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REVOLUTIONIZING STRUCTURAL BIOLOGY: ARTIFICIAL INTELLIGENCE (AI) APPROACHES FROM PROTEIN SEQUENCE TO FUNCTION

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ABSTRACT

Artificial intelligence (AI) is revolutionizing protein science and transforming the fields of analytical and bioanalytical chemistry by harnessing advanced machine learning and deep learning techniques to address longstanding challenges. AI can now predict protein structures from amino acid sequences with near-experimental accuracy, as exemplified by breakthroughs such as AlphaFold2, significantly enhancing our understanding of protein function, dynamics, and interactions. In analytical chemistry, AI enables high-throughput protein characterization, structural analysis, and real-time data interpretation. In bioanalytical chemistry, it supports precise biomarker identification, protein quantification, and modeling of complex protein–protein interactions. Beyond structure prediction, AI accelerates the design of novel proteins and enzymes, facilitates proteomic data analysis for biomarker discovery, and aids drug development. While challenges remain in modeling dynamic systems and intrinsically disordered regions, the integration of AI promises to revolutionize analytical and bioanalytical methodologies, improve precision, and drive innovations in drug discovery, synthetic biology, and personalized medicine, positioning AI as a cornerstone of modern protein research.

Keywords: Analytical, Bioanalytical Chemistry, Protein, Artificial intelligence (AI)

INTRODUCTION

Artificial intelligence (AI) is a revolutionary technology that enables machines to mimic human intelligence using advanced algorithms, large datasets, and increased computational power **(Radanliev, 2004).** Since its formal introduction in 1956 by John McCarthy, AI has progressed from automated reasoning to solving complex analytical and scientific problems **(Xu *et al.* 2024).** In bioanalytical chemistry, AI and machine learning (ML) enhance the analysis of complex biological datasets, improving workflow efficiency, precision, and reliability **(Rial, 2024; Shaikh and Uzgare, 2026; Schmidt, 2024).** AI is also accelerating advances in genomics, proteomics, pharmacogenomics, and drug discovery **(Rawat, 2024).** In protein science, AI enables accurate prediction, design, and evolution of proteins using pattern recognition and vector modeling, improving understanding and engineering of biological systems **(Villalobos-Alva et al., 2022; Baetu and Carl, 2015)**. The aim of this review is to highlight the role of artificial intelligence (AI) in transforming structural biology by enabling accurate prediction of protein structures, and functions. It focuses on the applications of AI in analytical and bioanalytical chemistry, including proteomic analysis. This review also discusses recent advancements, current challenges, and future perspectives of AI in protein science.

Literature review strategy

This review was conducted using a structured and systematic literature search strategy to ensure comprehensive coverage and scientific transparency. Relevant publications from 1986 to 2026 were identified through major scientific databases, including Scopus, Google Scholar, ResearchGate, and the Directory of Open Access Journals (DOAJ). Additional references were obtained through citation tracking of key articles to ensure completeness. The literature search was performed using specific keywords and their combinations, including “artificial intelligence,” “machine learning,” “protein science,” “proteomics,” “analytical chemistry,” “bioanalytical chemistry,” “neural networks,” and “AI in drug discovery,”. The selection process involved an initial screening of titles and abstracts, followed by full-text evaluation to confirm relevance and eligibility.

Exclusion criteria included duplicate records, non-peer-reviewed sources, articles without accessible full text, and studies not directly relevant to the review objectives. Following this systematic screening and eligibility assessment, approximately 53 studies were included based on their scientific quality, relevance, and contribution to the field. This structured methodology enhances the reliability, transparency, and scientific rigor of the review and ensures a comprehensive overview of the integration of artificial intelligence in protein science and analytical and bioanalytical chemistry.

