Fusion of Multidisciplinary Research, An International Journal (FMR) , Vol. **4**, Iss. **2**, 2023
https://doi.org/10.63995/MWCU4408

FMR

ARTICLE

Protein Structure Prediction Tools and Computational Approaches

Natalia Garavano, Francisca Sadosky, and Facundo Bulgheroni*

Ca tedra de Fisiologõ a Humana, Facultad de Ciencias Quõ micas, Universidad Nacional de Co rdoba, Casilla de Correo 61, 5000 Co rdoba, Argentina

*Corresponding author: bulgheroni.ndo@agro.uncor.edu

(Received: 09 April 2023; Revised: 07 June 2023; Accepted: 14 July 2023; Published: 25 July 2023)

Abstract

Protein structure prediction is a critical aspect of bioinformatics, aimed at determining the three-dimensional configuration of proteins from their amino acid sequences. With the advent of sophisticated computational approaches, this field has seen significant advancements. Methods like homology modeling, which relies on the similarity between the target protein and known structures, and ab initio modeling, which predicts structures from scratch, have become fundamental tools. Additionally, molecular dynamics simulations and machine learning techniques, such as AlphaFold, have revolutionized the accuracy and speed of predictions. These tools not only enhance our understanding of protein functions and interactions but also facilitate drug discovery and development. The integration of these computational approaches with experimental data is paving the way for more precise and reliable protein structure predictions, ultimately contributing to advancements in various scientific and medical fields.

Keywords: Ab initio modelling; AlphaFold; Bioinformatics; Homology modelling; Machine learning; Molecular dynamics simulations; Protein structure prediction

Abbreviations: AF2: AlphaFold2, CASP: Critical Assessment of Protein Structure Prediction, MD: Molecular dynamics, SBDD: Structure-Based Drug Discovery, SCOP: Structural Classification of Proteins

1. Introduction

Determining the three-dimensional structure of proteins is a fundamental challenge in biophysics and computational biology. Protein structure prediction tools and computational approaches aim to deduce the 3D conformation from the amino acid sequence, a complex task with far-reaching implications for biological research and drug discovery. The process typically involves initializing conformation, conducting conformational searches, selecting structures, reconstructing all-atom models, and refining the predicted tertiary structure. Template-based methods like alignment and threading utilize existing structural templates, while ab initio techniques such as Rosetta build the structure from scratch. Ongoing community efforts like the Critical Assessment of Protein Structure Prediction (CASP) experiments evaluate state-of-the-art methods and drive progress in this field. Key challenges include improving force fields, search algorithms, and modeling capabilities for large and membrane proteins [1, 2, 3, 4, 5].

2. Protein Structure Fundamentals

Determining the three-dimensional structure of proteins is a fundamental challenge in biophysics and computational biology. Proteins are complex biomolecules, and their structure is critical for their function. However, experimentally determining protein structures can be costly and time-consuming. Computational methods offer 'shortcuts' to predicting protein structure and function. Protein structures can be classified into folds, families, and superfamilies based on structural similarity. Despite often having low sequence similarity, proteins with the same fold share a common structural core. This makes structure prediction challenging, as sequence information alone may not be sufficient to accurately predict the folded conformation (Fig. 1). [6, 7, 8, 9].

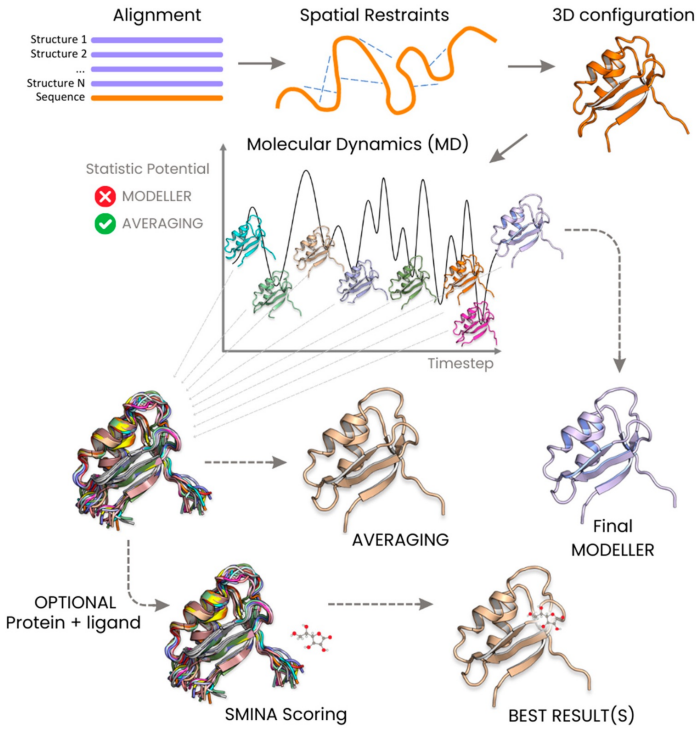

Figure 1. Comparative illustration depicting the workflow of the averaging method in contrast to MODELLER for dynamic protein structure prediction.

