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SPECIAL REPORT

Two decades of advances in sequence-based prediction of MoRFs, disorder-to-order transitioning binding regions

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ABSTRACT

Introduction: Molecular recognition features (MoRFs) are regions in protein sequences that undergo induced folding upon binding partner molecules. MoRFs are common in nature and can be predicted from sequences based on their distinctive sequence signatures.

Areas covered: We overview 20 years of progress in the sequence-based prediction of MoRFs which resulted in the development of 25 predictors of MoRFs that interact with proteins, peptides, and lipids. These methods range from simple discriminant analysis to sophisticated deep transformer networks that use protein language models. They generate relatively accurate predictions as evidenced by the results of a recently published community-driven assessment.

Expert opinion: MoRFs prediction is a mature field of research that is poised to continue at a steady pace in the foreseeable future. We anticipate further expansion of the scope of MoRF predictions to additional partner molecules, such as nucleic acids, and continued use of recent machine learning advances. Other future efforts should concentrate on improving availability of MoRF predictions by releasing, maintaining, and popularizing web servers and by depositing MoRF predictions to large databases of protein structure and function predictions. Furthermore, accurate MoRF predictions should be coupled with the equally accurate prediction and modeling of the resulting structures of complexes.

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Intrinsic disorder; MoRF; molecular recognition feature; prediction; deep learning; protein–protein interactions; protein–lipid interactions; protein–peptide interactions

1. Introduction

Intrinsically disordered regions (IDRs) are regions in protein sequences that lack a stable structure under physiological conditions [1–4]. Several bioinformatics studies demonstrate that proteins with IDRs are present across the entire taxonomy, with much higher rates of occurrence in the eukaryotic organisms [5–9]. Many IDRs interact with ligands that include a broad spectrum of biomolecules, such as proteins, peptides, DNA, RNA, lipids, and a variety of small molecules that include drugs [10–18]. The conformational flexibility of IDRs offers certain advantages when compared to ordered (structured) regions, including the one-to-many binding where one IDR interacts with multiple different molecules [19–23]. One of the most common types of interacting IDRs is the molecular recognition feature (MoRF) [11,24]. MoRFs are relatively short sequence segments that are embedded in longer IDRs and that typically undergo disorder-to-order transitions when interacting with ligands [11,24,25]. Some MORF regions can remain partly or even fully disordered in the bound state [26,27]. The limits on the MoRF region lengths differ across studies, with some defining them as in the 10 to 70 consecutive amino acids range [24,25] while other works considering shorter segments that span between 5 and 25 residues in length [11,24,28]. Moreover, MoRFs are classified into several types that are defined based on the primary type of the secondary structure that they fold into upon binding, i.e. α-MoRFs (composed mostly of α-helices), β-MoRFs (mostly β-sheets), γ-MoRFs (irregular structures), and complex-MoRFs (mixed secondary structures) [25]. A recent bioinformatics study that investigated nearly 900 species suggested that 20% to 30% of IDRs, depending on the taxonomic assignment, include MoRF regions [11]. Importantly, sequences of the MoRF segments have unique signatures that differ from other types of disordered and ordered regions [11]. These differences motivated the development of computational sequence-based predictors of MoRFs [29,30]. Scientists use these predictive tools in a wide range of investigations. For instance, one of the most popular MoRF predictors, MoRFpred [31], has been utilized recently to investigate cell signaling pathways [32], 20S proteasome substrates [33], a variety of viral proteomes including SARS-CoV-2 [34], rotavirus [35], and hepatitis E [36], and interactomes of YY1 [37], SNED1 [38], and G0S2 [39] proteins. Moreover, MoRF predictions have clinical relevance, as the dysfunction of proteins with binding IDRs was found to be associated with a number of human diseases [40–42]. One of the results of this dysfunction is misfolding that may induce a range of conformational illnesses including the prion, Alzheimer's, polyQ and Parkinson's diseases, and the Down's syndrome [41,43]. Furthermore, MoRF-containing proteins have regulatory and signaling functions that fundamentally rely on the protein–ligand interactions, and their dysfunction was linked to cardiovascular diseases, cancers, and viral pathogenesis [34,35,40,44,45]. A few specific examples include the tau and Aβ

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proteins that are associated with conformational diseases, BRCA-1, p53, and AFP proteins that are involved in cancers, and viral capsid proteins that were shown to be implicated in the pathogenesis of viral infections [34–36,40,45,46]. We note that these findings relied on bioinformatics analyses that took advantage of high-quality predictions of binding IDRs [34–36,40,45,46].