Advances in Protein Science Through Artificial Intelligence (AI)

Proteins are amino acid polymers joined by α-peptide bonds and are fundamental to biological structure, catalysis, signaling, and regulation **(Shaikh and Uzgare, 2026).** They are derived from plants, animals, and microorganisms, with plant proteins representing an abundant and economical source for therapeutic and nutritional applications **(Pikosky *et al.* 2022; Nehete *et al.* 2013).** Proteomics, defined as the comprehensive study of protein structures, functions, and interactions, provides critical insights into cellular processes and organismal biology **(Chandramouli and Qian, 2009; Al-Amrani *et al.* 2021).** Advances in fractionation, labeling, and analytical technologies have enabled detection of low-abundance proteins, yet the scale, heterogeneity, and multidimensional nature of proteomic data remain major analytical challenges **(Chandramouli and Qian, 2009; Yan *et al.* 2025).** Artificial intelligence (AI) addresses these challenges by improving pattern recognition, structural prediction, functional annotation, and integration of large biological datasets, thereby accelerating drug discovery, biomarker identification, and systems biology research **(Srivastava, 2024; Gholap *et al.* 2025; Wang *et al.* 2023; Percudani and Rito, 2025**). Figure 1 indicates Advances of AI in Protein Science.

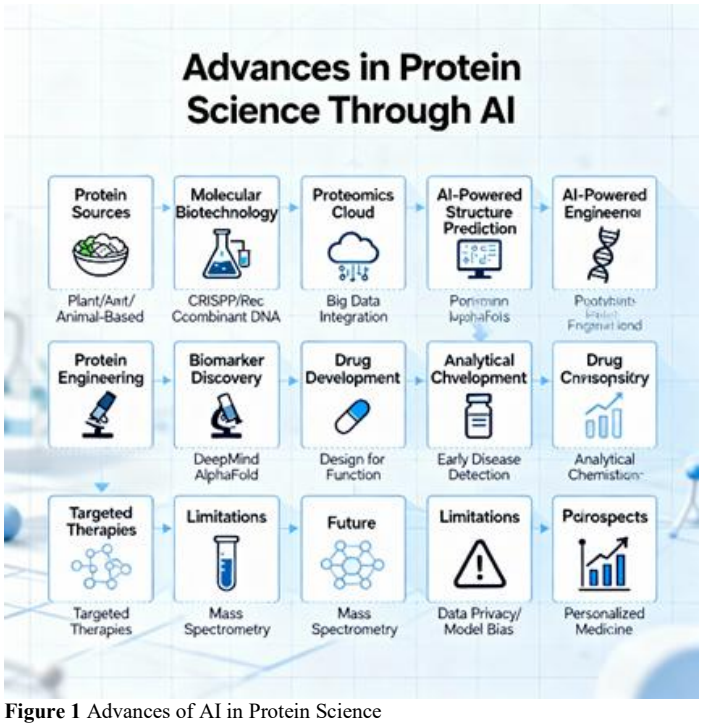

Figure 1 Advances of AI in Protein Science

A major area of advancement lies in AI-driven protein structure prediction, which addresses the long-standing protein folding problem. Traditional experimental methods such as X-ray crystallography and NMR spectroscopy are time-consuming and limited in scalability, resulting in structural data for only a fraction of known protein **sequences (Jumper *et al.* 2025; Schauperl and Denny, 2022).** AI models such as AlphaFold2, RoseTTAFold, and ESMFold have fundamentally transformed this field by enabling accurate prediction of protein three-dimensional structures directly from amino acid sequences **(Yang *et al.* 2023; Chen *et al.* 2024; Qiu *et al.* 2024).** AlphaFold2 represents a landmark breakthrough, achieving near-experimental accuracy by integrating evolutionary information, multiple sequence alignments, and deep neural networks, significantly outperforming traditional computational approaches in CASP benchmarks **(Jumper *et al.* 2025; Service, 2020; Versini *et al.* 2025).** RoseTTAFold complements AlphaFold2 through its three-track neural network architecture, enabling efficient modeling of protein complexes and biomolecular interactions, particularly with extensions such as RoseTTAFold All-Atom and RFdiffusion All-Atom **(Fang *et al.* 2024; Versini *et al.* 2025).** While, ESMFold and protein language model-based approaches reduce reliance on evolutionary alignments, enabling faster and scalable predictions suitable for large proteomic datasets **(Qiu *et al.* 2024; Bordin *et al.* 2023).** These complementary approaches demonstrate a transition from template-dependent and alignment-based prediction toward sequence-based inference using large-scale deep learning models.