The Structural Classification of Proteins (SCOP) database is a widely used resource that classifies proteins based on their structural and evolutionary relationships. The principal levels of classification in SCOP are:

1. **Family:** Proteins with clear evolutionary relationships, typically having >30% sequence identity.
2. **Superfamily:** Proteins with low sequence identity but whose structural and functional features suggest a common evolutionary origin.
3. **Fold:** Proteins with the same major secondary structures arranged in a similar topology, regardless of evolutionary relationships.

Secondary structure prediction is a crucial step in computational protein structure prediction. It involves predicting local secondary structures (alpha helices, beta sheets) based on the amino acid sequence [2]. This is often achieved by leveraging databases of known structures and machine learning techniques, such as:

- **DSSP:** A widely used program for assigning secondary structure to protein residues based on hydrogen bond patterns.
- **Neural Networks:** Artificial neural networks trained on known protein structures to recognize sequence patterns associated with different secondary structures.
- **Support Vector Machines:** Machine learning models that classify residues into secondary structure elements based on sequence features.

While secondary structure prediction can provide valuable insights, accurately predicting the overall three-dimensional fold remains a significant challenge, often requiring more advanced techniques like protein structure prediction tools and computational approaches [10].

3. Comparative Modeling Techniques

Comparative protein structure modeling, also known as homology modeling or template-based modeling, is a widely used technique for predicting the 3D structure of a target protein sequence based on its alignment to one or more known protein structures (templates) [6]. The comparative modeling process typically involves the following main steps:

1. **Fold Assignment:** Identifying suitable template structures that are evolutionarily related to the target sequence.
2. **Target-Template Alignment:** Aligning the target sequence with the selected template(s) to establish residue-residue correspondences.
3. **Model Building:** Constructing an initial 3D model for the target based on the alignment and template structure(s).
4. **Model Evaluation:** Assessing the quality and accuracy of the generated model(s).

Several computer programs and web servers have been developed to automate and streamline the comparative modeling process, including:

- **MODELLER:** A widely used program for comparative protein structure modeling based on satisfaction of spatial restraints derived from the template structures.
- **Phyre2:** A web server that combines multiple sources of structural information to generate 3D models.
- **I-TASSER:** An integrated platform for protein structure and function prediction, incorporating both template-based and ab initio approaches.
- **SWISS-MODEL:** A web server for automated comparative modeling, using rigid body assembly and energy minimization techniques.

4. Fold Recognition Methods

Fold recognition methods, also known as protein threading, are computational techniques used to predict the three-dimensional structure of a target protein by recognizing similarities in its sequence and fold to proteins with known structures. These methods are particularly useful when the target protein lacks homologous sequences with solved structures, making comparative modeling techniques less effective. Sequence similarity-based methods like BLAST can detect closely related proteins, but threading methods that match sequence and shape can identify more distantly related proteins. - Fold recognition methods often combine sequence and structural information, using an energy function to distinguish native from misfolded structures. - Examples of fold recognition servers include FFAS, 3D-PSSM, and GenTHREADER, which can provide annotations for 'orphan' protein sequences (Fig. 2) [11, 12, 13, 14].

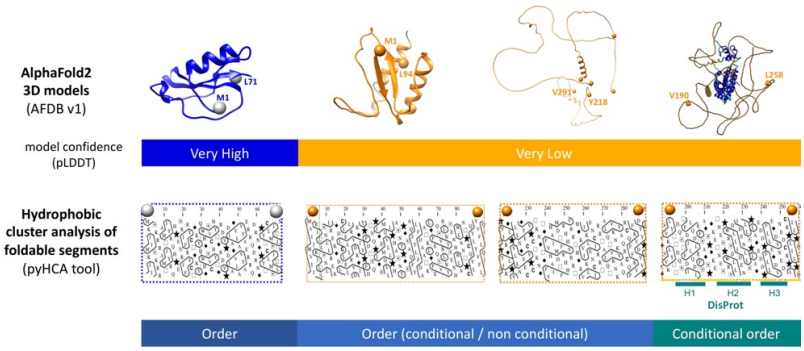

Figure 2. Protein Folding Prediction.

The protein threading process typically involves the following steps:

1. **Threading:** The target sequence is "threaded" or aligned onto a library of template structures, evaluating how well it fits each template.
2. **Scoring:** An energy function or scoring system is used to assess the compatibility of the target sequence with each template structure.
3. **Ranking:** The top-scoring alignments are ranked, with the highest-scoring template(s) considered the most likely structural match for the target protein.

