1 GM139738), The National Institute of Diabetes and Digestive and Kidney Diseases (R01 DK115398) to H.Y.

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