

# CAID prediction portal: a comprehensive service for predicting intrinsic disorder and binding regions in proteins

Alessio Del Conte<sup>1</sup>, Adel Bouhraoua<sup>1</sup>, Mahta Mehdiabadi<sup>1</sup>, Damiano Clementel<sup>1</sup>, Alexander Miguel Monzon<sup>2</sup>, CAID predictors, Silvio C.E. Tosatto<sup>1,\*</sup> and Damiano Piovesan<sup>1</sup>

<sup>1</sup>Department of Biomedical Sciences, University of Padova, via Ugo Bassi 58b, 35121 Padova, Italy and <sup>2</sup>Department of Information Engineering, University of Padova, via Giovanni Gradenigo 6/B, 35131 Padova, Italy

Received March 22, 2023; Revised April 26, 2023; Editorial Decision May 07, 2023; Accepted May 10, 2023

## ABSTRACT

Intrinsic disorder (ID) in proteins is well-established in structural biology, with increasing evidence for its involvement in essential biological processes. As measuring dynamic ID behavior experimentally on a large scale remains difficult, scores of published ID predictors have been tried to fill this gap. Unfortunately, their heterogeneity makes it difficult to compare performance, confounding biologists wanting to make an informed choice. To address this issue, the Critical Assessment of protein Intrinsic Disorder (CAID) benchmarks predictors for ID and binding regions as a community blind-test in a standardized computing environment. Here we present the CAID Prediction Portal, a web server executing all CAID methods on user-defined sequences. The server generates standardized output and facilitates comparison between methods, producing a consensus prediction highlighting high-confidence ID regions. The website contains extensive documentation explaining the meaning of different CAID statistics and providing a brief description of all methods. Predictor output is visualized in an interactive feature viewer and made available for download in a single table, with the option to recover previous sessions via a private dashboard. The CAID Prediction Portal is a valuable resource for researchers interested in studying ID in proteins. The server is available at the URL: <https://caid.idpcentral.org>.

## GRAPHICAL ABSTRACT



## INTRODUCTION

The study of intrinsically disordered proteins and regions (IDPs/IDRs), which do not adopt a fixed three-dimensional fold in isolation under physiological conditions, is now a well-established field in structural biology. Over the past two decades, there has been increasing evidence for the involvement of IDPs and IDRs in a variety of essential biological processes, making them promising novel targets for drug discovery (1). While experimental methods can detect intrinsic structural disorder, such as X-ray crystallography, nuclear magnetic resonance spectroscopy, small-angle X-ray scattering, circular dichroism, and Förster resonance energy transfer, directly measuring their dynamic behavior and their context-dependent structural disorder remains difficult (2). Furthermore, various types of experiments emphasize distinct functional mechanisms of IDPs, commonly identified as disorder ‘flavors’, including flexibility, folding-upon-binding and conformational heterogeneity (3).

Dozens of ID prediction methods have been published, and both predicted and experimentally derived properties of IDRs, as well as annotations related to their function, are stored in dedicated databases (4). However, the large variety of available predictors makes it difficult to compare their performance, which can confound biologists wanting to make an informed choice.

\*To whom correspondence should be addressed. Tel: +39 049 827 6269; Email: [silvio.tosatto@unipd.it](mailto:silvio.tosatto@unipd.it)

To address this issue, the Critical Assessment of Protein Intrinsic Disorder (CAID) (2) was introduced to benchmark ID and binding predictors on a community-curated dataset of novel proteins obtained from the DisProt database (5). In CAID, participants submit their implemented prediction software to the organizers, who generate predictions by executing the software on selected protein targets whose disorder annotations were not previously available. Given a new protein sequence, the task of an IDR predictor is to assign a score to each residue for the tendency to be intrinsically disordered at any stage of the protein life. In CAID, both the accuracy of prediction methods and technical aspects related to software implementation are evaluated. However, accessing the prediction power of the tools is not always possible. Often, the software is not publicly available, exists solely as a stand-alone executable, or is available as a web server with limitations. Moreover, publicly available methods are not standardized and require informed use, often entailing careful reading of the corresponding publication and interpreting predictors' output.

To address these issues, we present the CAID Prediction Portal, a web server that executes all CAID methods with a single click on a user-defined input sequence. The server generates a standardized output and facilitates comparing methods, and it produces a consensus prediction that highlights high-confidence disordered regions. Disordered (or binding) residues are identified by selecting a threshold on the prediction score. Depending on the type of benchmark, different thresholds can be selected, leading to different results. To guide the user in selecting the best parameters, the website is accompanied by extended documentation that explains the meaning of the different statistics presented in CAID and provides a brief description of all the methods. The predictors' output is rendered in a feature viewer and made available for download in a single table. While anonymous usage of the CAID Prediction Portal is always permitted, interested users can choose to use an optional log in to recover previous sessions via a private dashboard.

## IMPLEMENTATION

An overview of the CAID Prediction Portal is provided in Figure 1. The CAID Prediction Portal needs to execute many different predictors on the same input sequence, provided by the user. To do so, we implemented a back-end interface using the Django REST framework (DRF, <https://www.django-rest-framework.org>) that interacts with the scheduler controller of a computing cluster through the Distributed Resource Management Application API (DRMAA) (6), a high-level API that provides a standardized interface for submitting and managing jobs on a wide range of cluster systems. In our specific implementation, we used the Slurm Workload Manager (<https://slurm.schedmd.com>) as a job scheduler for the cluster. The purpose of this implementation is to allow users to submit, monitor and manage jobs on the computing cluster through a friendly web interface which exploits the RESTful API provided by the DRF. We also implemented various management features, such as the ability to stop or delete jobs, and to retrieve the job state, history and outputs for a particular user.