Table 1. Examples of popular protein threading software

Software	Description
HHpred	Uses profile-profile alignments and Hidden Markov Models for sensitive fold recognition.
RAPTOR	Combines threading with machine learning techniques for improved accuracy.
Phyre	Integrates multiple sources of structural information, including threading and ab initio modeling.
MUSTER	Employs a multi-threading approach to improve fold recognition performance.
SPARKS X	Incorporates structural profiles and machine learning for enhanced fold recognition.
BioShell	A comprehensive platform for protein structure prediction, including threading capabilities.

While fold recognition methods have shown some success in correctly predicting protein folds, their accuracy is generally around 50% at best, with correct folds often appearing among the top 10 predictions as given in Table 1. A practical approach is to use multiple fold recognition methods, consider the function of the target protein, and not rely solely on the program outputs, as human insight and manual curation can significantly improve the results [15, 16].

5. Ab Initio Prediction Approaches

Ab initio protein structure prediction refers to the challenging task of predicting a protein's three-dimensional structure based solely on its amino acid sequence, without relying on any known structural templates or homologous proteins. This approach is necessary when no suitable templates are

available for comparative modeling or threading methods. Ab initio prediction involves two key sub-problems [17]:

1. **Developing an Accurate Scoring Function:** A scoring function is required to distinguish native or native-like structures from non-native conformations. Currently, there is no reliable scoring function that can consistently drive the search towards the native fold.
2. **Effective Conformational Sampling:** A search method is needed to efficiently explore the vast conformational space and sample near-native structures. No general search method can guarantee significant sampling of these structures.

Pathway models combine the scoring function and the search method to tackle the protein folding problem. One such model is HMMSTR-CM, which uses a fragment library and a set of nucleation or propagation-based rules. This model was employed for ab initio predictions as part of the Critical Assessment of Protein Structure Prediction (CASP) experiment (Fig. 1) [18, 19, 20].

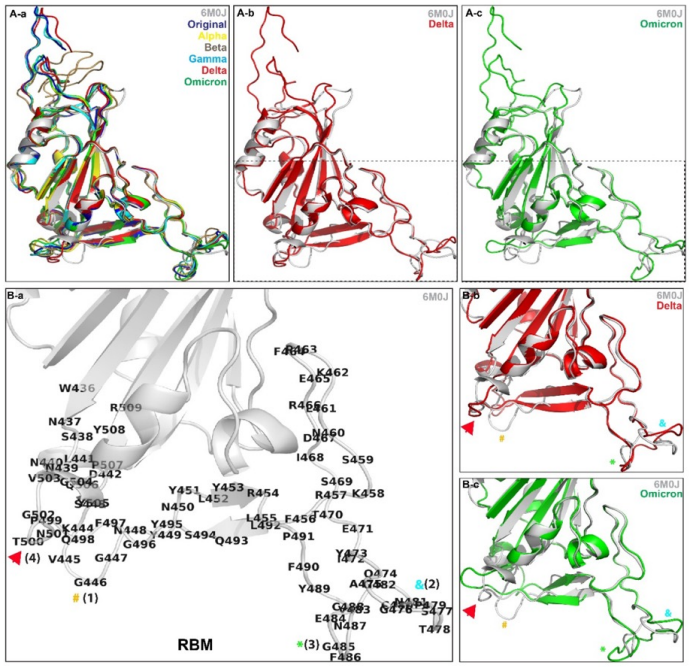

Figure 3. Receptor-Binding Domain (RBD) structures.

protein structure prediction tools and computational approaches have explored various strategies for ab initio prediction, including:

- **Physicochemical Potentials:** Using energy functions based on physicochemical principles to guide the conformational search.
- **Simplified Off-Lattice Models:** Employing simplified representations of protein structures to reduce computational complexity.
- **Fragment Libraries:** Assembling structures from short, overlapping fragments derived from known protein structures.
- **Energy Landscape Flattening:** Modifying the energy landscape to facilitate more efficient sampling of near-native conformations.

