NEWSLETTER

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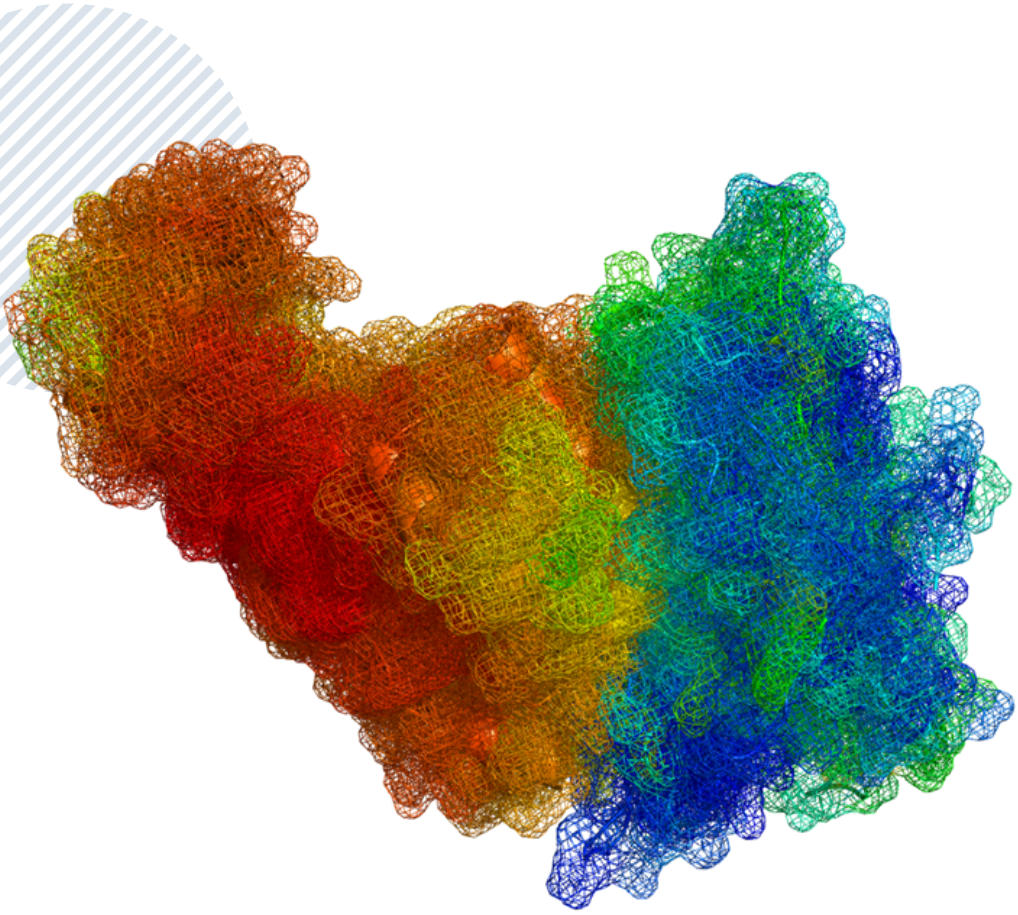

Surface representation of full-length Ataxin-3 structure predicted with AlphaFold. Figure prepared with PyMOL (The PyMOL Molecular Graphics System, Version 3.0, Schrödinger, LLC).

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IN THIS EDITION

Editorial

11th Edition

In this Edition:

IIn this issue, we feature an interview with Catarina Oliveira from the Faculty of Medicine of the University of Coimbra, who shares insights into her career path and her research on neuroscience and neurodegenerative disorders.

In the News and Views section, Sandra Macedo Ribeiro from the University of Porto discusses the impact of AlphaFold on structural biology, offering her perspective on recent advances in the field.

This newsletter also showcases a range of upcoming events, including the XXIII National Congress of Biochemistry, the Portuguese Ageing Research Group Web Seminars, the 50th FEBS congress and the FEBS-IUBMB-ENABLE Conference.

We wish all members of the SPB community a relaxing and enjoyable summer holiday!

The SPB Directive Committee

Interview

For this edition's Newsletter, we talked to Catarina Oliveira, MD, PhD, a retired full professor (*Jubilado*) from the Faculty of Medicine, University of Coimbra.

Catarina Oliveira. Photo by Luisa Ferreira (2015)

We'll begin by asking for a brief summary of your career and what motivated/attracted you at each stage.