The server provides OAuth 2.0 authentication for ORCID users. When authenticated the user is able to recover previous sessions via a private dashboard. Non-authenticated users are allowed to create new jobs and access the results. However, the amount of resources available to a single non-authenticated user is more limited, meaning that the number of daily and burst requests allowed is reduced.

The DRF back-end is also responsible for managing all the possible jobs that can be submitted to the cluster, the resources to allocate for each specific job (e.g. CPUs, random access memory), and the dependencies that can be created between different jobs.

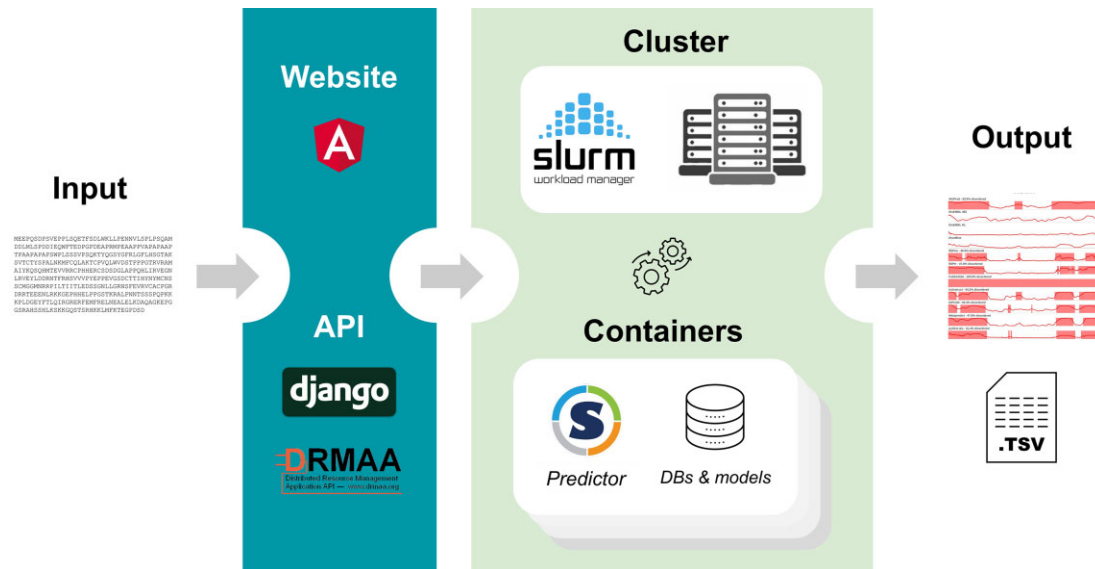
For the CAID Prediction Portal, we created separate jobs for each of the available predictors, and a few additional jobs for creating input data for some predictors such as PSI-BLAST (7), HHblits (8), SPIDER2 (9). This separation of predictors into different jobs is crucial as it provides flexibility to execute only the predictors of interest and display the results of fast predictors without waiting for others to finish.

The CAID Prediction Portal includes a server (dark background), which accepts a protein sequence as input, and a computing cluster (pale background), which generates the output, which is available as a table (TSV format) and rendered in a dynamic feature viewer on the web interface.

## Standardization

We used Singularity (<https://sylabs.io>) containers to containerize all the predictor software in order to standardize the input and output data, and ensure reproducible results. By containerizing the software, we can ensure that the software runs consistently across different machines, and most importantly it is not needed to install it manually in each machine. Furthermore, containerizing the predictors enables us to package all the necessary software and dependencies together, making it easier to deploy and update the predictors. With the creation of the container we also included scripts that are executed before and after the predictor, in order to standardize the input and output of the container, creating an interface with the predictor software. The input of the predictor is a FASTA file containing multiple sequences, and the predictor is executed on each sequence, producing one output per sequence (please note that this should not be confused with the input of the CAID server, which is restricted to a single sequence). The execution time of the predictor for each sequence is also recorded. If the predictor generates multiple outputs, each output will be stored in a distinct directory corresponding to the different variations, or 'flavors,' of the predictor.

Some software present in the CAID Prediction Portal requires additional inputs, such as the results of PSI-BLAST, HHblits, or SPIDER2, to make their predictions. These additional inputs can be created inside the software's container itself, but they can also be provided in most of the cases as an additional parameter. This ensures that the computation of common inputs is not duplicated, leading to faster and more efficient predictions.



**Figure 1.** Overview of the CAID Prediction Portal implementation.

We used Singularity containers over Docker (<https://www.docker.com>) containers because Singularity is designed specifically for high-performance computing environments and has several advantages in the context of computing clusters. Firstly, Singularity does not require root access, making it easier to deploy and manage in a shared computing environment. Secondly, Singularity is optimized for running scientific workloads, with features such as support for MPI (Message Passing Interface) and GPUs (Graphical Processing Units). Thirdly, Singularity images can be easily hosted on a variety of storage systems, such as local filesystems, networked file systems, and cloud storage.

To make the container size smaller, some large datasets such as UniRef90 (10), Uniclust30 (11) or large machine learning models are mounted inside the container at runtime. This approach allows the container to access these datasets only when needed, rather than including them in the container itself. However, it is important to note that if these mounts are not created, the script that runs the predictor inside the container will fail with an error, since it will not be able to access the required data.

In order to provide a comparison baseline, we also integrate the AlphaFold-disorder (12) method that infers disorder and binding predictions by exploiting AlphaFold predicted structures available in public databases (13).