6. Energy-based Scoring Functions

Energy-based scoring functions play a crucial role in protein structure prediction by evaluating the stability and accuracy of predicted structures. These functions aim to distinguish native or near-native conformations from non-native or misfolded structures by calculating their energetic favourability (Fig. **??**). Several approaches have been explored for developing effective scoring functions:

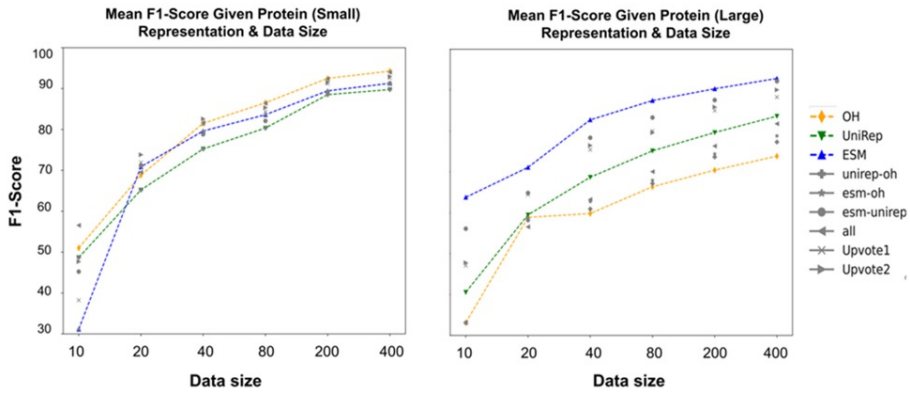

Figure 4. The effect of protein size on the performance of encoding methods.

1. **Physics-Based Force Fields:** These scoring functions are derived from fundamental physical principles, such as electrostatics, van der Waals interactions, and hydrogen bonding. Examples include AMBER, CHARMM, and OPLS force fields, which have been widely used in molecular dynamics simulations and protein structure prediction.
2. **Knowledge-Based Potentials:** These scoring functions are derived from statistical analysis of known protein structures. They capture the preferences and patterns observed in native protein structures, such as residue-residue contacts, torsion angles, and solvent accessibility. Examples include DFIRE, DOPE, and RAPDF potentials.
3. **Machine Learning-Based Approaches:** With the availability of large datasets of protein structures, machine learning techniques have been employed to develop scoring functions. These methods can capture complex patterns and relationships within the data, potentially leading to more accurate predictions. Examples include neural network-based scoring functions and support vector machine-based models.

Despite significant progress, developing accurate and reliable scoring functions remains a challenge in protein structure prediction. Existing scoring functions often struggle to capture the delicate balance of interactions that stabilize native protein structures, leading to inaccuracies in distinguishing native from non-native conformations. Additionally, the complexity of scoring functions can make them computationally expensive, limiting their applicability to large-scale protein structure prediction efforts [18, 19].

7. Molecular Dynamics Simulations

Molecular dynamics (MD) simulations have emerged as a powerful computational tool for studying protein structure, function, stability, dynamics, and interactions at an atomic level of detail. The history of MD simulations dates back to the 1940s, with seminal work by researchers like Ray Metropolis and John Teller. However, it was the development of empirical force fields in the 1950s-1970s, such as the CHARMM and AMBER force fields, that laid the foundation for modern MD simulations of biomolecules (Fig. 5) [21, 22].

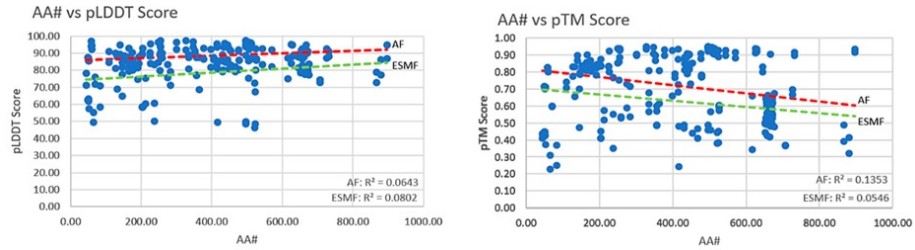

Figure 5. Comparison of the increasing complexity of therapeutic protein.

Force fields are essential components of MD simulations, providing the mathematical expressions and parameters to describe the inter- and intra-molecular forces acting on the system. Common force fields used in protein simulations include:

- **CHARMM:** Developed at Harvard University, the Chemistry at HARvard Macromolecular Mechanics force field is widely used for simulating proteins, nucleic acids, and lipids.
- **AMBER:** The Assisted Model Building with Energy Refinement force field, developed at the University of California, San Francisco, is another popular choice for biomolecular simulations.
- **GROMACS:** The GROningen MAchine for Chemical Simulations force field is widely used in academic and industrial research for simulating proteins, lipids, and other biomolecules.