Dozens of MoRF predictors have been developed to date, prompting the need to survey them. The last time the MoRF predictors were comprehensively surveyed was in 2019 [30]. That review provided a brief historical overview, covered 13 predictors (shown in bold font in Table 1), and discussed their predictive performance by relying on results collected from several articles that introduce individual predictors [30]. Several more recent surveys that focused on a broader collection of methods that predict binding IDRs are also listed and briefly summarized the MoRF predictors [75–77]. These broader predictors target-binding regions that are not limited in length and are not necessarily embedded in longer IDRs, and which interact with specific ligand types. Some popular examples include ANCHOR [78] and ANCHOR2 [79] that target protein and peptide binding IDRs; DisoRDPbind [80], DeepDISObind [81], and DisoFLAG [82] that predict DNA and RNA binding IDRs; and DisoLipPred [72], MemDis [83], and DisoFLAG that focus on the lipid binding IDRs. Importantly, the recent surveys have discussed MoRF predictors in passing and lacked coverage of the newest tools, beyond 2020 [75] and 2021 [76,77]. Motivated by the promiscuity and functional importance of MoRFs in nature, substantial amount of recent efforts toward the development of MoRF predictors, and a number of modern machine learning advances that were utilized in these efforts, herein we provide an updated, comprehensive, and practical overview of the MoRF prediction area. In particular, we cover 25 methods, provide an insightful historical overview that spans the 20 years of these development efforts, highlight recent advances that include the use of deep learning algorithms and protein language models, and summarize evaluation of representative methods based on arguably more objective results from a large community-organized assessment (compared to the past survey). In addition, as developers of these tools and authors of some of the past surveys, we also offer our opinion on the current issues and future progress in this active area of research.

2. Historical overview

Table 1 summarizes the key characteristics for the 25 MoRF predictors that include 7 methods that were released since 2020 and 12 methods that were not covered in the last survey [30]. This comprehensive list of methods was established by analyzing past surveys [30,75–77], manually scanning citations to the articles that introduce the listed predictors, and performing manual analysis of relevant PubMed searches. We focus our discussion of this active field of research on three important and complementary aspects. First, we provide a chronological historical overview that highlights major milestones. Second, we discuss the availability of these 25 predictors and analyze the relation of this aspect with their impact measured using citations. Third, we discuss recent community-driven efforts in measuring predictive performance and runtime and highlight the corresponding results for the MoRF predictors.

Figure 1 presents a chronological record of the 20-year-long development efforts and includes annotations of the five major milestones. The first milestone in 2005 marks the publication of the first α-MoRFpred method [28]. This method is limited to the prediction of the α-MoRFs and it was designed using a small dataset of 12 proteins with 14 α-MoRF regions. This design was improved 2 years later with the publication of α-MoRFpred-II by the same research group headed by Prof. Dunker [47]. MoRFpred-II used a larger training dataset with 99 proteins and 102 α-MoRFs and applied machine learning algorithm to produce the predictive model in a form of a shallow feed-forward neural network [47]. The second milestone (Figure 1) is the release of MoRFpred [31,49], the first tool that addresses the prediction of generic MoRFs that are not limited to a particular MoRF type (as compared to the α-MoRFs). This method was trained on a relatively large dataset with over 400 proteins and features a more advanced design that includes several sequence-derived inputs, such as an evolutionary profile and prediction of intrinsic disorder and solvent accessibility, which are input to a support vector machine model. MoRFpred was released as a free webserver that is available and operational to this date.