As the last step of our standardization process, we opted to create individualized tasks for each predictor that can be conveniently executed through the CAID Prediction Portal. This implementation grants users a heightened level of flexibility in their selection of methods, allowing them to make informed decisions that best suit their specific needs. Each predictor execution is linked to an API call through the portal's front-end interface, while also remaining compatible with stand-alone usage for batch executions. The API is publicly available and lets third party services request specific predictions on demand. Full documentation is available on the website.

## Benchmarking

The CAID Prediction Portal includes a CAID page (<https://caid.idpcentral.org/challenge>) which contains information about how the challenge is organized, a detailed description of the methods, and the main benchmarking results. In Table 1, we reported all methods available in the CAID server along with the corresponding publication when available. These methods are a subset of those evaluated in the second round of the CAID challenge, i.e. those for which the authors gave permission or those that were already publicly available and licensed for free use. Some of the methods can include more than one predictor (disorder and binding) and the same predictor can generate more than one output (different flavors) representing different implementations (fast, slow), training strategies (dataset), or prediction features (DNA/RNA/protein binding, linker, short/long region, etc.). Given the repertoire of different flavors predicted by the various methods, in the CAID Prediction Portal, we divided them into two broad disorder and binding categories. Users interested in specific subcategories or flavors are invited to read the description of the methods as reported on the website.

All methods generate predictions from the protein sequence. Some methods require additional input which is generated by helper methods, e.g. BLAST or HHblits for sequence profiles. In those cases, the additional input is generated once and shared with all dependent methods.

The AlphaFold-disorder (12) method, instead of using the sequence, takes as input the protein structure predicted by AlphaFold. In the CAID Prediction Portal the structure is retrieved directly from the AlphaFoldDB (13) database by searching the UniProtKB accession number. The server tries to retrieve the accession number by querying the UniProtKB mapping service with the provided sequence encoded with the CRC64 algorithm, and selecting the first result. If the protein sequence is not present in the

**Table 1.** Predictors included in the CAID prediction portal

Name	Type (flavour) *	Authors	Reference
AIUPred-0.5	Disorder	Gábor Erdős, Zsuzsanna Dosztányi	
AlphaFold-disorder	Disorder (Disorder, RSA), Binding	Damiano Piovesan, Alexander Miguel Monzon, Silvio C E Tosatto	(12)
ANCHOR2	Binding	Bálint Mészáros, Gábor Erdős, Zsuzsanna Dosztányi	(14)
APOD	Disorder	Zhenling Peng, Qian Xing, Lukasz Kurgan	(15)
AUCpred	Disorder	Sheng Wang, Jianzhu Ma, Jinbo Xu	(16)
bindEmbed2IHDR	Binding (idrGeneral, idrNuc, rawGeneral, rawNuc)	Burkhard Rost	(17)
DeepDISObind	Binding	Fuhao Zhang, Bi Zhao, Wenbo Shi, Min Li, Lukasz Kurgan	(18)
DeepIDP-2L	Disorder	Yi Jun Tang, Yi-He Pang, Bin Liu	(19)
DisEMBL	Disorder (dis465, disHL)	Rune Linding, Lars Juhl Jensen, Francesca Diella, Peer Bork, Toby J Gibson, Robert B Russell	(20)
DisoMine	Disorder	Gabriele Orlando, Daniele Raimondi, Francesco Codicè, Francesco Tabaro, Adrián Díaz, Wim Vranken	(21)
DisoPred	Disorder	Min Li, Yida Wang, Fuhao Zhang	
DISOPRED3	Disorder, Binding	David T Jones, Domenico Cozzetto	(22)
DisPredict2	Disorder	Sumaiya Iqbal, Md Tamjidul Hoque	(23)
DisPredict3	Disorder	Md Wasi Ul Kabir, Md Tamjidul Hoque	
DRPBind	Binding (DNA, RNA, Protein, DeepDNA, DeepRNA, DeepProtein)	Alok Sharma, Ronesh Sharma, Tatsuhiko Tsunoda	(24)
ENSHROUD	Binding (all, nucleic, protein)	Min Li, Fuhao Zhang, Pengzhen Jia	
ESpritz	Disorder (D, N, X)	Ian Walsh, Alberto J M Martin, Tomás Di Domenico, Silvio Tosatto	(25)
fIDPlr	Disorder	Gang Hu, Akila Katuwawala, Kui Wang, Zhonghua Wu, Sina Ghadermarzi, Jianzhao Gao, Lukasz Kurgan	(26)
fIDPnn	Disorder	Gang Hu, Akila Katuwawala, Kui Wang, Zhonghua Wu, Sina Ghadermarzi, Jianzhao Gao, Lukasz Kurgan	(26)
FoldUnfold	Disorder	Oxana V Galzitskaya, Sergiy O Garbuzynskiy, Michail Yu Lobanov	(27)
IDP-Fusion	Disorder	Yi Jun Tang, Bin Liu	
IsUnstruct	Disorder	Oxana V Galzitskaya, Michail Yu Lobanov	(28)
IUPred3	Disorder	Gábor Erdős, Mátyás Pajkos, Zsuzsanna Dosztányi	(29)
Metapredict (V2)	Disorder	Ryan J Emenecker, Daniel Griffith, Alex S Holehouse	(30)
MobiDB-lite	Disorder	Marco Necci, Damiano Piovesan, Zsuzsanna Dosztányi, Silvio C E Tosatto	(31)
MoRFchibi	Binding (web, light)	Nawar Malhis, Matthew Jacobson, Jörg Gspöner	(32)
OPAL	Binding	Ronesh Sharma, Gaurav Raicar, Tatsuhiko Tsunoda, Ashwini Patil, Alok Sharma	(33)
PredIDR	Disorder (long, short)	Kun-Sop Han, Chol-Song Kim, Myong-Chol Ma	
PreDisorder	Disorder	Xin Deng, Jesse Eickholt, Jianlin Cheng	(34)
ProBiPred	Binding (nucleic, protein)	Lea I M Krautheimer, Michael Bernhofer, Burkhard Rost	
pyHCA	Disorder	Isabelle Callebaut, Tristan Bitard Feildel	(35)
rawMSA	Disorder	Claudio Mirabello, Björn Wallner	
RONN	Disorder	Zheng Rong Yang, Rebecca Thomson, Philip McNeil, Robert M Esnouf	(36)
s2D-2	Disorder	Pietro Sormanni, Carlo Camilloni, Piero Fariselli, Michele Vendruscolo	(37)
SETH_0	Disorder	Dagmar Ilzhöfer, Michael Heinzinger, Burkhard Rost	(38)
SETH_1	Disorder	Dagmar Ilzhöfer, Michael Heinzinger, Burkhard Rost	(38)
SPOT-Disorder	Disorder	Jack Hanson, Yuedong Yang, Kuldip Paliwal, Yaoqi Zhou	(39)
SPOT-Disorder-Single	Disorder	Jack Hanson, Kuldip Paliwal, Yaoqi Zhou	(40)