MD simulations have been widely applied to study the structure, dynamics, and interactions of membrane proteins, which play crucial roles in various biological processes and are important drug targets. Examples include:

- **G-Protein Coupled Receptors (GPCRs):** MD simulations have provided insights into the activation mechanisms, conformational changes, and ligand binding of GPCRs, which are targets for many drugs.
- **ACE2 Receptor:** Simulations have helped elucidate the interactions between the SARS-CoV-2 spike protein and the human ACE2 receptor, which is the primary entry point for the virus into host cells.
- **SARS-CoV-2 Spike Protein:** MD simulations have been used to study the conformational dynamics and potential druggable sites of the SARS-CoV-2 spike protein, aiding in the development of therapeutic strategies against COVID-19.
- **AWSEM-Suite:** An automated webserver for molecular dynamics simulation based on template-guided, coevolutionary-enhanced optimized folding landscapes, enabling efficient simulations of protein folding and dynamics [23, 24].
- **Pharmacology Applications:** MD simulations have been useful in pharmacology for analyzing communication and allosteric effects within proteins, studying the effects of ligand binding on protein dynamics, and identifying specific protein conformations that can be targeted by conformationally-selective drugs [25].

Despite the significant progress in MD simulations, several challenges and opportunities remain:

1. **Managing Large Simulation Datasets:** As computational power increases, simulations can generate vast amounts of data, necessitating efficient data management, analysis, and visualization techniques.
2. **Improving Force Field Accuracy:** Ongoing efforts aim to improve the accuracy of force fields by incorporating more advanced physics-based models and leveraging experimental data and

machine learning techniques.

3. **Integrating Machine Learning/Deep Learning:** The integration of machine learning and deep learning techniques with MD simulations holds promise for enhancing analysis capabilities, identifying patterns, and accelerating simulations.
4. **Quantifying Simulation Information:** Developing rigorous methods for identifying specific protein conformations and quantifying the information from simulations remains a challenge, particularly in the context of drug discovery and design.

Several integrated pipelines have also been developed to streamline the protein structure prediction process. For instance, a software suite was developed to predict protein structures from sequence by integrating multiple non-commercial programs. This suite is intended for use by the Army and DoD medical and scientific communities to annotate structures of sequenced pathogenic and host genomes, with applications in therapeutic and vaccine design, as well as basic biological research [26, 27, 28, 29, 30].

Another example is a standalone Perl-based software pipeline that integrates multiple freely available software packages and databases for protein structure prediction. This pipeline can parallelize computationally intensive tasks like ab initio modeling across multiple processing cores, and has been used for large-scale structural annotation of viral proteomes like the smallpox virus. It participated in the CASP7 protein structure prediction competition, with some top-ranked models [31, 32, 33, 34].

8. Applications in Drug Discovery

Protein structure prediction tools and computational approaches are expected to play a pivotal role in accelerating and enhancing structure-based drug discovery (SBDD) efforts. The breakthrough of AlphaFold2 (AF2), developed by DeepMind, has garnered significant attention due to its remarkable ability to predict protein structures with atomic-level accuracy using advanced deep learning algorithms [35, 36].

The key factors contributing to AF2's success include:

- Utilization of state-of-the-art deep learning techniques, particularly attention mechanism-based transformers
- Integration of self-distillation training data
- Availability of extensive protein sequence and structure databases

While AF2 represents a major milestone, certain limitations persist, such as the accuracy of side-chain modeling and the need for further improvements in specific areas. Accurate protein structure prediction by tools like AF2 can facilitate various aspects of drug discovery (Fig. 1) [37, 38]:

1. **Target Assessment and Prioritization**
   - Assess the druggability and tractability of potential protein targets identified based on biology
   - Rank targets based on factors like confidence level of structure prediction, binding pocket size/accessibility, and similarity to known ligand-binding proteins
2. **Structure-based Virtual Screening**
   - Use AF2 models as accurate templates for virtual screening to identify hit molecules that bind to the target
3. **Lead Optimization**
   - Employ computational methods like docking and free energy calculations on AF2 models to optimize hit molecules into lead candidates with improved drug-like properties
4. **Off-target Analysis and Drug Repositioning**