Despite their success, current structural AI models have important limitations. They often struggle to accurately capture intrinsically disordered proteins, conformational dynamics, membrane protein structures, and multi-component biomolecular assemblies **(Longhi *et al.* 2025; Ramanathan *et al.* 2021; Versini *et al.* 2025; Fang *et al.* 2024).** Specialized AI models such as RibbonFold incorporate amyloid-specific constraints to improve prediction of amyloid fibril polymorphism, outperforming conventional AlphaFold-based methods **(Guo *et al.* 2025)**. Ensemble-based approaches such as FoldScript further improve reliability by comparing multiple AI-generated structural models rather than relying on a single prediction, enabling better assessment of structural variability and intermolecular interactions **(Robert *et al.* 2025).** AI has also expanded structural coverage through integration with biological databases such as the RCSB Protein Data Bank and Pfam, which now incorporate millions of AI-predicted protein structures and enhance functional annotation and classification **(Burley *et al.* 2023; Paysan-Lafosse *et al.* 2025).** These advances have accelerated structural biology, drug discovery, and protein function prediction, including applications in disease research, anesthesia, and biomedical engineering **(Zhang *et al.* 2025; Schauperl and Denny, 2022).**

Beyond structure prediction, AI has enabled a paradigm shift toward protein design and generative modeling. Traditional protein engineering relied heavily on natural templates and experimental screening, whereas modern AI approaches use deep learning, diffusion models, and protein language models to generate entirely novel protein sequences with specific structural and functional properties **(Jin *et al.* 2025; Khakzad *et al.* 2023; Mahmoudi *et al.* 2025).** Generative AI enables design of proteins with improved catalytic efficiency, stability, and therapeutic potential, expanding beyond naturally occurring protein space **(Jin *et al.* 2025).** Systems such as ProtAgents integrate large language models with physics-based simulations to automate protein design and functional optimization **(Ghafarollahi and Buehler, 2024**). Hybrid approaches combining AI predictions with physics-based force fields, such as TriCombine, demonstrate improved performance in protein redesign compared to individual methods **(Cianferoni *et al.* 2025).** AI also enables prediction of mutation effects, protein stability, and functional consequences of sequence variation, facilitating protein engineering and disease research **(Pucci *et al.* 2022; Pandurangan and Blundell, 2019).** However, generative AI still faces challenges in preserving biological function, ensuring experimental validation, and addressing biosecurity concerns, highlighting the need for robust evaluation frameworks **(Ikonomova *et al.* 2025).**

AI has also transformed proteomics by enabling large-scale analysis of protein expression, interactions, and functional networks. Mass spectrometry-based proteomics generates complex datasets requiring advanced computational tools, and AI methods significantly improve peptide identification, spectrum prediction, and protein quantification **(Shao *et al.* 2025; Liu *et al.* 2025).** Deep learning models enable accurate prediction of protein–DNA and protein–RNA interactions, facilitating functional annotation and regulatory analysis **(Cui *et al.* 2022).** AI also enables prediction of post-translational modifications, molecular interactions, and biological pathways, improving understanding of disease mechanisms and therapeutic targets **(Yan *et al.* 2025).** Context-aware models such as PINNACLE integrate multi-organ and single-cell proteomic data to generate biologically meaningful protein representations, enhancing prediction of protein interactions and therapeutic targets **(Li *et al.* 2023)**. Explainable AI approaches such as layer-wise relevance propagation enable reconstruction of patient-specific protein interaction networks, supporting precision medicine and personalized therapeutic strategies (**Keyl *et al.* 2022).** These advances demonstrate that proteomics-focused AI complements structural prediction by providing functional and systems-level insights into protein behavior.