**Table 1.** Continued

Name	Type (flavour) *	Authors	Reference
SPOT-Disorder2	Disorder	Jack Hanson, Kuldip Paliwal, Thomas Litfin, Yaoqi Zhou	(41)
VSL2	Disorder	Kang Peng, Predrag Radivojac, Slobodan Vucetic, A Keith Dunker, Zoran Obradovic	(42)

UniprotKB, no structure can be downloaded and the predictor will fail to execute.

Methods are listed in alphabetical order. (\*) The same package can include multiple predictors, each generating multiple outputs. The Type column indicates the type of output and the values in parentheses indicate the predictor name suffixes which correspond to different flavors or different implementations. When available, the corresponding publication is provided along with the corresponding authors. For new methods, authors are those that submitted the method to CAID.

### Website

The CAID Prediction Portal website allows users to execute the available predictors on a provided protein sequence. The server can process only one sequence at a time. The predictors that are going to be executed can be configured, with some pre-made settings (e.g. running only disorder, binding or quick predictors), or manually, selecting the predictors of interest. When submitting a new job, the user can also decide to associate a description to the job and an email address that will be used to send a notification when all the predictors will finish executing. The job name is helpful to attach a text description or just a meaningful identifier to the input sequence, while the user email can be used to receive a notification when the calculation is done.

After the submission, the user will be redirected to the results page. At the top of the page, a header card will be displayed, this contains various information about the execution status of the predictors, along with a control for stopping the jobs still executing, and a button to download all the currently available results in tab-separated values (TSV) format.

The result page will poll the back-end server to update the status of the jobs that did not finish yet, to retrieve their current status and download the results from the server when available. These results will be used to create and update a feature viewer, to display the outputs of the predictors. These outputs are all aligned to the protein sequence that was submitted, and they can be of two different types, a binary score and a probability score.

The feature viewer offers various controls to manipulate the display of the results. The predictions can be filtered based on their type (disorder or binding), the threshold for the binary score can be changed from the predictor's default to optimized thresholds as provided by CAID. Optimized thresholds correspond to a selection of metrics reported by the CAID challenge. The optimization strategy depends on the type of metric and validation dataset, those available in the CAID Prediction Portal are described in the website documentation, while we refer to the CAID paper (2) for

a full description of all possible benchmarks. The methods can be sorted based on their performance in CAID, disorder (or binding) content, or alphabetically based on their names.

In the feature viewer, a consensus is also computed with the prediction of the available predictors, divided in the two categories, disordered and binding. This consensus is calculated as a majority vote of the binary predictions available. The consensus will also be influenced by the chosen threshold. In order to compare predictions with structural and functional domains, Pfam (43) and Gene3D (44) assignments from the InterProScan (45) output are reported. These annotations are calculated in parallel on a separate job, and shown as separate tracks on the feature viewer when available.

While anonymous usage of the CAID Prediction Portal is always permitted, interested users can choose to recover previous sessions via a private dashboard after a login using their ORCID credentials, where all the previously submitted jobs can be accessed. An anonymous user can recover a previous job by saving its UUID and later use it to access the results again.

### CONCLUSIONS

The CAID Prediction Portal is a valuable resource for researchers and scientists working in the field of protein structure and intrinsic disorder prediction. By combining state-of-the-art ID and binding prediction methods with the CAID optimization strategy, the portal allows users to calculate and compare different predictions in a single view. Predictions can be dynamically adapted on the fly by choosing different CAID optimization strategies. For example, the user can focus on precision over recall, or on the contrary, can relax the optimization cutoffs to expand disorder detection.

One of the key advantages of the portal is its speed and dynamic nature, as the server displays the results of a method as soon as the calculation is completed. Additionally, the portal's modular and extensible design makes it easy to add or remove prediction methods at any time, providing maintainers with the flexibility to adapt to new developments in the field. Finally, all methods are standardized and their output is made available in the same format.

The CAID section of the portal provides benchmarking results and statistics that can guide users in the evaluation of the performance of the predictors. This information is particularly useful for researchers who are looking to improve their methods and algorithms.

