

Surveying over 100 Predictors of Intrinsic Disorder in Proteins

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Abstract

Introduction: Intrinsic disorder prediction field develops, assesses and deploys computational predictors of disorder in protein sequences and constructs and disseminates databases of these predictions. Over 40 years of research resulted in the release of numerous resources.

Areas covered: We identify and briefly summarize the most comprehensive to date collection of over 100 disorder predictors. We focus on their predictive models, availability and predictive performance. We categorize and study them from a historical point of view to highlight informative trends.

Expert opinion: We find a consistent trend of improvements in predictive quality as newer and more advanced predictors are developed. The original focus on machine learning methods has shifted to meta-predictors in early 2010s, followed by a recent transition to deep learning. The use of deep learners will continue in foreseeable future given recent and convincing success of these methods. Moreover, a broad range of resources that facilitate convenient collection of accurate disorder predictions is available to users. They include web servers and standalone programs for disorder prediction, servers that combine prediction of disorder and disorder functions, and large databases of pre-computed predictions. We also point to the need to address the shortage of accurate methods that predict disordered binding regions.

Keywords: Database; deep learning; intrinsic disorder; intrinsically disordered regions; machine learning; prediction; predictive performance; protein function.

1 Introduction

Intrinsically disordered proteins (IDPs) contain both structured domains and intrinsically disordered regions (IDRs) or could be fully disordered, i.e., composed of one sequence-wide IDR [1]. IDRs are defined by the lack of stable secondary and tertiary structures under physiological conditions [2-4]. They are instrumental for a wide range of cellular functions including molecular assembly, molecular recognition, cell cycle regulation, transcription, translation, and signal transduction [5-11]. Bioinformatics studies suggest that intrinsic disorder is abundant across all kingdoms of life and virus, with substantially higher levels in eukaryotes [12-14]. Studies approximate that around one-third of eukaryotic proteins have long IDRs, i.e., regions with 30 or more consecutive disordered residues [12-15].

Several databases, such as DisProt [16], PDB [17], IDEAL [18], DIBS [19], and MFIB [20], store the experimentally established annotations of IDRs and/or their associated functions. However, the amount of these annotations is relatively low. For instances, the current version 8.3 of DisProt covers about 2 thousand IDPs [16] and a recent study extracted about 25 thousand IDPs from PDB [21]. This is just a miniscule fraction of the 220 million protein sequences that are available in the 2021_03 release of the UniProt database [22]. The large gap between the huge number of protein sequences and the small number of experimentally annotated IDPs motivates the development of computational predictors of IDRs. These methods identify putative disordered residues and regions in an input protein sequence.

Many disorder predictors have been developed to date [23,24]. Consequently, numerous surveys that summarize the field of the computational disorder prediction were published [2,23-32]. These works provide historical overview, categorize and describe disorder predictors and, in some cases, compare their predictive performance. The most comprehensive of these surveys cover as many as 70 [23], 55 [25] and 45 predictors [24]. Moreover, about a dozen large-scale comparative studies were carried out to assess predictive performance of the intrinsic

disorder predictors [21,33-42]. These studies include several community assessments where predictors are evaluated on blind test datasets (i.e., datasets that were not available to the authors of the predictors) by independent assessors who do not take part in the competitions. The community assessments include Critical Assessment of Structure Prediction (CASP) between CASP5 to CASP10 [37-42] and Critical Assessment of Intrinsic Protein Disorder (CAID) [36]. The largest of these assessments reported results for 28 disorder predictors in CASP10 [40] and 32 in CAID [36]. Our objective is to compile and summarize the most complete list of disorder predictors to date. We identify 103 methods and provide an updated historical perspective on the progression of the efforts to develop these methods that covers a recent infusion of the deep learning models. We summarize the predictive models that these methods utilize and comment on their availability to end users. Moreover, we analyze results of the two largest and most recent community assessments, CASP 10 and CAID, to study whether and how the predictive performance of disorder predictors changed over the years as new methods have become available.

Table 1. Summary of 67 predictors of intrinsic disorder that are available to the users. The methods are sorted in the chronological order of their publication.