I was born in Coimbra, graduated in Medicine from the Faculty of Medicine of the University of Coimbra in 1970, and was awarded a PhD degree in Neurology in 1984, at the same University, where I developed my teaching and research career.

At the University of Coimbra, I was President of the Institute of Interdisciplinary Research (3is) from 2003 to 2005, and a member of the University first General Council.

I was President of the Center for Neuroscience and Cell Biology (CNC) from 2003 to 2013, and Coordinator of the CNC.IBILI consortium (2013 - 2016).

At the Faculty of Medicine, I held several management positions: I was President of the Scientific Council (2004-2008), participated and chaired several committees, and was involved in the curricular reforms of this medical school. I collaborated in the creation of, and coordinated, the PhD Programme in Health Sciences and the Inter-University PhD Programme in Aging and Chronic Diseases, together with the Universities of Minho and New University of Lisbon.

Furthermore, I participated in the pedagogical projects developed by the school in collaboration with the Universities of the Azores and Cape Verde. At Coimbra University Hospitals (CHUC) I was Coordinator of the Unit for Innovation and Development (UID).

I was also involved in developing the proposal to promote translational medicine and training at Coimbra Clinical Academic Centre (CACC), of which I later became a member of the board of directors. I was a member of the Health Sciences Scientific Council of the FCT and EDAB and sub-director of the Portugal Harvard Medical School Programme (2008-2015), as well as being a member of the board of directors of Health Cluster Portugal (HCP) from 2008 to 2017. More recently, I coordinated the organizing committee and was the first president of the National Agency of Clinical Research and Biomedical Innovation (AICIB).

Can you tell us about your scientific career?

My scientific career was profoundly marked by my supervisors, António Nunes Vicente, Professor of Neurology and Director of the Neurology Service at Coimbra University Hospital, from whom I learned the importance of scientific knowledge in clinical decision-making, and Arsélio Pato de Carvalho, Professor of Biology and President of the Center for Cell Biology at the University of Coimbra, who instilled in me the importance of rigor in research.

I would say that my scientific career began when I started the neurology internship at Coimbra University Hospitals.

At that time, I was challenged to set up the neurochemistry laboratory in the Neurology Department, a laboratory that would develop into what is now a reference in the study of biomarkers of neurological diseases, namely the most prevalent neurodegenerative diseases, Alzheimer's and Parkinson's.

The choice of topic for my doctoral thesis, focused on the biochemical and pharmacological characterization of brain dopamine receptors, allowed me to take advantage of the best of both worlds: the clinical practice of Parkinson's disease and research in animal models of the disease.

This translational perspective came to dominate my future research path, later focused on the molecular and cellular mechanisms of neurodegeneration involving oxidative stress, changes in calcium homeostasis and mitochondrial dysfunction, and on the identification of biomarkers for Alzheimer's disease.

Later, I was the leader of the Advanced Diagnosis and Biomarkers of Aging and Brain Diseases research group at the CNC and a member of the JPND European Consortium dedicated to the study of Biomarkers of Alzheimer's and Prion Diseases.

What inspired you to work in neuroscience and neurodegenerative disorders?

My interest in the study of the brain arose in the early years of medical school, when I had the opportunity to undertake an integrated study of brain structure and function, that is, of anatomical aspects along with those related to neurophysiology.

This interest grew as I progressed into the clinical areas of neurology and psychiatry. Being faced with an organ that gives us the ability to interact with the world around us, allows us to acquire and retain new information, and allows us to remember and forget, is truly fascinating.

Understanding the loss of some of these abilities as we age and how a slow and progressive impairment sets in, leading to the loss of identity and self-memory during the neurodegeneration process occurring in Alzheimer's disease, is a huge challenge.

What discovery has surprised you the most?

The experimental result from my working group that perhaps excited me the most and that marked the group's area of work was the observation of the determining role of mitochondria in the neurodegenerative process.

We verified, in Alzheimer's disease models, that functional mitochondria are necessary for the neurotoxicity of the beta-amyloid protein, a protein that accumulates in the extracellular environment in the brains of Alzheimer's patients, in senile plaques, which are one of the hallmarks of the disease.

This experimental data was crucial for the subsequent research interests of the group, focused on the role of mitochondria and the alteration of the mechanisms involved in the communication between cellular organelles in disease models.