Moreover, the CAID Prediction Server is integrated into the OpenEBench (46) infrastructure for community benchmarking experiments of computational methods in the life

sciences, which displays the results of various CAID editions in a dedicated section. This integration allows for the prediction output generated by the portal to be used in generating assessment results, thereby facilitating a transition from a timeframe-based challenge (as was the case for CAID rounds 1 and 2) into a continuous assessment.

Last but not least, the CAID portal will help inform and improve the selection ID predictors available in the Mo-biDB database (47) for large-scale annotation of ID in proteins. The latter is the main source of ID data for core data resources such as InterPro (48) and UniProtKB (49). Any small improvement in ID prediction performance documented in the CAID Portal therefore has a large potential knock-on effect in improving ID annotations across the known protein universe.

In summary, the CAID Prediction Portal is a valuable resource that can help researchers develop more accurate and effective methods for predicting intrinsic protein disorder and their binding regions. By enabling continuous assessment and benchmarking of different prediction methods, the portal can help accelerate progress in this important field and benefit the scientific community at large.

## DATA AVAILABILITY

The CAID Prediction Portal is freely available at <https://caid.idpcentral.org>.

## ACKNOWLEDGEMENTS

This publication is part of a project that has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreements No 778247 and No 823886. This work was supported by ELIXIR, the research infrastructure for life-science data. The authors are grateful to members of the BioComputing UP group for insightful discussions.

## FUNDING

The European Union's Horizon 2020 research and innovation programme MSCA-RISE [778 247, 823 886, 952 334]; ELIXIR, the research infrastructure for life-science data; COST Action ML4NGP [CA21160] is supported by COST (European Cooperation in Science and Technology) under the EU Framework Programme Horizon Europe; Italian Ministry of University and Research (MIUR) – PRIN [2017483NH8]; NextGenerationEU, PNRR – 'ELIXIR × NextGenerationIT: Consolidamento dell'Infrastruttura Italiana per i Dati Omici e la Bioinformatica – ElixirxNextGenIT' [IR0000010]. Funding for open access charge: University of Padova.  
*Conflict of interest statement.* None declared.

## REFERENCES

- Piovesan,D., Arbesú,M., Fuxreiter,M. and Pons,M. (2022) Editorial: fuzzy interactions: many facets of protein binding. *Front. Mol. Biosci.*, **9**, 947215.
- CAID Predictors, DisProt Curators, Necci,M., Piovesan,D. and Tosatto,S.C.E. (2021) Critical assessment of protein intrinsic disorder prediction. *Nat. Methods*, **18**, 472–481.
- Necci,M., Piovesan,D. and Tosatto,S.C.E. (2016) Large-scale analysis of intrinsic disorder flavors and associated functions in the protein sequence universe. *Protein Sci. Publ. Protein Soc.*, **25**, 2164–2174.
- Piovesan,D., Monzon,A.M., Quaglia,F. and Tosatto,S.C.E. (2022) Databases for intrinsically disordered proteins. *Acta Crystallogr. Sect. Struct. Biol.*, **78**, 144.
- Quaglia,F., Mészáros,B., Salladini,E., Hatos,A., Pancsa,R., Chemes,L.B., Pajkos,M., Lazar,T., Peña-Díaz,S., Santos,J. *et al.* (2021) DisProt in 2022: improved quality and accessibility of protein intrinsic disorder annotation. *Nucleic Acids Res.*, **50**, D480–D487.
- Troger,P., Rajic,H., Haas,A. and Domagalski,P. (2007) Standardization of an API for distributed resource management systems. In: *Seventh IEEE International Symposium on Cluster Computing and the Grid (CCGrid'07)*. pp. 619–626.
- Schäffer,A.A., Aravind,L., Madden,T.L., Shavirin,S., Spouge,J.L., Wolf,Y.I., Koonin,E.V. and Altschul,S.F. (2001) Improving the accuracy of PSI-BLAST protein database searches with composition-based statistics and other refinements. *Nucleic Acids Res.*, **29**, 2994–3005.
- Steinegger,M., Meier,M., Mirdita,M., Vöhringer,H., Haunsberger,S.J. and Söding,J. (2019) HH-suite3 for fast remote homology detection and deep protein annotation. *BMC Bioinf.*, **20**, 473.
- Yang,Y., Heffernan,R., Paliwal,K., Lyons,J., Dehngang,A., Sharma,A., Wang,J., Sattar,A. and Zhou,Y. (2017) SPIDER2: a package to predict secondary structure, accessible surface area, and main-chain torsional angles by deep neural networks. In: Zhou,Y., Kloczkowski,A., Faraggi,E. and Yang,Y. (eds.) *Prediction of Protein Secondary Structure, Methods in Molecular Biology*. Springer, New York, NY, pp. 55–63.
- UniProt Consortium, Suzek,B.E., Wang,Y., Huang,H., McGarvey,P.B. and Wu,C.H. (2015) UniRef clusters: a comprehensive and scalable alternative for improving sequence similarity searches. *Bioinforma. Oxf. Engl.*, **31**, 926–932.
- Mirdita,M., von den Driesch,L., Galiez,C., Martin,M.J., Söding,J. and Steinegger,M. (2017) Uniclust databases of clustered and deeply annotated protein sequences and alignments. *Nucleic Acids Res.*, **45**, D170–D176.
- Piovesan,D., Monzon,A.M. and Tosatto,S.C.E. (2022) Intrinsic protein disorder and conditional folding in AlphaFoldDB. *Protein Sci.*, **31**, e4466.
- Varadi,M., Anyango,S., Deshpande,M., Nair,S., Natassia,C., Yordanova,G., Yuan,D., Stroe,O., Wood,G., Laydon,A. *et al.* (2022) AlphaFold Protein Structure Database: massively expanding the structural coverage of protein-sequence space with high-accuracy models. *Nucleic Acids Res.*, **50**, D439–D444.
- Mészáros,B., Erdős,G. and Dosztányi,Z. (2018) IUPred2A: context-dependent prediction of protein disorder as a function of redox state and protein binding. *Nucleic Acids Res.*, **46**, W329–W337.
- Peng,Z., Xing,Q. and Kurgan,L. (2020) APOD: accurate sequence-based predictor of disordered flexible linkers. *Bioinformatics*, **36**, i754–i761.
- Wang,S., Ma,J. and Xu,J. (2016) AUCpreD: proteome-level protein disorder prediction by AUC-maximized deep convolutional neural fields. *Bioinformatics*, **32**, i672–i679.
- Littmann,M., Heinzinger,M., Dallago,C., Weissenow,K. and Rost,B. (2021) Protein embeddings and deep learning predict binding residues for various ligand classes. *Sci. Rep.*, **11**, 23916.
- Zhang,F., Zhao,B., Shi,W., Li,M. and Kurgan,L. (2022) DeepDISOBind: accurate prediction of RNA-, DNA- and protein-binding intrinsically disordered residues with deep multi-task learning. *Brief. Bioinform.*, **23**, bbab521.
- Tang,Y.-J., Pang,Y.-H. and Liu,B. (2022) DeepIDP-2L: protein intrinsically disordered region prediction by combining convolutional attention network and hierarchical attention network. *Bioinformatics*, **38**, 1252–1260.
- Linding,R., Jensen,L.J., Diella,F., Bork,P., Gibson,T.J. and Russell,R.B. (2003) Protein disorder prediction: implications for structural proteomics. *Structure*, **11**, 1453–1459.
- Orlando,G., Raimondi,D., Codicè,F., Tabaro,F. and Vranken,W. (2022) Prediction of disordered regions in proteins with recurrent neural networks and protein dynamics. *J. Mol. Biol.*, **434**, 167579.