AI has further expanded protein science through integration with computational biology, molecular databases, and experimental workflows. AI-driven tools accelerate drug discovery, biomarker identification, and personalized medicine by enabling rapid structural prediction and functional analysis **(Gholap *et al.* 2025; Wang *et al.* 2025).** Advances in machine learning also support hypothesis generation, experimental design, and molecular discovery through self-supervised learning and geometric deep learning **(Wang *et al.* 2023)**. AI contributes to functional annotation of protein families and structural classification through databases such as Pfam and RCSB PDB, improving biological interpretation and discovery **(Burley *et al.* 2023; Paysan-Lafosse *et al.* 2025**). AI methods have also enabled novel conceptual approaches to protein representation and design, including sequence embedding, protein language modeling, and innovative representations such as musical encoding of protein sequences **(Yu *et al.* 2019; Bordin *et al.* 2023).**

Overall, AI has transformed protein science across multiple interconnected domains, including structural prediction, protein engineering, and proteomics. Structural AI models such as AlphaFold2, RoseTTAFold, and ESMFold provide highly accurate structural predictions, while generative AI enables design of novel proteins with customized functions. Proteomics-focused AI complements these advances by enabling large-scale functional analysis and systems-level understanding of protein interactions and disease mechanisms. Despite challenges related to protein dynamics, functional validation, interpretability, and ethical considerations, AI continues to expand the scope of structural biology, proteomics, and biomedical research, accelerating scientific discovery and enabling new therapeutic applications **(Zhan e*t al.* 2025; Longhi *et al.* 2025; Mahmoudi *et al.* 2025).**

Applications, Advantages, and Limitations of Artificial Intelligence (AI) in Protein Science

Artificial intelligence has significantly transformed multiple areas of protein science, although its performance, reliability, and limitations vary depending on the specific application (Table 1). In protein structure prediction, advanced deep learning models such as AlphaFold and RoseTTAFold have achieved near-experimental accuracy, greatly accelerating structural characterization and reducing reliance on traditional experimental techniques such as X-ray crystallography and cryo-electron microscopy **(Jin *et al.* 2025; Gainza *et al.* 2020).** Despite these advances, challenges remain in accurately predicting intrinsically disordered proteins, protein complexes, and conformational dynamics, highlighting the need for integration with molecular dynamics and experimental validation. In protein design and engineering, AI enables the generation and optimization of novel protein sequences with improved stability and functional properties, significantly accelerating enzyme development and therapeutic protein engineering **(Langan *et al.* 2023).** However, AI-generated protein designs often lack mechanistic interpretability and require experimental verification, limiting their immediate practical implementation.

Similarly, AI-based protein–protein interaction prediction has enhanced drug discovery and improved understanding of biological interaction networks by identifying potential binding interfaces and functional relationships **(Senior *et al.* 2020; Zhang *et al.* 2025).** Nevertheless, predictive accuracy is constrained by incomplete datasets, biological variability, and high false-positive rates. In protein folding studies, AI has provided faster alternatives to traditional simulation approaches and improved understanding of folding mechanisms and misfolding-

related diseases **(Chothia and Lesk, 1986).** However, current AI models often oversimplify complex folding pathways and lack accurate kinetic and thermodynamic representation. Furthermore, AI has shown substantial potential in disease mechanism analysis and biomarker discovery by identifying disease-associated proteomic patterns and supporting precision medicine approaches **(Service, 2020)**. Despite these advantages, limitations such as dataset bias, lack of standardized validation, and challenges in clinical translation remain significant barriers. Overall, while AI has revolutionized protein science, addressing these limitations through improved model interpretability, hybrid experimental-computational approaches, and high-quality datasets will be essential for advancing future applications, as summarized in Table 1.

Table 1 Applications, Advantages, Limitations and Research Gap of Artificial Intelligence (AI) in Protein Science

Application Area	Description	Advantages	Limitations	Validation Level	Research Gaps	References
Protein Structure Prediction	AI predicts 3D protein structures from sequences.	High accuracy; faster and cheaper than experimental methods.	Limited for disordered proteins and dynamics.	In silico, experimental	Dynamic structure prediction and complex proteins	**Jin *et al.* (2025); Gainza *et al.* (2020)**
Protein Design and Engineering	AI designs proteins with desired functions.	Speeds up protein and enzyme development.	Needs experimental confirmation.	In silico, limited experimental	Improving functional reliability	**Langan *et al.* (2023)**
Protein–Protein Interaction Prediction	AI predicts protein interaction partners.	Supports drug discovery and pathway analysis.	False positives and limited data.	In silico, partial experimental	Improving prediction accuracy	**Senior *et al.* (2020); Zhang *et al.* (2025)**
Protein Folding Simulation	AI models protein folding processes.	Faster than traditional simulations.	Limited kinetic and dynamic accuracy.	In silico	Modeling real folding dynamics	**Chothia and Lensk (1986)**
Disease Mechanism and Biomarker Discovery	AI identifies disease-related proteins.	Enables early diagnosis and precision medicine.	Requires large, high-quality datasets.	In silico, experimental	Clinical validation and interpretation	**Service (2020)**