Predictor name	Year published	Reference ¹	Algorithms used ²	Meta prediction ³	Availability ⁴
SEG	1994	[43]	SSM	No	SP+WS
PONDR CaN-XT	1997	[44]	SNN	No	WS
PONDR XL1	1997	[44]	SNN	No	WS
PONDR VL-XT	2001	[45]	SNN	No	WS
DisEMBL-REM465	2003	[46]	SNN	No	SP+WS
DisEMBL-HL	2003	[46]	SNN	No	SP+WS
DisEMBL-COIL	2003	[46]	SNN	No	SP+WS
GlobPlot	2003	[47]	SSM	No	SP+WS
NORSp	2003	[48]	SSM	No	WS
DISOPRED	2003	[49]	SNN	No	SP
DISOPRED2	2004	[12]	SVM+SNN	No	SP
DISpro	2005	[50,51]	SNN	No	SP+WS
FoldIndex	2005	[52]	SSM	No	WS
IUPred-long	2005	[53,54]	SSM	No	SP+WS
IUPred-short	2005	[53,54]	SSM	No	SP+WS
PONDR VL3	2005	[55]	SNN	No	WS
PONDR VL3H	2005	[55]	SNN	No	WS
PONDR VL3E	2005	[55]	SNN	No	WS
RONN (JRONN)	2005	[56]	SNN	No	WS
PONDR VSL1	2005	[57]	RM	No	WS
PROFbval	2006	[58]	SNN	No	SP+WS
PONDR VSL2B	2006	[57,59]	SVM	No	WS
PONDR VSL2P	2006	[57,59]	SVM	No	WS
NORSnet	2007	[60]	SNN	No	SP+WS
PrDOS (PrDOS2)	2007	[61]	SVM	No	WS
Pdisorder	2007	No	SNN	No	SP
UCON	2007	[60]	SNN	No	SP+WS
DISOclust	2008	[62]	SSM	No	SP+WS
DRIPPRED	2008	No	SSM	No	SP
metaPrDOS (metaPrDOS2)	2008	[63]	SVM	Yes	WS
MD	2009	[64]	SNN	Yes	SP+WS
MFDp	2010	[65]	SVM	Yes	WS
PONDR FIT	2010	[66]	SNN	Yes	WS
Cspritz	2011	[67]	SNN	Yes	WS
DISOclust3 (IntFOLD)	2011	[68]	CS	No	SP+WS
IsUnstruct	2011	[69]	SSM	No	SP+WS
Espritz-D	2012	[70]	SNN	No	SP+WS
Espritz-N	2012	[70]	SNN	No	SP+WS
Espritz-X	2012	[70]	SNN	No	SP+WS
GSmetaDisorderMD	2012	[71,72]	CS	Yes	WS
GSmetaDisorder	2012	[71,72]	CS	Yes	WS
GSmetaServer	2012	[71,72]	CS	Yes	WS
GsmetaDisorder3D	2012	[71,72]	CS	No	WS
SPINE-D	2012	[73]	SNN	No	SP
MFDp2	2013	[74,75]	SVM	Yes	WS
DisMeta	2014	[76]	SSM	Yes	WS
disCoP	2014	[77,78]	RM	Yes	WS
DynaMine	2014	[79,80]	RM	Yes	SP+WS
PON-Diso	2014	[81]	RF	No	WS
DISOPRED3	2015	[82]	SVM+SNN+NN	No	SP+WS
DisPredict (DisPredict2)	2016	[83]	SVM	No	SP

Predictor name	Year published	Reference ¹	Algorithms used ²	Meta prediction ³	Availability ⁴
MobiDB-lite	2017	[84]	CS	Yes	WS
SPOT-Disorder1	2017	[85]	DNN(R)	No	SP+WS
IUpred2A-long	2018	[86]	SSM	No	SP+WS
IUpred2A-short	2018	[86]	SSM	No	SP+WS
pyHCA	2018	No	SSM	No	SP
SPOT-Disorder-Single	2018	[87]	DNN(C+R)	No	SP+WS
rawMSA	2019	[88]	DNN(C+R)	No	SP
SPOT-Disorder2	2019	[89]	DNN(C+R)	No	SP+WS
DisoMine	2020	No	DNN(R)	No	WS
ODiNPred	2020	[90]	SNN	No	WS
IDP-Seq2Seq	2020	[91]	DNN(R)	No	WS
fIDPnn	2021	[92]	DNN(F)	No	SP+WS
fIDPlr	2021	[92]	RM+RF	No	SP+WS
IUPred3	2021	[93]	SSM	No	SP+WS
RFPR-IDP	2021	[94]	DNN(C+R)	No	WS
Metapredict	2021	[95]	DNN(R)	Yes	SP

¹“No” means that a given predictor was not published in a peer-reviewed journal.