22. Jones, D.T. and Cozzetto, D. (2015) DISOPRED3: precise disordered region predictions with annotated protein-binding activity. *Bioinformatics*, **31**, 857–863.
23. Iqbal, S. and Hoque, M.T. (2016) Estimation of position specific energy as a feature of protein residues from sequence alone for structural classification. *PLoS One*, **11**, e0161452.
24. Sharma, R., Tsunoda, T. and Sharma, A. (2023) DRPBind: prediction of DNA, RNA and protein binding residues in intrinsically disordered protein sequences. bioRxiv doi: <https://doi.org/10.1101/2023.03.20.533427>, 23 March 2023, preprint: not peer reviewed.
25. Walsh, I., Martin, A.J.M., Di Domenico, T. and Tosatto, S.C.E. (2012) ESpritz: accurate and fast prediction of protein disorder. *Bioinformatics*, **28**, 503–509.
26. Hu, G., Katuwawala, A., Wang, K., Wu, Z., Ghadermarzi, S., Gao, J. and Kurgan, L. (2021) fIDPnn: accurate intrinsic disorder prediction with putative propensities of disorder functions. *Nat. Commun.*, **12**, 4438.
27. Galzitskaya, O.V., Garbuzynskiy, S.O. and Lobanov, M.Y. (2006) FoldUnfold: web server for the prediction of disordered regions in protein chain. *Bioinformatics*, **22**, 2948–2949.
28. Lobanov, M.Y., Sokolovskiy, I.V. and Galzitskaya, O.V. (2013) IsUnstruct: prediction of the residue status to be ordered or disordered in the protein chain by a method based on the Ising model. *J. Biomol. Struct. Dyn.*, **31**, 1034–1043.
29. Erdős, G., Pajkos, M. and Dosztányi, Z. (2021) IUPred3: prediction of protein disorder enhanced with unambiguous experimental annotation and visualization of evolutionary conservation. *Nucleic Acids Res.*, **49**, W297–W303.
30. Emenecker, R.J., Griffith, D. and Holehouse, A.S. (2021) Metapredict: a fast, accurate, and easy-to-use predictor of consensus disorder and structure. *Biophys. J.*, **120**, 4312–4319.
31. Necci, M., Piovesan, D., Clementel, D., Dosztányi, Z. and Tosatto, S.C.E. (2020) MobiDB-lite 3.0: fast consensus annotation of intrinsic disorder flavours in proteins. *Bioinformatics*, **36**, 5533–5534.
32. Malhis, N., Jacobson, M. and Gsponer, J. (2016) MoRFchibi SYSTEM: software tools for the identification of MoRFs in protein sequences. *Nucleic Acids Res.*, **44**, W488–W493.
33. Sharma, R., Raicar, G., Tsunoda, T., Patil, A. and Sharma, A. (2018) OPAL: prediction of MoRF regions in intrinsically disordered protein sequences. *Bioinformatics*, **34**, 1850–1858.
34. Deng, X., Eickholt, J. and Cheng, J. (2009) PreDisorder: ab initio sequence-based prediction of protein disordered regions. *BMC Bioinf.*, **10**, 436.
35. Mirabello, C. and Wallner, B. (2019) rawMSA: end-to-end deep learning using raw multiple sequence alignments. *PLoS One*, **14**, e0220182.
36. Yang, Z.R., Thomson, R., McNeil, P. and Esnouf, R.M. (2005) RONN: the bio-basis function neural network technique applied to the detection of natively disordered regions in proteins. *Bioinformatics*, **21**, 3369–3376.
37. Sormanni, P., Camilloni, C., Fariselli, P. and Vendruscolo, M. (2015) The s2D method: simultaneous sequence-based prediction of the statistical populations of ordered and disordered regions in proteins. *J. Mol. Biol.*, **427**, 982–996.
38. Ilzhöfer, D., Heinzinger, M. and Rost, B. (2022) SETH predicts nuances of residue disorder from protein embeddings. *Front. Bioinforma.*, **2**, 1019597.
39. Hanson, J., Yang, Y., Paliwal, K. and Zhou, Y. (2017) Improving protein disorder prediction by deep bidirectional long short-term memory recurrent neural networks. *Bioinforma. Oxf. Engl.*, **33**, 685–692.
40. Hanson, J., Paliwal, K. and Zhou, Y. (2018) Accurate single-sequence prediction of protein intrinsic disorder by an ensemble of deep recurrent and convolutional architectures. *J. Chem. Inf. Model.*, **58**, 2369–2376.
41. Hanson, J., Paliwal, K.K., Litfin, T. and Zhou, Y. (2019) SPOT-Disorder2: improved protein intrinsic disorder prediction by ensembled deep learning. *Genomics Proteomics Bioinformatics*, **17**, 645–656.
42. Peng, K., Radivojac, P., Vucetic, S., Dunker, A.K. and Obradovic, Z. (2006) Length-dependent prediction of protein intrinsic disorder. *BMC Bioinf.*, **7**, 208.
43. Mistry, J., Chuguransky, S., Williams, L., Qureshi, M., Salazar, G.A., Sonnhammer, E.L.L., Tosatto, S.C.E., Paladin, L., Raj, S., Richardson, L.J. *et al.* (2021) Pfam: the protein families database in 2021. *Nucleic Acids Res.*, **49**, D412–D419.
44. Lewis, T.E., Sillitoe, L., Dawson, N., Lam, S.D., Clarke, T., Lee, D., Orengo, C. and Lees, J. (2018) Gene3D: extensive prediction of globular domains in proteins. *Nucleic Acids Res.*, **46**, D1282.
45. Paysan-Lafosse, T., Blum, M., Chuguransky, S., Grego, T., Pinto, B.L., Salazar, G.A., Bileschi, M.L., Bork, P., Bridge, A., Colwell, L. *et al.* (2023) InterPro in 2022. *Nucleic Acids Res.*, **51**, D418–D427.
46. Capella-Gutierrez, S., Iglesia, D.d., Haas, J., Lourenco, A., Fernández, J.M., Repchevsky, D., Dessimoz, C., Schwede, T., Notredame, C., Gelpi, J.L. *et al.* (2017) Lessons learned: recommendations for establishing critical periodic scientific benchmarking. bioRxiv doi: <https://doi.org/10.1101/181677>, 31 August 2017, preprint: not peer reviewed.
47. Piovesan, D., Del Conte, A., Clementel, D., Monzon, A.M., Bevilacqua, M., Aspromonte, M.C., Iserle, J.A., Orti, F.E., Marino-Buslje, C. and Tosatto, S.C.E. (2023) MobiDB: 10 years of intrinsically disordered proteins. *Nucleic Acids Res.*, **51**, D438–D444.
48. Blum, M., Chang, H.-Y., Chuguransky, S., Grego, T., Kandasamy, S., Mitchell, A., Nuka, G., Paysan-Lafosse, T., Qureshi, M., Raj, S. *et al.* (2021) The InterPro protein families and domains database: 20 years on. *Nucleic Acids Res.*, **49**, D344–D354.
49. The UniProt Consortium (2021) UniProt: the universal protein knowledgebase in 2021. *Nucleic Acids Res.*, **49**, D480–D489.