This data allows not only an integrated understanding of the mechanisms of neuronal survival and death but also opens up new perspectives for potential therapeutic approaches.

What was your greatest professional challenge?

My greatest professional challenge, as a teacher of Neurology and Biochemistry and researcher in Neuroscience, was to awaken in young people an interest in knowledge, critical thinking, and the possibility of applying that knowledge in the search for solutions to the problems that society faces.

To be able to convey to them that it is worthwhile dedicating ourselves, with passion, to the causes we believe in.

News & Views

The AlphaFold Revolution in Structural Biology: Bridging Prediction and Experimental Validation

Sandra Macedo Ribeiro, Instituto para a Investigação e Inovação em Saúde - i3S, Universidade do Porto, Porto, Portugal

Structure prediction using AlphaFold (Jumper *et al.* 2021) and other artificial intelligence (AI) tools (Krishna *et al.* 2024; Chen *et al.* 2024) has changed structural biology and greatly expanded the number of predicted protein structures (Varadi *et al.* 2024). These models, however, do not eliminate the need for experimental validation. Instead, they accelerate and broaden research impact by improving hypotheses and experimental design, routinely integrating into structure-determination workflows (Figure 1), while remaining limited by biases in available structural data used for training, as well as by disorder, dynamics, and biological context.

Protein Structural Models Accessible for All

Structural biology has always relied on the ability to see molecules: X-ray crystallography, nuclear magnetic resonance (NMR), and cryo-electron microscopy (cryo-EM) have revealed how proteins and complexes work, how drugs bind, and how mutations cause disease. Yet the field still faces persistent bottlenecks, including difficulties in crystallizing proteins and protein complexes, unstable or aggregation-prone constructs, heterogeneous or transient assemblies, and dynamic or intrinsically disordered proteins that resist high-resolution characterization by standard experimental approaches.

Complementary methods, such as native mass spectrometry, small-angle X-ray scattering (SAXS), chemical crosslinking coupled to mass spectrometry (XL-MS), and hydrogen-deuterium exchange mass spectrometry (HDX-MS), have broadened what we can do with structural biology by providing independent evidence for composition, topology, and dynamics. However, these approaches require substantial expertise and specialized infrastructure and were mostly available to a limited community of structural biologists.

Novel structure prediction tools have transformed this reality. For many proteins, three-dimensional structural models can now be generated rapidly. As a structural biologist, I still find it remarkable how predicted structures now appear in publications and presentations across disciplines. As a result, structurally anchored hypotheses that once depended on specialized pipelines are now accessible to many more labs, thereby encouraging more studies of structure-function relationships across life sciences.

The widespread availability of predicted protein structures has changed how research projects are initiated. In many labs, the first step is to ask, "What does the predicted structure suggest we should test?" Therefore, predicted protein structures help formulate hypotheses and design experiments, rather than replacing experimental structure determination.

Building Better Hypotheses and Improved Experimental Design

A key contribution of modern structure prediction methods is their ability to support more robust, experimentally verifiable hypotheses earlier in research projects. Predicted protein structures often uncover functional (*e.g.*, active-site configurations or potential metal-binding motifs), mechanistic (*e.g.*, whether a loop could regulate substrate access), or interaction hypotheses (e.g., candidate binding surfaces or domain orientations in multi-domain proteins).

Even when not fully correct, predictions can be valuable for narrowing the set of plausible mechanisms and for proposing key experiments. These predicted models also have a practical impact on experimental design.

They help define domain boundaries, pinpoint disordered regions, and suggest stable truncations for expression constructs. They also guide mutagenesis strategies by highlighting residues that may affect stability, catalytic activity, or interface formation.

AI models are now routinely used as standard tools in structure determination workflows (Rosignoli *et al.* 2025; Schwalbe *et al.* 2024). In cryo-EM, predicted subunit structures can accelerate model building, particularly at medium resolution or in complex assemblies.

In crystallography, predicted models are often used as molecular replacement templates. Predictions also serve as starting points that are refined in light of experimental restraints from XL-MS, HDX-MS, and/or SAXS. Across these methods, predicted structural models mainly reduce trial-and-error, supporting construct selection, phasing/model building, and interpretation, while experimental data still define the final validated model (Figure 1).