²Algorithms used: “SSM” (Sequence scoring function-based methods); Machine learning methods including “SVM” (support vector machine), “DT” (decision tree), “RF” (random forest), “CS” (consensus score), “RM” (regression model), “CRF” (conditional random field), “NN” (nearest neighbor), “BC” (Bayesian classifier), “RBFN” (radial basis function networks), “SNN” (shallow neural network); and “DNN” (deep neural network) where “C” stands for convolutional network, “R” for recurrent network, and “F” for feed-forward network.

³Meta prediction refers to the predictors that use outputs of multiple disorder predictors as input.

⁴Availability: released as “SP” (standalone program), “WS” (web server).

2 Intrinsic Disorder Prediction

We search for the disorder predictors using a variety of sources including databases that provide access to disorder predictions, MobiDB [96] and D²P² [97], community assessments of the disorder predictors, such as CASP 5, CASP 6, CASP 7, CASP 8, CASP 9, CASP 10 and CAID [36-42], 12 previously published surveys of disorder predictors [21,23-28,31,33-35], and a manual search of relevant articles collected from PubMed using the “(disorder[Title]) AND (prediction[Title]) AND protein” query. This extensive search produced a list of 103 disorder predictors [12,43-47,49-74,76,77,79,80,82-95,98-127]. This list includes four unpublished methods that participated in CASP and/or CAID assessments.

We summarize these predictors in Table 1, which focuses on the 67 methods that are currently available to users, and Suppl. Table S1, which covers 36 methods that were published but are presently unavailable. These tables identify when and where these tools were published and summarize key characteristics of the underlying predictive models, such as the type of an algorithm used and whether meta-prediction is utilized.

2.1 Predictive models

The predictive models cover a broad spectrum of alternatives. We classify predictors into four categories based on the type of predictive models that they utilize: (1) sequence scoring function-based methods; (2) machine learning approaches; (3) deep learning methods; and (4) meta-predictors. This classification is inspired by past surveys [23,24,26,28,31], but with the addition of the deep learning category that is fueled by the most recent developments. The sequence scoring function-based methods aggregate information extracted from the input protein sequence and sequence-derived structural and evolutionary information using additive and/or weighted functions. Some of these functions are grounded in physical principles governing protein folding processes. Representative examples include FoldIndex [52], IUPred [53,54], and IUPred2A [86], and IUPred3 [94]. The machine learning predictors rely on more sophisticated predictive models that are trained from data using a variety of machine learning algorithms. These algorithms include support vector machine [61,65,74,83,105], regression [77,79,128], conditional random field [113,121,124,125], random forest [81,129], nearest neighbor [106,109], Bayesian classifier [130], radial basis function networks [104,131], and shallow neural networks [46,55,66,114]. Two or more models generated by different machine learning algorithms are sometimes used in tandem with the aim to improve predictive performance when compared to using one model [82,123,126]. Examples of popular machine learning methods include DisEMBL [46], DISOPRED [49], PONDR [55], PrDOS [61] and DISOPRED3 [82]. The deep learning methods rely on deep neural networks, which is a specific type of machine learning algorithms. The deep neural networks differ from shallow networks by inclusion of multiple

