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Debbie C. Crans,
Colorado State University, United States

*CORRESPONDENCE
Andrea Ilari,
andrea.ilari@cnr.it

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Editorial: Insights in theoretical modelling, structure prediction and design

Andrea Ilari[1]*, Veronica Morea[1] and Adriana Erica Miele[2]

[1]IBPM Institute of Molecular Biology and Pathology, Consiglio Nazionale delle Ricerche (CNR), Rome, Italy, [2]UMR 5280 Institute of Analytical Sciences, Centre National de la Recherche Scientifique (CNRS), Université Claude Bernard Lyon 1, Villeurbanne, France

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Editorial on the Research Topic
Insights in theoretical modelling, structure prediction and design

The first quarter of the XXI century has seen a growth explosion of the field of Theoretical Modelling, Structure Prediction and Design. Therefore, we decided it was timely to dedicate a Research Topics of Frontiers to highlight the latest advancements across the field of Chemical Biology. As underlined in the grand Challenge of this session (Exertier and Ilari, 2025) our era is particularly stimulating for the field of structural study of biological macromolecules and their interactions with molecular partners. The competition among structural prediction methods in the 13th and 14th editions of the Critical Assessment of Structure Prediction (CASP 13 and 14) (Kryshtafovych et al., 2019; Alexander et al., 2021), witnessed the extraordinary success of the artificial intelligence programs AlphaFold and AlphaFold2 (Jumper et al., 2021). Indeed, artificial intelligence is now spreading through most aspects of life science research (Caudai et al., 2021).

A special attention was given to the challenges on top of the novel developments. In particular, we wanted to shed light on studies involving macromolecules structure-function relationships implying both experimental and computational methods. Therefore, we aimed at investigations on molecular structures, folding, design, evolution, interactions and structure-based drug design of small molecules. The research topics consists of four manuscripts representing very different areas, despite being contemporary to other similar topics in different Frontiers journals. This research topic illustrates the variety of approaches used in this field and the attractiveness of a chemical biology platform for exploration of detailed characterization in the field of Theoretical Modelling, Structure Prediction and Design.

According to the published research, a special attention is devoted to the investigation of protein interfaces, whether intramolecular oligomers or intermolecular partners. The aim of these studies was to unveil the properties of these surfaces in order to better exploit them for the rational design of non-competitive, also called allosteric, inhibitors. Investigation of protein interface properties dates back to the end of the 20th century (Lo Conte et al., 1999; Morea et al., 1997; Tsumoto et al., 1994; Vallone et al., 1998), however it was at the turn of the new century that the field sprouted, thanks to the progresses in genome sequencing, molecular and structural biology, medicinal chemistry and, of course, computing power. The first quarter of this century has seen a boost in both computational and experimental

researches, especially after having understood the principles of the neural networks involved in sensing (Katayama et al., 2000; Paulin, 2005; Victor, 2005) and having transposed them into a computer architecture, paving the way to machine learning that was employed also to predict protein-protein interactions (Liu et al., 2025).

Two of the papers in this research topics, by Padilla Franzotti et al. and Testi et al., explore the hub of interfaces in two proteins important for gene transcription regulation, namely the retinoblastoma protein (pRb) and the transcription factor NANOG, respectively. pRb regulates cell proliferation by binding to E2F transcription factor. The large T antigen of simian virus 40 (LTSV40) interferes with this control pathways by binding pRb. Padilla-Franzotti and colleagues deeply investigated this interaction by Molecular Dynamic simulations and shed light on a mechanism used by viral oncoproteins to cause uncontrolled cell proliferation. The resulting knowledge of the interaction mechanisms and dynamics may pave the way for design of anticancer therapeutics blocking cell proliferation (Padilla Franzotti et al.).

In the second example of gene transcriptional regulation, described in the paper by Testi et al., one orphan point mutation is analysed and correlated with the function of NANOG-TET2 complex in the frame of haematopoiesis. Tet methylcytosine dioxygenase (TET2) catalyses the conversion of the modified DNA base methylcytosine to 5- hydroxymethylcytosine; this is the first step of DNA demethylation, which is an important epigenetic modification. TET2 is positioned at the centre of a complex interaction network, and any impairment in one of these interactions could potentially trigger a cascading effect on cellular functionality. Transcription factors like the homeobox protein NANOG bind to TET2 to regulate target gene expression, thus enabling cell differentiation processes. The authors discovered that the single point mutation from Gln to Pro at residue 1084 of TET2 compromises this interaction, thereby affecting hematopoietic stem and progenitor cells (HSPCs) differentiation, leading to an impairment of the hematopoiesis process.

The papers by Exertier et al. and Attili et al. explore the interaction of small organic molecules with surfaces of protein targets with the aim of drug screening and design. Exertier and colleagues used fragment screening to identify new fragments able to bind to the Trypanothione reductase from *Trypanosoma brucei* (TbTR), with the aim to design new lead compound against Human African Trypanosomiases (HAT) and the other diseases caused by Trypanosomatids, which comprise both Trypanosoma and Leishmania species. TR is a key enzyme in the redox metabolism of Trypanosomatids and is essential for parasite survival inside the human host. Since the residues lining the trypanothione binding cavity are conserved among Trypanosomatids family members, the discovery of effective inhibitors would pave the way for the developments of drugs effective against all pathologies caused by this protozoan family. The Authors performed soaking of TbTR monoclinic crystals with fragments from DSIpoised and EubOPEN DSIp libraries, at the XCHEM facility (Diamond Light Sources, United Kingdom). The first paper is a very interesting study identifying eight new fragments binding to different regions of the trypanothione reductase enzyme, including the trypanothione and the NADPH binding cavities. It also highlights the importance of this type of analysis even if such fragments do not significantly affect enzyme activity.

The second example of the interaction of small organic molecules with surfaces of protein targets is a MD simulation study of the MDM2/MDM4 heterodimer interface region, which effectively inhibits p53 oncosuppressive function. The disruption of the MDM2/MDM4 heterodimer activates p53 oncosuppressive function *in vitro* and *in vivo*; therefore, knowledge of the interaction dynamics could be exploited for the development of new lead compounds aimed at disrupting the heterodimer. Using molecular dynamics simulation followed by umbrella sampling, the Authors identified a short peptide and derivatives thereof, with increased binding affinity and better pharmacodynamics features compared with previously identified interface inhibitors.

This study explores and elucidates the intrinsic plasticity of the MDM2 RING domain, which is characterized by different binding clefts. The study also highlights the key residues involved in the interaction with peptide inhibitors and provides insight that will be useful for the design of next-generation therapeutic inhibitors.

The articles collected in this special issue provide evidence of the extent to which *in silico* computational techniques and experimental methods in the field of structural biology have advanced, opening up enormous possibilities for understanding pathophysiological phenomena and for designing new drugs. We hope that this article collection will inspire, inform and provide direction and guidance to researchers in the field.

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