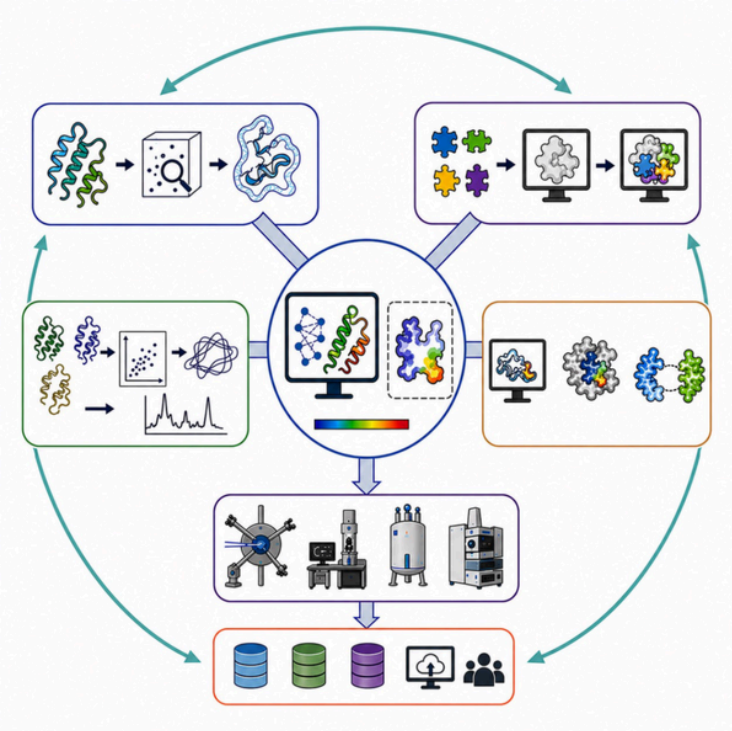

Figure 1. Schematic overview showing how computationally predicted structural models are used in structural biology workflows. AI-based structural models are used in X-ray crystallography, cryo-EM, and NMR, while facilitating construct design and the prediction of binding interfaces and protein interactions. Experimental data validate structure predictions, with experimental structures deposited into community databases such as the PDB providing additional training data to support further structure prediction methods. (Created using OpenAI DALL·E; scientific content and design curated by the author).

Built on Open Access: The PDB and as a Foundational Database

Current protein structure prediction methods are inseparable from the Protein Data Bank (PDB). The PDB is widely recognized as the first open-access database in life sciences and represents a longstanding community commitment to producing and depositing structural data and associated metadata (Velankar *et al.* 2021). Predictive models extract structural features from this database and, by extension, from the experiments that elucidated protein structures (Abramson *et al.* 2024; Varadi *et al.* 2024).

This legacy both enabled modern protein structure prediction and constrained it: the PDB is not a representative sample of protein space, and models inherit its historical sampling biases. It over-represents well-folded, stable proteins, soluble domains, and targets with favorable crystallization propensity or predictable behavior during purification.

Conversely, it under-represents intrinsically disordered regions, transient complexes, dynamic conformational ensembles, and many membrane proteins or complex assemblies, despite notable progress.

This means that AI models are trained on the subset of proteins that experimentalists have been able to resolve. They are exceptionally powerful predictors of soluble, globular proteins, but less reliable for non-globular and membrane proteins.

Where Prediction Still Struggles: Disorder, Dynamics and Context

The future of structural biology will be determined by the increasingly close integration between prediction and experiment. Intrinsically disordered proteins (IDPs) drive regulation, signaling, and phase separation, and their "structure" is often best represented as a conformational ensemble rather than a single fold.

Predictors may assign low confidence or propose unstable folds that can mislead interpretation, showing a conceptual mismatch, as many proteins do not have a single well defined native structure.

Function is also frequently encoded in dynamics, including conformational switching, allosteric coupling, induced fit upon binding, and long-timescale motions. Current predictors typically return a main structural model, which can be valuable but may miss biologically relevant states, although this is slowly changing (Li *et al.* 2026; Brotzakis *et al.* 2025; Bryant and Noe 2024).

Experimental techniques such as NMR, single-molecule approaches, time-resolved methods (in crystallography, cryo-EM, or SAXS), HDX-MS, fluorescence resonance energy transfer (FRET), and kinetic analyses are still essential for understanding motion rather than static structure alone.

Predicting stable complexes is improving (Abramson *et al.* 2024), but many assemblies are shaped by transient interactions, crowded cellular environments, post-translational modifications, and cooperative binding.