## APPENDIX

### CAID predictors

Alex S Holehouse<sup>3,4</sup>, Daniel Griffith<sup>3,4</sup>, Ryan J Emenecker<sup>3,4</sup>, Ashwini Patil<sup>5</sup>, Ronesh Sharma<sup>6</sup>, Tatsuhiko Tsunoda<sup>7,8,9</sup>, Alok Sharma<sup>9,10</sup>, Yi Jun Tang<sup>11</sup>, Bin Liu<sup>11</sup>, Claudio Mirabello<sup>12</sup>, Björn Wallner<sup>12</sup>, Burkhard Rost<sup>13</sup>, Dagmar Ilzhöfer<sup>13</sup>, Maria Littmann<sup>13</sup>, Michael Heinzinger<sup>13</sup>, Lea I M Krautheimer<sup>13</sup>, Michael Bernhofer<sup>13</sup>, Liam J McGuffin<sup>14</sup>, Isabelle Callebaut<sup>15</sup>, Tristan Bitard Feildel<sup>16</sup>, Jian Liu<sup>17</sup>, Jianlin Cheng<sup>17</sup>, Zhiye Guo<sup>17</sup>, Jinbo Xu<sup>18</sup>, Sheng Wang<sup>18,19</sup>, Nawar Malhis<sup>20</sup>, Jörg Gsponer<sup>21</sup>, Chol-Song Kim<sup>22</sup>, Kun-Sop Han<sup>22</sup>, Myong-Chol Ma<sup>22</sup>, Lukasz Kurgan<sup>23</sup>, Sina Ghadermarzi<sup>23</sup>, Akila Katuwawala<sup>23,24</sup>, Bi Zhao<sup>25</sup>, Zhenling Peng<sup>26</sup>, Zhonghua Wu<sup>27</sup>, Gang Hu<sup>28</sup>, Kui Wang<sup>28</sup>, Md Tamjidul Hoque<sup>29</sup>, Md Wasi Ul Kabir<sup>29</sup>, Michele Vendruscolo<sup>30</sup>, Pietro Sormanni<sup>30</sup>, Min Li<sup>31</sup>, Fuhua Zhang<sup>31</sup>, Pengzhen Jia<sup>31</sup>, Yida Wang<sup>32</sup>, Michail Yu Lobanov<sup>33</sup>, Oxana V Galzitskaya<sup>33,34</sup>, Wim Vranken<sup>35,36</sup>, Adrián Díaz<sup>35,36</sup>, Thomas Litfin<sup>37</sup>, Yaoqi Zhou<sup>37,38</sup>, Jack Hanson<sup>39</sup>, Kuldip Paliwal<sup>39</sup>, Zsuzsanna Dosztányi<sup>40</sup>, Gábor Erdős<sup>40</sup>.