hidden layers. They also typically use more advanced types of neurons and connections. We separate deep networks from the other machine learning methods since many recent methods use these types of predictive models. These disorder predictors rely on several different types of deep networks including feed-forward networks, recurrent networks, convolutional networks, and their hybrids that combine convolutional and recurrent topologies (Table 1 and Suppl. Table S1). The focus on the deep networks stems from the fact that they provide favorable levels of predictive performance when compared with the other categories of disorder predictors. In particular, the best performing methods that participated in the most recent CAID competition [36,132], which include fIDPnn [92], SPOT-Disorder2 [89], RawMSA [88] and AUCpred [123], rely on the deep learning models. We highlight the diversity of the deep network types that they utilize including feed-forward by fIDPnn, convolutional by AUCpred, and a hybrid by SPOT-Disorder2 and RawMSA. The meta-predictors apply multiple disorder predictions as inputs to (re)predict disorder with the underlying aim to improve predictive performance when compared to the input predictions. The development of these methods was motivated by the availability of many diverse machine learning and sequence scoring function-based methods that could be used as the inputs. Moreover, several empirical studies show that well-designed meta-predictors indeed produce predictions that outperform their inputs [77,84,133]. A few illustrative examples in this category include metaPrDOS [63], MFDp [65], Cspritz [67], GSmetadisorder [71,72], MFDp2 [74,75], disCoP [77,78], and MobiDB-lite [84]. We note that some meta-predictors use machine learning models to process their inputs (e.g., metaPrDOS [63] and MFDp [65]), which means that they belong in both categories of disorder predictors. Moreover, a few methods, such as PrDOS[61], DISOclust[62] and Gsmetadisorder3D[72], utilize homology modelling to predict disorder.

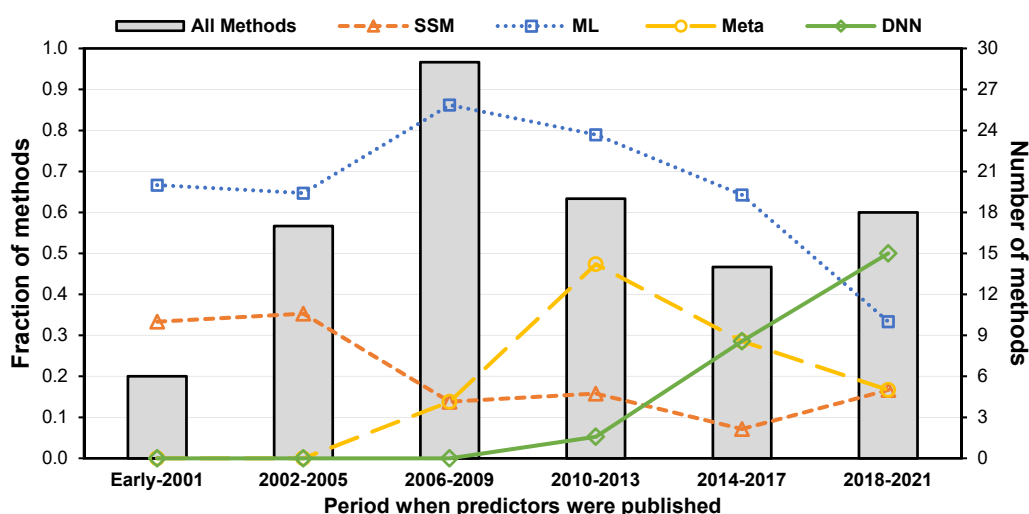


Figure 1. Distribution of disorder predictors categorized by their predictive models over time. The x-axis represents the periods when the predictors were published. The left/right y-axis gives the fraction/number of methods in the given time period. The light grey bars represent the number of all disorder predictors. Color-coded lines show fractions of different categories of predictors: orange with triangle markers for SSM (sequence scoring function-based methods); blue with square markers for ML (machine learning methods); yellow with circle markers for meta (meta-predictors); and green with diamond markers for DNN (deep neural networks).

Among the 103 disorder predictors 19 use the sequence scoring function-based models, 70 are machine learning methods, and 14 predictors rely on the deep learning. Moreover, there are 20 meta-predictors. **Figure 1** summarizes major trends in popularity of these four categories of methods over time. Only six predictors were released before 2002, with four that rely on the machine learning models, specifically shallow neural networks, and two that apply sequence scoring function-based models. On average five new methods were developed annually after 2002, with a sharp peak between 2006 and 2009. The least popular type of methods are the scoring function-based models, although new methods of that type are developed consistently over the years. We note a relatively steady stream of the most numerous class of the machine learning methods, with a modest decline in the recent years. The first meta-predictors were published in 2008, and their development was fueled by the availability of over 40 disorder predictors at that time. However, after a spike in popularity of meta-predictors in early 2010s, with nearly half of all predictors developed in 2010-2013 period in this category, the

number of these methods is in a steady decline. The first deep learning method was released in 2013 and gradually more of these methods are being developed in the recent years. The deep learners became the most popular category of disorder predictors in the last three years. This is likely fueled by the overall popularity of deep learners in the area of structural bioinformatics of protein [134,135] and the success of deep learners in the recent assessments of the disorder predictions [31,33,36]. To summarize, recent years have produced a substantial shift in the development efforts where the decreasing numbers of meta-predictors are coupled with the rising popularity of the deep neural networks.