The third milestone is defined by the first use of a deep learning-based model in the en_DCNNMoRF predictor that was published in early 2019 [61]. This marks a major shift in the design of the MoRF predictors since the substantial majority of the subsequently developed methods also rely on the deep neural network models, i.e. 8 out of 11 have been released since 2019 (Table 1). The en_DCNNMoRF's model includes two deep convolutional neural networks which results are averaged to produce the final MoRF predictions [61]. The other deep learning-based MoRF predictors utilize a wide range of network topologies including feedforward networks [62,74], convolutional networks [64,66], recurrent networks [65,67], and transformers [73]. The fourth milestone marks the recent expansion of the scope of the MoRF predictors. Until 2023, these methods targeted the prediction of MoRFs that interact with proteins and peptides. This can be explained by the fact that the ground truth annotations of these proteins and peptide-binding MoRFs, which were used for training and assessment of these methods, were relatively easy to collect from existing databases, such as Protein Data Bank [84] and MobiDB [85]. The first method that considers other types of partner molecules is CoMemMoRFPred, which predicts lipid-binding MoRFs [69]. Development of this method was possible because of the preceding release of the MemMoRF database in 2021 [86], which was used to source the corresponding ground truth annotations. The most recent milestone is associated with the first use of the protein language models (PLMs), which occurred in 2024 [73]. PLMs are used to generate inputs into the predictive models, and they are typically applied in conjunction with deep neural networks, which is the case for both MoRF predictors that applied PLMs [73,74]. More specifically, MoRF_ESM uses the ESM-2 PLM [87] and a deep transformer network [73], and IDBindT5 uses the ProtT5 PLM [88] and a deep feedforward

Table 1. Detailed summary of MoRF predictors. Methods are sorted chronologically; bold font denotes the methods covered in the 2019 survey [30]. 'Predictive model' column includes a feed forward network (FNN), a convolutional network (CN), a Bidirectional Long Short-Term Memory (BLSTM) network, and a support vector machine (SVM). 'Availability' column includes web server (WS), source code (SC), both (WS+SC), never available (NA; original article does not provide information on availability), and no longer available (NLA; original article provides links to WS and/or SC but these links no longer work). 'URL' gives pages where a given method was available as of September 2024. 'Citations' column includes total citations with annual citations inside brackets; these data were collected from Google Scholar in September of 2024. For methods published in multiple articles, we use the reference with the highest citation count to avoid duplicate counting.