<sup>3</sup>Department of Biochemistry and Molecular Biophysics, Washington University School of Medicine, St. Louis, Missouri

<sup>4</sup>Center for Biomolecular Condensates, Washington University in St. Louis, St. Louis, MO, USA

<sup>5</sup>Combinatics Inc. Ichikawa-shi, Chiba 272-0824, Japan

<sup>6</sup>Fiji National University, Suva, Fiji

<sup>7</sup>Laboratory for Medical Science Mathematics, Department of Biological Sciences, School of Science, The University of Tokyo, Tokyo, 113-0033, Japan

<sup>8</sup>Laboratory for Medical Science Mathematics, Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences, The University of Tokyo, Tokyo 113-0033, Japan

<sup>9</sup>Laboratory for Medical Science Mathematics, RIKEN Center for Integrative Medical Sciences, Yokohama 230-0045, Japan



- <sup>10</sup>Institute for Integrated and Intelligent Systems, Griffith University, Nathan, Brisbane, QLD 4111, Australia
- <sup>11</sup>School of Computer Science and Technology, Beijing Institute of Technology, Beijing 100081, China
- <sup>12</sup>Division of Bioinformatics, Department of Physics, Chemistry, and Biology, Linköping University
- <sup>13</sup>TUM School of Computation, Information and Technology, Department of Computer Science, TUM (Technical University of Munich), Garching/Munich 85748, Germany
- <sup>14</sup>School of Biological Sciences, University of Reading, Whiteknights, Reading RG6 6AS, UK
- <sup>15</sup>Sorbonne Université, Muséum National d'Histoire Naturelle, UMR CNRS 7590, IMPMC, 75005 Paris, France
- <sup>16</sup>DGA Maîtrise de l'information, 35170 Bruz, France
- <sup>17</sup>Department of Electrical Engineering and Computer Science, University of Missouri – Columbia, Columbia, MO 65211, USA
- <sup>18</sup>Toyota Technological Institute at Chicago, Chicago, IL, USA
- <sup>19</sup>Department of Human Genetics, University of Chicago, Chicago, IL, USA
- <sup>20</sup>Michael Smith Laboratories, The University of British Columbia, Vancouver, BC V6T 1Z4, Canada
- <sup>21</sup>Michael Smith Laboratories, Department of Biochemistry and Molecular Biology, The University of British Columbia, Vancouver, BC V6T 1Z4, Canada
- <sup>22</sup>University of Sciences, Pyongyang, D.P.R. of Korea
- <sup>23</sup>Department of Computer Science, Virginia Commonwealth University, Richmond, VA, USA
- <sup>24</sup>Adimab LLC, Computational Biology, Palo Alto, CA, USA
- <sup>25</sup>Genomics program, College of Public Health, University of South Florida, Tampa, FL, USA
- <sup>26</sup>Research Center for Mathematics and Interdisciplinary Sciences, Shandong University, Qingdao, 266237, China
- <sup>27</sup>School of Mathematical Sciences and LPMC, Nankai University, Tianjin 300071, China
- <sup>28</sup>School of Statistics and Data Science, LPMC and KLM-DASR, Nankai University, Tianjin, China
- <sup>29</sup>Department of Computer Science, University of New Orleans, New Orleans, LA, USA
- <sup>30</sup>Centre for Misfolding Diseases, Yusuf Hamied Department of Chemistry, University of Cambridge, Cambridge CB2 1EW, UK
- <sup>31</sup>Hunan Provincial Key Lab on Bioinformatics, School of Computer Science and Engineering, Central South University, Changsha, 410083, China
- <sup>32</sup>Department of Computer Science and Engineering, School of Electronic Information and Electrical Engineering, Shanghai Jiao Tong University, Shanghai 200240, China
- <sup>33</sup>Institute of Protein Research of the Russian Academy of Sciences, 4 Institutskaya str., Pushchino, Moscow Region 142290, Russia
- <sup>34</sup>Institute of Theoretical and Experimental Biophysics, Russian Academy of Sciences, 142290 Pushchino, Russia
- <sup>35</sup>Interuniversity Institute of Bioinformatics in Brussels, ULB-VUB, Brussels 1050, Belgium
- <sup>36</sup>Structural Biology Brussels, Vrije Universiteit Brussel, Brussels 1050, Belgium
- <sup>37</sup>Institute for Glycomics, Griffith University, Parklands Dr. Southport, QLD 4222, Australia
- <sup>38</sup>Institute of Systems and Physical Biology, Shenzhen Bay Laboratory, Shenzhen 518107, China
- <sup>39</sup>Signal Processing Laboratory, School of Engineering and Built Environment, Griffith University, Brisbane, QLD 4111, Australia
- <sup>40</sup>Department of Biochemistry, Eötvös Loránd University, Pázmány Péter stny 1/c, Budapest H-1117, Hungary