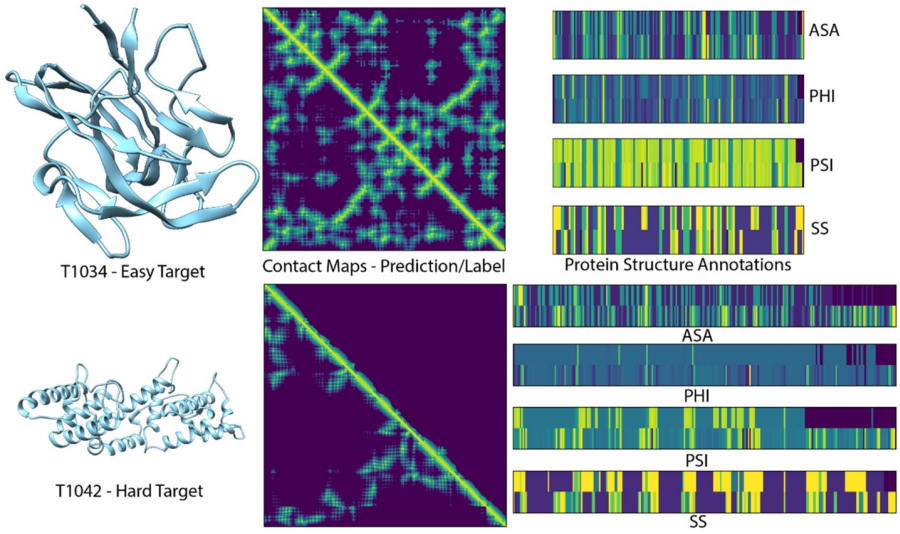

Figure 6. Two example targets from the CASP14 test set.

- Compare AF2 models to structures of similar proteins to identify potential off-target effects and opportunities for drug repositioning

5. **Animal Model Selection**
   - Leverage the availability of AF2 models across species to select appropriate animal models for preclinical testing based on target protein similarity

- Naceri et al. confirmed the presence of a highly druggable binding site within the RNA-binding domain of the influenza A virus NS1 protein, which could lead to a universal therapeutic strategy targeting this conserved site. - Bhowmick et al. utilized the trRosetta algorithm to predict protein structure and mutations in the SARS-CoV-2 Receptor-Binding Domain, experimentally validating the effects of mutations P499S and T500R on increased ACE-2 receptor binding and transmissibility. - Dick et al. generated computational models of HIV-1 capsid proteins from diverse clades, which can aid in understanding biological processes and designing antiviral drugs targeting the capsid.

Beyond the realm of traditional small molecule drug discovery, generative AI models like AF2 have also emerged as catalysts in the development of novel drug candidates, particularly in the field of cancer therapeutics. However, challenges remain, such as the need for more comprehensive datasets and the interpretability of AI models, as the field of AI-driven drug discovery continues to evolve and expand beyond cancer to other disease areas [39, 40].

8.1 Challenges and Future Directions

The field of protein structure prediction has witnessed remarkable advancements, fuelled by the integration of computational approaches and cutting-edge technologies. These tools and methodologies have revolutionized our ability to decipher the intricate three-dimensional structures of proteins, unlocking a wealth of insights into their function, dynamics, and interactions. With continued progress in areas such as deep learning, force field accuracy, and conformational sampling, we can anticipate even more accurate and efficient structure prediction capabilities in the future. Despite the significant strides made, challenges persist, including the accurate modelling of larger proteins, membrane proteins, and complex biomolecular systems. Overcoming these hurdles will require concerted efforts from the scientific community, fostering interdisciplinary collaborations and harnessing the

power of high-performance computing and emerging technologies. The impact of these advancements extends far beyond the realm of basic research, as they hold the potential to accelerate drug discovery, enhance our understanding of disease mechanisms, and pave the way for personalized medicine approaches.

9. CONCLUSION

In conclusion, protein structure prediction tools and computational approaches have significantly advanced our understanding of protein biology. Techniques like homology modeling, ab initio modeling, molecular dynamics simulations, and innovative machine learning algorithms such as AlphaFold have substantially improved the accuracy and efficiency of predicting protein structures. These advancements are crucial for elucidating protein functions, interactions, and mechanisms, which are essential for various applications in biotechnology, medicine, and drug discovery. The synergy between computational methods and experimental data is continually enhancing the reliability of predictions, paving the way for breakthroughs in personalized medicine and targeted therapies. As computational power and algorithms evolve, the precision and applicability of protein structure prediction will continue to expand, opening new frontiers in biological research and clinical applications. The ongoing integration of these tools into the scientific workflow promises to drive further innovations and discoveries in the field.

References

[1] Minkyung Baek, Frank DiMaio, Ivan Anishchenko, Justas Dauparas, Sergey Ovchinnikov, Gyu Rie Lee, Jue Wang, Qian Cong, Lisa N Kinch, R Dustin Schaeffer, et al. "Accurate prediction of protein structures and interactions using a three-track neural network". In: *Science* 373.6557 (2021), pp. 871–876.

[2] Lorenza Bordoli, Florian Kiefer, Konstantin Arnold, Pascal Benkert, James Battey, and Torsten Schwede. "Protein structure homology modeling using SWISS-MODEL workspace". In: *Nature protocols* 4.1 (2009), pp. 1–13.

[3] Hanka Venselaar, Tim AH Te Beek, Remko KP Kuipers, Maarten L Hekkelman, and Gert Vriend. "Protein structure analysis of mutations causing inheritable diseases. An e-Science approach with life scientist friendly interfaces". In: *BMC bioinformatics* 11 (2010), pp. 1–10.