Method name (year published)	Ref.	Uses machine learning (ML)	Predictive model	Uses deep learning (protein language model)	Availability as of Sept 2024	URL	Citations total (per year)
α-MoRFpred (2005)	[28]	Yes	Discriminant analysis	No	NA	NA	703 (35.2)
α-MoRFpred II (2007)	[47]	Yes	FFN	No	NA	NA	355 (19.7)
retro-MoRFs (2010)	[48]	No	Sequence alignment	No	NA	NA	53 (3.5)
MoRFpred (2012)	[31,49]	Yes	SVM	No	WS	http://biomine.cs.vcu.edu/servers/MoRFpred/	367 (28.2)
MFSPSSMpred (2013)	[50]	Yes	SVM	No	NLA		68 (5.7)
$MoRF_{CHiBi}$ (2015)	[51]	Yes	SVM	No	WS+SC	https://morf.msl.ubc.ca/index.xhtml (WS) https://gsponerlab.msl.ubc.ca/software/morf_chibi/(SC)	83 (8.3)
DISOPRED3 (2015)	[52]	Yes	SVM	No	WS+SC	http://bioinf.cs.ucl.ac.uk/psipred/(WS) http://bioinfadmin.cs.ucl.ac.uk/downloads/DISOPRED/(SC)	886 (88.6)
$MoRF_{CHiBi}$ SYSTEM (2015)	[53,54]	Yes	Meta predictor that combines $MoRF_{CHiBi}$ [51] and ESpritz [55]	No	WS+SC	https://morf.msl.ubc.ca/index.xhtml (WS) https://gsponerlab.msl.ubc.ca/software/morf_chibi/(SC)	146 (14.6)
fMoRFpred (2016)	[11]	Yes	SVM	No	WS	http://biomine.cs.vcu.edu/servers/fMoRFpred/	156 (17.3)
Predict-MoRFs (2016)	[56]	Yes	SVM	No	SC	https://github.com/roneshsharma/Predict-MoRFs (SC)	34 (3.8)
Fang et al. (2018)	[57]	Yes	SVM	No	NA	NA	8 (1.1)
MoRFPred-plus (2018)	[58]	Yes	SVM	No	SC	https://github.com/roneshsharma/MoRFpred-plus/wiki/MoRFpred-plus (SC)	52 (7.4)
OPAL (2018)	[59]	Yes	SVM	No	WS+SC	http://www.alok-ai-lab.com/tools/opal/(WS) https://github.com/roneshsharma/OPAL/wiki/OPAL-download (SC)	69 (9.9)
OPAL+ (2019)	[60]	Yes	SVM	No	WS+SC	http://www.alok-ai-lab.com/tools/opal_plus/(WS) https://github.com/roneshsharma/OPAL-plus/wiki/OPAL-plus-Download (SC)	41 (6.8)
en_DCNNMoRF (2019)	[61]	Yes	CN	Yes	NLA		17 (2.8)
$MoRF_{MLP}$ (2019)	[62]	Yes	Hybrid of FFN and Naïve Bayes	Yes	NA		10 (1.7)
$MoRF_{MPM}$ (2019)	[63]	Yes	Minimax probability machine	No	SC	https://github.com/HHJHgithub/MoRFs_MPM	8 (1.3)
MoRFPred_en (2019)	[64]	Yes	Hybrid of CNs and SVM	Yes	NLA		9 (1.5)
SPOT-MoRF (2020)	[65]	Yes	Hybrid of Inception-Residual-Squeeze and Excitation network and BLSTM network	Yes	WS+SC	https://sparks-lab.org/server/spot-morf/(WS) http://zhouyq-lab.szbl.ac.cn/download/(SC)	51 (10.2)
$MoRF_{CNN}$ (2021)	[66]	Yes	CN	Yes	NA		6 (1.5)
Res-BiLstm (2021)	[67]	Yes	BLSTM network	Yes	SC	https://github.com/Yanzziang/Transition_Disorder_Prediction (SC)	0 (0)
MoRF-FUNCpred (2022)	[68]	Yes	Ensemble of SVM, Logistic Regression, Decision Tree and Random Forest	No	SC	https://github.com/LiangYu-Xidian/MoRF-FUNCpred (SC)	5 (1.7)
CoMemMoRFPred (2023)	[69]	Yes	Meta predictor that combines flDPnn [70,71], DisoLipPred [72] and $MoRF_{CHiBi}$ [51]	No	WS	http://biomine.cs.vcu.edu/servers/CoMemMoRFPred/(WS)	2 (1)
MoRF_ESM (2024)	[73]	Yes	Transformer network	Yes (ESM-2)	NA		0 (0)
IDBindT5 (2024)	[74]	Yes	FFN	Yes (ProtT5)	SC	https://github.com/jahnl/binding_in_disorder (SC)	2 (2)

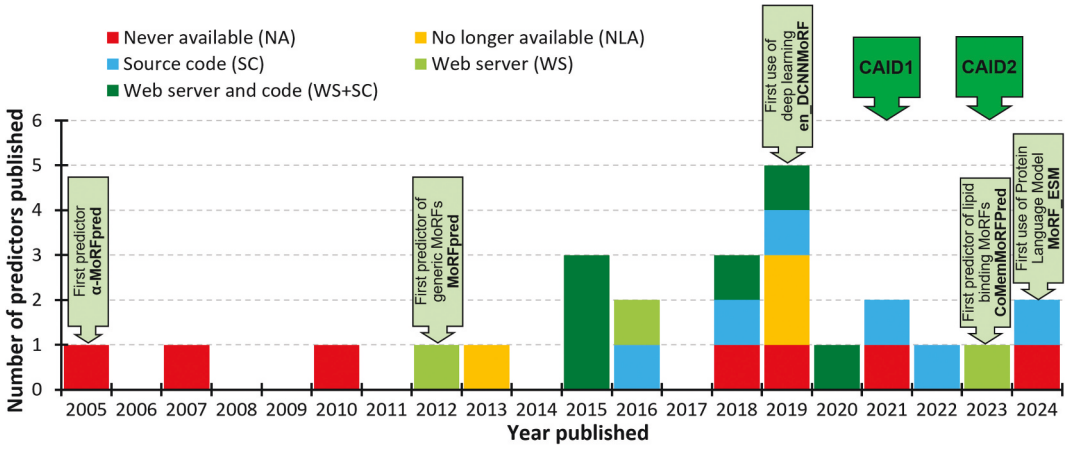

Figure 1. Timeline of the development of MoRF predictors. Color-coded bars denote modes of availability, which include never available (NA), no longer available (NLA), source code (SC), web server (WS), and web server and code (WS+SC). Dark green callouts show major community assessment events. Light green callouts identify major milestones.

network [74]. We believe that this field of research has reached a mature stage, as evidenced by the steady rate of the development efforts over the last 5 year, after a spike between 2015 and 2019 (Figure 1). The new methods will continue to be released at a steady pace that will be fueled by the last three milestones, in particular the development of new deep network architectures and new PLMs, and the expansion of the scope.