2.2 Availability

Table 1 summarizes 67 disorder predictors that are currently available to the users and explains how these methods are shared, i.e., as web servers and/or standalone programs. The web servers are an attractive option for less computer savvy users and those who perform predictions in an ad hoc manner. They are accessible via a web site where users input their sequences and collect the corresponding disorder predictions. The entire prediction process is done on the server side, which means that users do not need to invest in any hardware or software to collect the results. On the other hand, the standalone programs are more suited for bioinformaticians who perform predictions regularly and/or who aim to embed these predictions into larger bioinformatics platforms. These programs must be downloaded and have to be installed and run on the user's hardware. Our analysis reveals that nearly two-thirds of predictors are available as web servers and/or standalone software. The other one-third of predictors, which we summarize in **Supplementary Table S1**, were not released at the time of publication or were released but were unavailable as of August 2021 when we tested the access. We also provide URLs of the available predictors in **Supplementary Table S2**.

2.3 Historical perspective

Previous surveys define three distinct periods in the development of the disorder predictors [23,25]. We expand this timeline to four periods to recognize recent advances that resulted in the development of the deep learners. The *first-generation* methods were released between 1979 and 2001. Only a few methods were developed during that time. The first method, which was published in 1979 targets prediction of random coil conformations in protein sequences [98]. However, due to limited availability of data on IDRs at that time, this method could not be sufficiently tested at the time of publication. Later evaluations show that its predictive performance is relatively poor [25]. The first machine learning-based method was proposed by Romero, Obradovic, and Dunker in 1997 [99]. It uses a shallow neural network model that relies on physical and chemical properties of protein sequences. Interestingly, some of these early methods are still available online as webservers and/or standalone code (**Table 1** and **Supplementary Table S2**).

The *second-generation* methods date between 2002 and 2006. The key characteristic of this period is the rapid intensification of the efforts to develop disorder predictors. Moreover, most of these methods are based on relatively simple predictive models, often relying on the sequence scoring functions and shallow neural networks. The key innovation was the use of evolutionary profiles that are generated from the position specific score matrix (PSSM) produced by PSI-BLAST from the input protein sequences [128,136]. A significant event during the period of time was the inclusion of the disorder prediction assessment into CASP5 in 2003 [41]. This resulted in popularization of this predictive area [25]. Some of the prominent second-generation methods include sequence scoring-function-based models, such as GlobPlot [47], FoldUnfold [102,103], and IUPred [53,54], and machine learning methods including PONDR family of disorder predictors [45,55,57,59], DISOPRED [49], DisEMBL [46], and RONN [56].

The *third-generation* predictors were released between 2007 and 2015. The defining characteristics of this period is the introduction of the meta-predictors. Nearly all meta-predictors, 16 out of the total of 20, were published during that timeframe. Popular third-generation meta-predictors include MFDp [65], PONDR-FIT [66], and CSpritz [67], GSmetadisorder [71,72] and DisCoP [77,78]. The disorder predictions continued to be biannually evaluated in the CASP experiments [38-40,42]. This resulted in a steady influx of new methods, totaling 48 for this time period. However, the inclusion of disorder predictions in CASP ended with CASP10 that was held in 2012 [40].

The *fourth-generation* period started in 2016. Its defining feature is the rapid acceleration in the development of the deep learning models. While the first deep learning method was developed in 2013 [118], these efforts intensified in the last five years. About half of the fourth-generation disorder predictors, 11 out of 23, rely on the deep neural networks. This is the largest of the four categories of the predictive models during this time period (**Figure 1**). A few representative deep learners include fIDPnn that utilizes deep feed-forward topology [92]; AUCpred which integrates conditional random field with a convolutional network [123]; SPOT-Disorder predictors that rely on the recurrent networks [85,87,89]; and RawMSA which combines convolutional and bidirectional recurrent networks [88]. As we mention above, the strong focus on designing deep networks was motivated by their popularity and ability to produce accurate results, culminated in a convincing success by this class of methods in the most recent CAID community assessment [36,132].