[4] Oliver Ava, Muhammad Oscar, and Tommy George. "The Impact and Prevention of Latch-up in CMOS in VLSI Design". In: *Fusion of Multidisciplinary Research, An International Journal (FMR)* 1.1 (2020), pp. 1–13.

[5] Yang Zhang. "I-TASSER server for protein 3D structure prediction". In: *BMC bioinformatics* 9 (2008), pp. 1–8.

[6] Konstantin Arnold, Lorenza Bordoli, Jürgen Kopp, and Torsten Schwede. "The SWISS-MODEL workspace: a web-based environment for protein structure homology modelling". In: *Bioinformatics* 22.2 (2006), pp. 195–201.

[7] Pascal Benkert, Marco Biasini, and Torsten Schwede. "Toward the estimation of the absolute quality of individual protein structure models". In: *Bioinformatics* 27.3 (2011), pp. 343–350.

[8] Haoyu Yuze and He Bo. "Microbiome Engineering: Role in Treating Human Diseases". In: *Fusion of Multidisciplinary Research, An International Journal (FMR)* 1.1 (2020), pp. 14–24.

[9] Debora S Marks, Lucy J Colwell, Robert Sheridan, Thomas A Hopf, Andrea Pagnani, Riccardo Zecchina, and Chris Sander. "Protein 3D structure computed from evolutionary sequence variation". In: *PloS one* 6.12 (2011), e28766.

[10] Jianyi Yang and Yang Zhang. "I-TASSER server: new development for protein structure and function predictions". In: *Nucleic acids research* 43.W1 (2015), W174–W181.

[11] Seth Cooper, Firas Khatib, Adrien Treuille, Janos Barbero, Jeehyung Lee, Michael Beenen, Andrew Leaver-Fay, David Baker, Zoran Popović, et al. "Predicting protein structures with a multiplayer online game". In: *Nature* 466.7307 (2010), pp. 756–760.

[12] Henry H. James, Razu Pawel, and Gawin Saduf. "Autonomous Vehicles and Robust Decision-Making in Dynamic Environments". In: *Fusion of Multidisciplinary Research, An International Journal (FMR)* 1.2 (2020), pp. 110–121.

[13] Matthew P Jacobson, David L Pincus, Chaya S Rapp, Tyler JF Day, Barry Honig, David E Shaw, and Richard A Friesner. "A hierarchical approach to all-atom protein loop prediction". In: *Proteins: Structure, Function, and Bioinformatics* 55.2 (2004), pp. 351–367.

[14] James C Whisstock and Arthur M Lesk. "Prediction of protein function from protein sequence and structure". In: *Quarterly reviews of biophysics* 36.3 (2003), pp. 307–340.

[15] V Srinivasa Rao, K Srinivas, GN Sujini, and GN Sunand Kumar. "Protein-protein interaction detection: methods and analysis". In: *International journal of proteomics* 2014.1 (2014), p. 147648.

[16] Jimeno Estanislau, Federico Hermogenes, and Bernardo Clemente. "Battery Energy Transformation and Unravelling the Thermodynamics of Energy Storage and Conversion". In: *Fusion of Multidisciplinary Research, An International Journal (FMR)* 2.1 (2021), pp. 122–135.

[17] Min-yi Shen and Andrej Sali. "Statistical potential for assessment and prediction of protein structures". In: *Protein science* 15.11 (2006), pp. 2507–2524.

[18] Predrag Radivojac, Wyatt T Clark, Tal Ronnen Oron, Alexandra M Schnoes, Tobias Wittkop, Artem Sokolov, Kiley Graim, Christopher Funk, Karin Verspoor, Asa Ben-Hur, et al. "A large-scale evaluation of computational protein function prediction". In: *Nature methods* 10.3 (2013), pp. 221–227.

[19] Kathryn Tunyasuvunakool, Jonas Adler, Zachary Wu, Tim Green, Michal Zielinski, Augustin Žídek, Alex Bridgland, Andrew Cowie, Clemens Meyer, Agata Laydon, et al. "Highly accurate protein structure prediction for the human proteome". In: *Nature* 596.7873 (2021), pp. 590–596.

[20] Bauyrzhan Satipaldy, Taigan Marzhan, Ulugbek Zhenis, and Gulbadam Damira. "Geotechnology in the Age of AI: The Convergence of Geotechnical Data Analytics and Machine Learning". In: *Fusion of Multidisciplinary Research, An International Journal (FMR)* 2.1 (2021), pp. 136–151.

[21] Andrew W Senior, Richard Evans, John Jumper, James Kirkpatrick, Laurent Sifre, Tim Green, Chongli Qin, Augustin Žídek, Alexander WR Nelson, Alex Bridgland, et al. "Improved protein structure prediction using potentials from deep learning". In: *Nature* 577.7792 (2020), pp. 706–710.