3. Availability and impact

We summarize the availability of 25 MoRF predictors in Table 1. We enumerated five scenarios: available as a web server (WS; 3 predictors); available as downloadable source code (SC; 6 predictors); available as both server and code (WS+SC; 6 predictors); never available (NA; 7 predictors) when the corresponding article that introduced a given method did not provide information on availability; and no longer available (NLA; 3 predictors) when the links to the code or server that were provided in the original article no longer work. The WS option is arguably convenient since users can easily access servers using a web browser and the entire prediction process is typically done in the server side without installing software on the user's side. However, servers typically limit individual prediction requests to one protein or a small batch of proteins (for load balancing between users) and the runtime of a given prediction is affected by the current server load. The SC option is less convenient since the code has to be downloaded and installed by users and the computations have to be done on the user's hardware. Some of these installations can be challenging since they rely on multiple third-party applications and may require specific hardware and/or software infrastructure. On the other hand, the SC option facilitates generation of predictions at a large scale and embedding of the corresponding predictor into other bioinformatics pipelines. Altogether, 15 of the 25 methods are available to the end users (60% availability rate), with 6 of them available as both WS and SC. This is similar to the recently estimated 65% availability rate for the predictors of the intrinsic disorder [89] and a bit higher than the below 50% availability for predictors of protein and nucleic acid-binding residues [90,91].

We investigated whether the mode (lack) of availability is associated with the impact of MoRF predictors, which we approximate based on their citations in Google Scholar as of September 2024 (Table 1). We quantified the total number of citations and the annual number of citations (total divided by the number of years since publication), and we used the latter to compare impact across methods. We excluded predictors from 2024 since their citation data is not reliable. The 25 MoRF predictors were cited altogether about 3100 times. More importantly, we found that predictors that offer WS were cited at a much higher rate, i.e. median annual citations of 17.3 for the methods available as only WS and 10.1 for the tools available as code and web server, when compared with the other three options, i.e. median annual citations of 2.6, 2.8, and 1.7 for the predictors that were never available, no longer available, and available as only SC, respectively. Our observation that the availability of the WS option substantially boosts citations agrees with a recently released broader analysis of the availability and impact of sequence-based predictors of protein structure and function [92]. We hypothesize that tools available as WSs are more popular because users may need their predictions in an *ad hoc* manner that would not justify the installation effort and/or may not have the computational resources and experience needed to install and run the predictors locally.

4. Predictive performance

Assessments of the predictions of ligand-binding IDRs were included in the two recently completed community-organized Critical Assessment of Intrinsic Disorder (CAID) events: CAID1 in 2021 [93] and CAID2 in 2023 [94] (Figure 1). This inclusion demonstrates the importance and relevance of MoRF predictors. These evaluations were performed by independent assessors who evaluated predictors that were provided by their authors before the event started. A large number of predictors were tested on blind test datasets (authors of predictors did not have access to the test proteins) using community-accepted

metrics that quantify predictive quality. The CAID evaluations are arguably more objective when compared to the smaller-scale tests that are performed when individual predictive tools are published. Moreover, the fact that the participating predictors are run by the same assessors on the same hardware platform facilitates reliable and consistent comparison of runtime.