2.4 Related resources

Table 1 shows that users can secure disorder predictions by using webservers and standalone applications. Another arguably more convenient alternative is to collect pre-computed disorder predictions from one of the three currently available databases: Database of Disorder Protein Predictions (D²P²) [97], MobiDB [137], and DescribePROT [138]. Each database provides access to results produced by several disorder predictors for large collections of proteins ranging from 1.35 million proteins in DescribePROT, 10.43 million proteins in D²P², to 189.52 million proteins in MobiDB. The main advantage of these resources is the instantaneous access to the pre-computed predictions generated by several different methods (i.e., users do not have to wait for the predictions to complete) and the corresponding consensus prediction. However, webservers or standalone applications must be used when users want to predict sequences that are not included in a given database.

Another useful resource is the recently developed DisorderEd Prediction CenTER (DEPICTER) [139], a large-scale webserver that produces predictions of disorder and disorder functions. The latter predictions identify IDRs that share the same molecular function, such as binding to proteins or nucleic acids. DEPICTER produces disorder predictions from UPred-short [54], IUPred-long [54] and SPOT-Disorder-Single [87] that are accompanied by the predictions of disordered linkers by DFLpred [140], disordered moonlighting regions by DMRpred [141], and disordered regions that interact with proteins and nucleic acids by fMoRFpred [142], DisoRDPbind [143] and ANCHOR2 [86]. While disorder function predictions are outside of the scope of this survey, several recent reviews offer in-depth treatment of this topic [23,144,145]. We highlight the fact that assessment of the methods that predict binding IDRs (i.e, disordered regions that interact with proteins, DNA, RNA and small ligands) was introduced in the CAID experiment [36]. This experiment identified ANCHOR2 [86], DisoRDPbind [143,146,147] and MoRFCHiBi [148] as the top-three most accurate predictors of binding IDRs.

3 Predictive Performance of Intrinsic Disorder Predictors

One of the key aspects of disorder predictors is their predictive performance. These methods produce two types of outputs: numeric propensities that quantifies likelihood that a given residue in the input protein is disordered, and binary value that categorizes this residue as either disordered or structured. The predictive quality of the propensities is typically evaluated with the Area Under receiver operating characteristic Curve (AUC), while Matthews Correlation Coefficient (MCC) is used to assess the binary values [21,23,24,27,33,36,40,42]. We note that these metrics were used in the most recent community assessments [36,40]. The MCC is defined as:

$$MCC = \frac{TP * TN - FP * FN}{\sqrt{(TP + FP) * (TP + FN) * (TN + FP) * (TN + FN)}}$$

where TP (true positive) and TN (true negative) represent the number of correctly predicted disordered and structured residues, respectively, while FP (false positive) and FN (false negative) quantify the number of misclassified structured and disordered residues, respectively.