[22] Jianyi Yang, Ivan Anishchenko, Hahnbeom Park, Zhenling Peng, Sergey Ovchinnikov, and David Baker. "Improved protein structure prediction using predicted interresidue orientations". In: *Proceedings of the National Academy of Sciences* 117.3 (2020), pp. 1496–1503.

[23] Jianlin Cheng, Arlo Z Randall, Michael J Sweredoski, and Pierre Baldi. "SCRATCH: a protein structure and structural feature prediction server". In: *Nucleic acids research* 33.suppl_2 (2005), W72–W76.

[24] ChoHee Kim, Donghyun Gwan, and Minho Sena Nam. "Beyond the Atmosphere: The Revolution in Hypersonic Flight". In: *Fusion of Multidisciplinary Research, An International Journal (FMR)* 2.1 (2021), pp. 152–163.

[25] Alexey Drozdetskiy, Christian Cole, James Procter, and Geoffrey J Barton. "JPred4: a protein secondary structure prediction server". In: *Nucleic acids research* 43.W1 (2015), W389–W394.

[26] Nicolas Guex, Manuel C Peitsch, and Torsten Schwede. "Automated comparative protein structure modeling with SWISS-MODEL and Swiss-PdbViewer: A historical perspective". In: *Electrophoresis* 30.S1 (2009), S162–S173.

[27] Ambrish Roy, Alper Kucukural, and Yang Zhang. "I-TASSER: a unified platform for automated protein structure and function prediction". In: *Nature protocols* 5.4 (2010), pp. 725–738.

[28] Chung Yip, Lokyi Seol, and Xu Zhu Hon. "A Step-by-Step Approach to Partial Differential Equations". In: *Fusion of Multidisciplinary Research, An International Journal (FMR)* 3.1 (2022), pp. 302–315.

[29] Marc A Martí-Renom, Ashley C Stuart, András Fiser, Roberto Sánchez, Francisco Melo, and Andrej Šali. "Comparative protein structure modeling of genes and genomes". In: *Annual review of biophysics and biomolecular structure* 29.1 (2000), pp. 291–325.

[30] Lawrence A Kelley and Michael JE Sternberg. "Protein structure prediction on the Web: a case study using the Phyre server". In: *Nature protocols* 4.3 (2009), pp. 363–371.

[31] John Jumper, Richard Evans, Alexander Pritzel, Tim Green, Michael Figurnov, Olaf Ronneberger, Kathryn Tunyasuvunakool, Russ Bates, Augustin Žídek, Anna Potapenko, et al. "Highly accurate protein structure prediction with AlphaFold". In: *nature* 596.7873 (2021), pp. 583–589.

[32] Linnea Daniel, Sondre Robin, and Matthew Aleksander. "Future Facts: Unveiling Mental Health Issues in the Digital Age". In: *Fusion of Multidisciplinary Research, An International Journal (FMR)* 3.2 (2022), pp. 354–365.

[33] Gregory Sliwoski, Sandeepkumar Kothiwale, Jens Meiler, and Edward W Lowe. "Computational methods in drug discovery". In: *Pharmacological reviews* 66.1 (2014), pp. 334–395.

[34] Carol A Rohl, Charlie EM Strauss, Kira MS Misura, and David Baker. "Protein structure prediction using Rosetta". In: *Methods in enzymology*. Vol. 383. Elsevier, 2004, pp. 66–93.

[35] David E Kim, Dylan Chivian, and David Baker. "Protein structure prediction and analysis using the Robetta server". In: *Nucleic acids research* 32.suppl_2 (2004), W526–W531.

[36] Fernanda Hernández, Leonardo Sánchez, Gabriela González, and Andrés Ramírez. "Revolutionizing CMOS VLSI with Innovative Memory Design Techniques". In: *Fusion of Multidisciplinary Research, An International Journal (FMR)* 3.2 (2022), pp. 366–379.

[37] David Baker and Andrej Sali. "Protein structure prediction and structural genomics". In: *Science* 294.5540 (2001), pp. 93–96.

[38] Georg E Schulz and R Heiner Schirmer. *Principles of protein structure*. Springer Science & Business Media, 2013.

[39] Roded Sharan, Igor Ulitsky, and Ron Shamir. "Network-based prediction of protein function". In: *Molecular systems biology* 3.1 (2007), p. 88.

[40] Johannes Söding, Andreas Biegert, and Andrei N Lupas. "The HHpred interactive server for protein homology detection and structure prediction". In: *Nucleic acids research* 33.suppl_2 (2005), W244–W248.