CAID2 evaluated 32 predictors of binding IDRs that included 4 MoRF predictors: DISOPRED3 [52], MoRFchibi_light and MoRFchibi_web that are part of the MoRFchibi SYSTEM [53,54], and OPAL [59]. Figure 2 summarizes these results by comparing the top 10 predictors of binding IDRs that were ranked based on two popular metrics: Area Under the ROC Curve (AUC; *y*-axis in Figure 2) and Area Under the Prediction–Recall Curve (AUPRC, *x*-axis in Figure 2). Following CAID2, we also include the F1 metric that quantifies performance based on the highest point on the precision – recall curve, i.e. maximal F1 values that can be obtained by a given predictor [94] (callouts in Figure 2). We observed that 3 of the 4 MoRF predictors were ranked among the top 10 predictors of binding IDRs in CAID2 (Figure 2). These three methods secured the highest AUPRC values and relatively high AUC values, which placed them in the best top-right quadrant in Figure 2. Moreover, their F1 scores were 0.36 for MoRFchibi_web, 0.35 for OPAL, and 0.34 for MoRFchibi_light. MoRFchibi_web was arguably the best predictor when considering both the predictive performance and runtime. It generated predictions in about 2.5 min per protein, secured the highest AUPRC of 0.284, the second highest AUC of 0.751, and MCC of 0.36, behind only the ENSHROUD method that obtained nearly identical AUC of 0.753 and MCC of 0.36 but much lower AUPRC of 0.252. Altogether, these results demonstrate that current MoRF predictors offer competitive levels of predictive performance.

5. Expert opinion

Computational prediction of MoRFs in protein sequences is a mature field of research with deep historical roots that stretch over 20 years. We show that the current tools are relatively accurate and that recently developed methods have already taken advantage of recent machine learning advances, including the use of sophisticated deep neural networks (e.g. transformers) and protein language models (e.g. EMS-2 and ProtT5). We believe that these efforts will continue at a steady pace in the foreseeable future as new deep network architectures and PLMs will be developed and released. In particular, we observe a recent trend in the development of PLMs that have begun to target specific classes/families of proteins, with examples of ProGen that focuses on certain families of lysozymes [95] and IgLM on antibodies [96]. Similar efforts toward developing PLMs that target proteins with MoRFs should drive further improvements in accuracy for the MoRF predictors. We also foresee further expansion of the scope

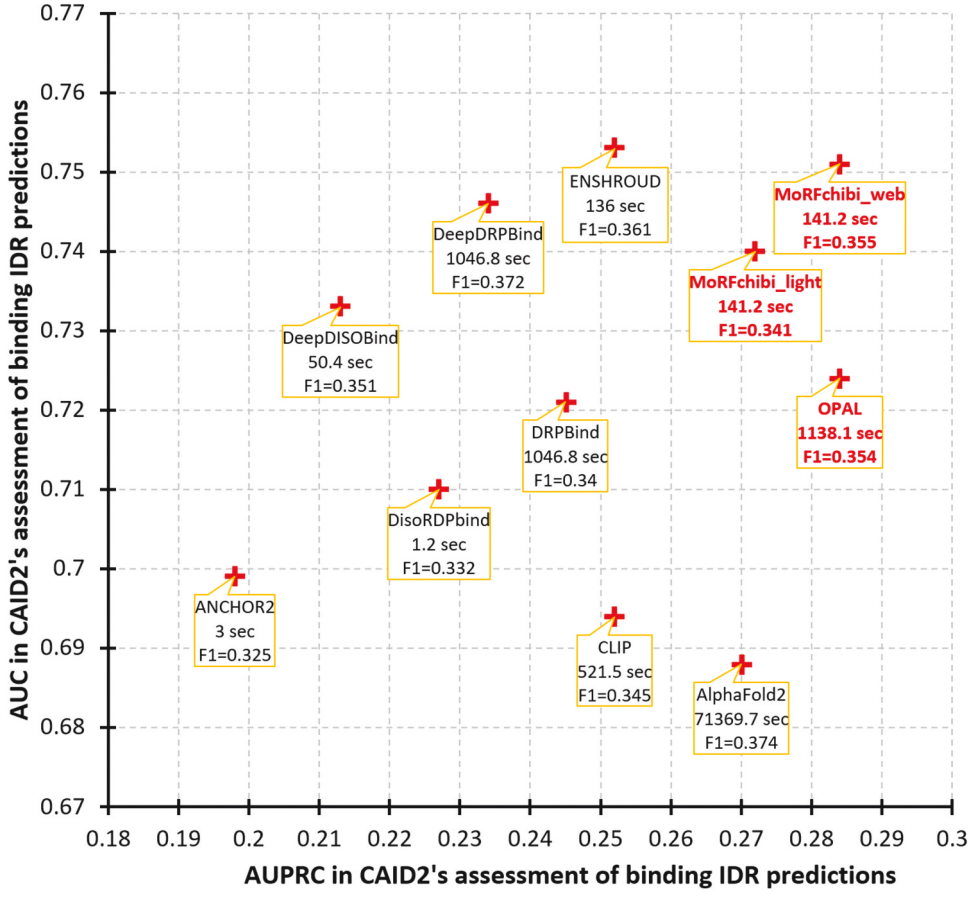

Figure 2. Comparison of predictive performance for the prediction of binding IDRs in the CAID2 experiment [94]. The performance was measured using AUC (*y*-axis), AUPRC (*x*-axis), F1 (callouts), and runtime measured per 1000 amino acids long protein (callouts). MoRF predictors are highlighted by bold font in red color in the callouts.