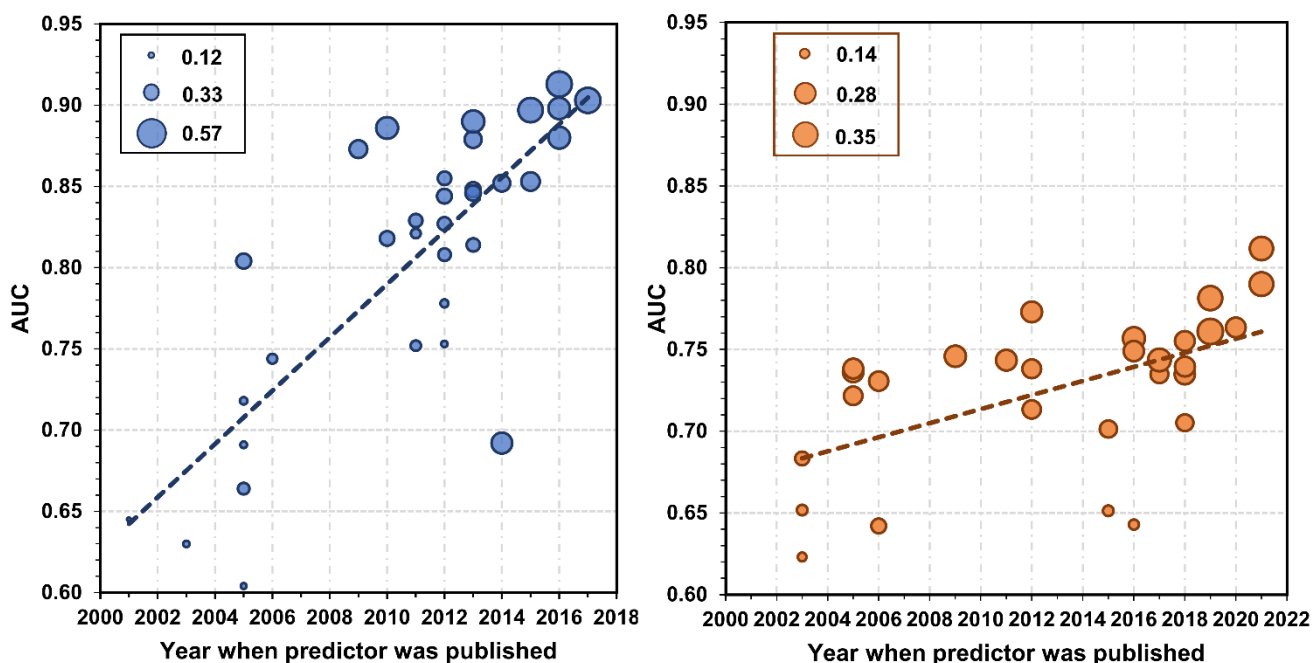


Figure 2. Relation between year of publication and predictive performance measured in CASP10 (panel A in blue) and in CAID (panel B in orange) for disorder predictors. The predictive performance is quantified with AUC (y-axis) and MCC (size of the markers). Figure legends show the size of markers for the minimal, median, and maximal MCC values. The dashed lines correspond to a linear fit into the year vs. AUC data.

We use results produced in the two most recent community assessments, CASP10 [40] and CAID [36], to study whether and how the predictive performance has changed over the years, as newer and more sophisticated predictors were developed. We consider the two assessments since they rely on complementary sources of the ground truth data: CASP10 from PDB [17] while CAID from DisProt [16]. We collect the AUC and MCC values directly from the corresponding CASP10 and CAID articles [36,40] and from other published works that reported results on these benchmark datasets. The numerical values of AUC and MCC are listed in **Supplementary Table S3** for CASP10 and **Supplementary Table S4** for CAID. **Figure 2** visualizes the relation between the predictive performance and the year of publication of the corresponding disorder predictors. Panel 2A focuses on the results of 33 predictors that were assessed on the CASP10 data while panel 2B on the CAID results of 29 disorder predictors. The dashed lines show linear fit that approximates the relation between the AUC values and the year of publication. This analysis suggests that more recently published predictors offer on average higher values of AUC. Furthermore, we observe that larger AUC values are usually accompanied by the larger sizes of markers, which correspond to higher MCC values. We quantify the relations between AUC or MCC values and the year of publication using Pearson correlation coefficients (PCCs). PCCs for the CASP10 dataset results, which we compute using data from **Supplementary Table S1**, are 0.78 for AUC and 0.75 for MCC. The corresponding PCCs for the CAID data (**Supplementary Table S2**) are 0.55 and 0.50. The linear trends combined with the correlations suggest that the predictive performance trends upwards as newer methods are released. These improvements are consistent across both assessments and both measures of predictive quality. The more recent CAID assessment identifies several accurate methods, all of which rely on deep learning [36,132]. They include fIDPnn [92], SPOT-Disorder2 [89], RawMSA [88] and AUCpred [123]. We note that fIDPnn additionally offers prediction of molecular functions for the putative IDRs that it generates, covering predictions of linkers and IDRs that interact with proteins, DNA and RNA [92]. Moreover, fIDPnn produces these predictions very quickly, in a few seconds per proteins, which is at least an order of magnitude faster than the other three methods [36].