Even when predicted interfaces appear plausible, experimental validation is required to establish stoichiometry, affinity, regulation, and physiological relevance.

Moreover, many functional states depend on metal ions, cofactors, lipids, small molecules, glycosylation, phosphorylation, protonation states, and water networks. Accurately modeling these features and how they reshape conformational landscapes remains challenging; experimental validation is therefore often the most reliable route to clear mechanistic conclusions.

Finally, confidence metrics can be misleading: high confidence does not guarantee correctness, and errors in domain orientation, interfaces, or flexible regions can persist despite apparently plausible local geometry.

The Missing Link: Predicting the Structure of Nucleic Acids

Despite major advances in protein structure prediction, nucleic acids remain a challenge. RNA and DNA structures depend not only on base pairing but also on complex tertiary interactions, dynamics, and environmental context, including ions, ligands, and protein partners.

While RNA secondary structure prediction is well established, accurate three-dimensional modeling for large, flexible, or multi-domain RNAs remains limited.

Recent advances include approaches such as RhoFold+ (Shen *et al.* 2024) and trRosettaRNA (Wang *et al.* 2023; Wang *et al.* 2026). By contrast, DNA structure prediction has largely focused on sequence-dependent shape features (Li *et al.*, 2024). This gap reflects both the intrinsic complexity of nucleic acids and the smaller pool of high-resolution experimental training data. Because many nucleic acids function within ribonucleoprotein or chromatin assemblies, future progress will require models that integrate structure, dynamics, and molecular context.

Teaching Structural Biology After AlphaFold

Given the ease with which protein structure predictions are now obtainable, educational efforts should focus on the more challenging and scientifically rigorous aspects: interpretation, validation, and contextual insight.

Essential skills must include: (1) Model literacy: distinguishing experimentally determined structures from predictions; understanding confidence metrics, bias, and uncertainty; using predictions to identify domain boundaries, disorder, truncation, and solubility; (2) Mechanistic thinking: linking structure to function, but do not regard models as conclusive evidence; (3) Ensemble thinking: recognizing disorder and dynamics as central concepts rather than exceptions. Importantly, it must be highlighted that AI-based predictions depend on decades of experimental data, open-data initiatives such as the PDB, and established community standards.

Conclusion

AI structure prediction marks an important breakthrough in structural biology, by improving experimental workflows rather than replacing them.

It allows rapid hypothesis development, guides construct and experimental design, and integrates with cryo-EM and crystallography, expanding the scope of structural investigation. At the same time, predictions remain shaped by existing data and continue to struggle with the complexity of biology (disorder, dynamics, context, chemistry, and transient interactions).

The future of the field will come from methods that combine prediction with experimental validation and open data, turning an immense set of structural models into validated mechanistic understanding.

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Calendar & Events

DATE	EVENT	PLACE	LINK
Monthly Online Seminars	**PAGE 2026: Web Seminars of the Portuguese Ageing Research Group**	Monthly Online Seminars	LINK
04 - 08/07	**The 50th FEBS Congress**	Maastricht The Netherlands	LINK
07 - 09/07	**EuroCurvoBioNet Training School 2026, Curvature Across Scales**	Delft University of Technology, Delft The Netherlands	LINK
31/08 - 04/09	**25th European Conference on Computational Biology**	Geneva, Switzerland	LINK
16 - 18/09	**3rd RNA Horizons Conference**	Munich, Germany	LINK
21 - 27/09	**VI International Symposium on Fungal Stress – ISFUS**	São José dos Campos, Brazil	LINK
04 - 06/10	**19th Congress of the International Union of Microbiological Societies (IUMS 2026)**	Lisboa, Portugal	LINK

DATE	EVENT	PLACE	LINK
07- 09/10	**4th International Conference on Nitric Oxide Therapeutics in Cancer and Other Diseases**	Lisboa, Portugal	LINK
10- 16/10	**Champalimaud Research Symposium 2026** - *Neural and Immune Codes in Cancer*	Lisboa, Portugal	LINK
14- 16/10	**FEBS–IUBMB–ENABLE Conference**	Kraków, Poland	LINK
22- 23/10	**XXIII National Congress of Biochemistry**	University of Beira Interior, Covilhã, Portugal	LINK
28- 30/10	**European Rosetta Con**	Lisboa, Portugal	LINK