of the MoRF predictions to additional types of partner molecules, such as DNAs and RNAs.

Given that this field has reached the mature stage, we believe that efforts should be shifted to improving the availability of the MoRF predictions to the end users. This could be done in three complementary ways. **First**, the authors of the new predictors should be required to offer and maintain a web server for their tools. This should substantially increase impact, as we demonstrated empirically for the already published predictors, and we argue that the corresponding cost is relatively low. We believe that the requirement to support web servers for an extended period of time should be enforced at the point of their publication. Several venues stipulate these requirements including the *Bioinformatics* journal (application notes articles; minimum of 2 years of support), *Journal of Molecular Biology* ('Computation Resources for Molecular Biology' issue; 3 years of support), and *Nucleic Acids Research* journal (web server issue; 5 years of support). These requirements should be unified and potentially extended to over 5 years, which in our view would benefit both the developers (boosted impact) and users (improved access). **Second**, the web servers of the leading MoRF predictors should be popularized via inclusion into centralized predictive resources, which provide easy access to multiple predictors that cover a broad spectrum of structural and functional aspects of proteins. Several such resources are available including (alphabetically) Brewery [97,98], CAID prediction portal [99], DEPICTER [100,101], MULTICOM [102,103], PredictProtein [104,105], RIDAO [106] and PSIPRED workbench [107,108]. As of October 2024, the CAID portal includes three MoRF predictors (DISOPRED3, MoRFchibi SYSTEM, and OPAL) [99], DEPICTER covers the MoRFchibi SYSTEM [101], and PSIPRED workbench includes DISOPRED3 [108]. These efforts should be strengthened by expanding into other resources. **Third**, pre-computed results generated by MoRF predictors should be made available via the existing databases of the intrinsic disorder predictions, which include D^2P^2 [109], MobiDB [85,110] and DescribePROT [111,112]. These resources offer access to large collections of pre-computed predictions that span hundreds and even thousands of organisms, and which can be conveniently searched and obtained nearly instantly via a web interface. These databases address several issues related to the direct use of predictors which could be difficult (i.e. finding server or code could be challenging and making predictions could be time-consuming) and wasteful (different users make the same predictions when studying the same proteins). However, predictors still have to be used when attempting to obtain results for proteins that are not included in these databases. We note that as of October 2024 DescribePROT includes prediction of the MoRFchibi SYSTEM [101] for 2.3 million proteins from 273 organisms while the other two databases do not cover MoRF predictions. Adding MoRF predictors to the other resources, particularly MobiDB that covers 245 million proteins, would substantially improve the availability of the MoRF predictions.

Prediction of the MoRFs in protein sequences should be subsequently followed by modeling structures of the resulting protein–protein, protein–peptide, and protein-lipid complexes (i.e. MoRFs typically fold upon binding). Modeling these interactions for IDRs, including MoRF regions, is rather challenging and relatively few suitable tools are currently available. One of the first methods that can handle docking for intrinsically disordered regions is IDP-LZerD [113,114]. Importance of docking for modeling these interactions can be supported with numerous examples, such as the work on the intrinsically disordered NUPR1 protein [115–117]. A relatively recent investigation of methods for docking with IDRs reveals that three tools produce relatively good results [118]: IDP-LZerD [113,114], CABS-Dock [119] and AlphaFold-Multimer [120]. However, the atomic-level details of the structures that they produce require further improvements [118]. Coupling accurate sequence-based MoRF predictions with an equally accurate subsequent predictions of the complex structure would provide powerful means to enable a more comprehensive understanding of the protein–ligand interactions. These investigations, particularly when performed jointly between these two research communities, deserve more attention.

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Declaration of interest

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