4 Expert opinion

Disorder prediction is an active field of research characterized by steady progress fueled by use of recent innovations, such as meta and deep learning, vibrant research community and deep historical roots. We identify 103 disorder predictors were developed over the last four decades. This provides us with ample amount of historical data to identify interesting trends and patterns.

The field of disorder prediction has a strong tradition of community assessments where large collections of methods are evaluated by independent assessors on blind benchmark datasets. Our empirical analysis of results from two most recent community assessments, CASP10 [40] and CAID [36], shows a clear trend of improvements in predictive quality as newer and more advanced predictors are being developed over time. We find that the original focus on machine learning methods has shifted towards the meta-predictors in early 2010s, which was followed by a transition to the deep learning methods in the last 5 years. We anticipate that the current strong focus on the development of deep learning models will continue in a foreseeable future. This is motivated by the recent and rather convincing success of deep learners in the CAID experiment [36]. The entire collection of the top performing methods in that experiment relies on the deep learners [132], including fDPnn that applies deep feed-forward network [92], SPOT-Disorder2 and RawMSA that combine convolutional and recurrent networks [88,89], and AUCpred that utilizes convolutional network [123]. A few other well-performing predictors in this assessment, such as SPOT-Disorder1, SPOT-Disorder-Single and DisoMine, also apply a variety of different deep networks (**Table 1**) [36]. The diversity of the underlying deep network types suggests that there is no one best type of neural network for this predictive problem. Results published in the recent fDPnn article suggest that predictive performance can be strengthened by innovating the predictive inputs of the deep networks [92]. Possible options include development of extended sequences profiles that cover relevant sequence-derived protein characteristics and formulation of protein-level features that express an overall bias of a given input sequence, for instance to be disordered or structured. Innovating both of these aspects, deep network topologies and predictive inputs, is likely to bring further progress in predictive performance.

An often-overlooked factor in this research area is the availability of a broad spectrum of resources that facilitate convenient collection of accurate disorder predictions. We find that about two-thirds of disorder predictors are available as web servers and/or standalone programs. This is a much higher rate of availability than in other related areas, such as prediction of protein-binding and RNA-binding residues where the availability was estimated to be at around 40% [149,150]. This perhaps stems from maturity of the intrinsic disorder prediction field that has over 40 years-long history compared to a much shorter timeframe of the efforts towards the prediction of protein-binding and RNA-binding residues [149,150]. Moreover, users can conveniently obtain disorder and disorder function predictions with the DEPICTER server [139] and collect pre-computed disorder predictions from several large databases, such as MobiDB [137], D²P² [97], and DescribePROT [138]. Availability of this large collection of facilities should ensure that the disorder predictions will continue to make significant impact in related areas of research, such as systems medicine [32], drug design [151-155], and target selection for structural genomics [46,156,157].

While we show that modern disorder predictors offer high-quality results, prediction of disordered binding regions remains a challenge. There are well over a dozen predictors of disordered protein-binding regions [145], including recent methods, such as FLIPPER [158] and SPOT-MoRF [159]. However, recent CAID assessment concludes that “*disordered binding regions remain hard to predict*” and that the corresponding predictors should be substantially improved in the future [36]. This is particularly acute for the prediction of the disordered protein-binding regions [33]. We also highlight a shortage of methods that predict disordered regions which interact with nucleic acids, with only two such methods that were released to date, DisoRDPbind [143,147] and DeepDISOBind [160]. Similarly, there is only one method capable of predicting IDRs that bind lipids, DisoLipPred [161]. This points to the need to develop novel tools that address prediction of different functional flavors of IDRs.

Article highlights

- Over 100 disorder predictors were developed to date
- The original focus on machine learning methods has shifted to meta-predictors in early 2010s, followed by a transition to deep learning predictors since 2016
- Empirical analysis shows that newer and more advanced predictors provide more accurate results when compared to older methods
- The focus on the development of the deep learning predictors will continue in a foreseeable future motivated by the recent and convincing success of these methods in the recent CAID experiment
- Users have access to a broad range of resources that facilitate convenient collection of accurate disorder predictions

Declaration of interest

The authors declare no conflicts of interest.

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