The Future of AI-Driven Protein Science

Artificial intelligence (AI) is transforming protein science by enhancing the prediction and design of protein structures and functions. Deep learning methods now predict 3D protein structures from amino acid sequences with remarkable accuracy and speed, surpassing traditional techniques. Innovations like DeepMind's AlphaFold2 enable near-experimental precision, accelerating research and expanding access to complex protein data. By integrating multi-omics information, AI advances the understanding of protein dynamics and interactions, driving progress in drug discovery, synthetic biology, analytical and bioanalytical science and personalized medicine (**Fang *et al.* 2024; Jumper *et al.* 2021; Das, 2025)**. Integrating AI in protein science lies in developing advanced systems that model dynamic biomolecular assemblies and predict diverse protein behaviors. Emerging techniques, such as generative models, enable the design of novel proteins, antibodies, and enzymes for therapeutics and biotechnology. AI-driven simulations allow high-throughput screening of protein interactions, speeding candidate identification while reducing resources. Improvements in predicting protein stability, function, and interactions promise to transform proteomics, accelerate vaccine development, and uncover new biological insights, solidifying AI as a key driver of protein science innovation.

Despite major breakthroughs in AI-driven protein science, several important research gaps remain that must be addressed to fully realize its potential. Current deep learning systems primarily predict static protein structures, while proteins are inherently dynamic and exist in multiple conformational states; thus, improved modeling of folding pathways, conformational flexibility, and transient intermediates is needed. Accurately predicting protein–protein interactions, multi-component assemblies, and binding affinities also remains challenging, particularly for weak or transient interactions within complex cellular networks. Although structural prediction has advanced significantly, linking structure to precise biological function, enzymatic activity, and regulatory mechanisms is still limited. In addition, predicting the effects of mutations on protein stability and function critical for understanding genetic diseases, drug resistance, and personalized medicine requires greater accuracy and generalizability. Many AI models rely on biased and incomplete datasets, with underrepresentation of membrane proteins, intrinsically disordered proteins, and diverse organisms, highlighting the need for more comprehensive experimental data and validation. Integration of multi-omics data and realistic cellular context, including post-translational modifications and molecular crowding, remains insufficient, restricting biological relevance. While generative models show promise in designing novel proteins, challenges persist in ensuring correct folding, long-term stability, safety, and in vivo functionality. Furthermore, high computational demands limit accessibility, and the black-box nature of many deep learning systems raises concerns regarding interpretability, reliability, and ethical governance. Addressing these gaps will be essential for advancing AI applications in drug discovery, synthetic biology, proteomics, vaccine development, and precision medicine.

CONCLUSION

The integration of artificial intelligence (AI) has significantly reshaped protein science, shifting it from a field centered on observation to one driven by prediction and rational design. Major breakthroughs, particularly AlphaFold2, have addressed the long-standing protein folding challenge by predicting highly accurate three-dimensional structures, thereby accelerating progress in de novo protein design, interaction analysis, proteomics, and drug discovery. By processing vast and complex biological datasets with speed and precision, AI has streamlined research workflows and expanded possibilities across biotechnology, medicine, and synthetic biology. Nevertheless, important challenges persist. Many AI models still have limitations in capturing protein dynamics, complex biomolecular assemblies, functional relationships, and the influence of the cellular environment, and their lack of interpretability can hinder biological understanding. Addressing these challenges will require more comprehensive and transparent AI frameworks that integrate physical principles with multi-scale and multi-omics biological data while maintaining ethical and responsible use. The future of protein science will rely on effective collaboration between human expertise and AI-driven tools, enabling deeper insights into molecular mechanisms and supporting the development of innovative solutions for healthcare, sustainability, and technological progress.

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