Computational Molecular Biology 2024, Vol.14, No.6, 229-238
http://bioscipublisher.com/index.php/cmb

Meta Analysis Open Access

Exploring Molecular Interactions: the Role of Biophysics in Understanding Biological Processes

Wenzhong Huang
Biomass Research Center, Hainan Institute of Tropical Agricultural Resouces, Sanya, 572025, Hainan, China
Corresponding email: wenzhong.huang@hitar.org
Computational Molecular Biology, 2024, Vol.14, No.6 doi: 10.5376/cmb.2024.14.0026
Received: 03 Nov., 2024
Accepted: 05 Dec., 2024
Published: 16 Dec., 2024

Preferred citation for this article:
Huang W.Z., 2024, Exploring molecular interactions: the role of biophysics in understanding biological processes, Computational Molecular Biology, 14(6): 229-238 (doi: 10.5376/cmb.2024.14.0026)

Abstract Biophysics provides a unique perspective for the study of molecular interactions by combining physical principles and techniques. Research over the past few decades has shown that methods such as single-molecule biophysics have innovated molecular research and promoted the understanding of dynamic biomolecular processes. This study reviews the role of biophysics in studying molecular interactions in biological systems, focusing on the latest biophysical technologies and their applications in the study of complex and dynamic biomolecules. By analyzing the contributions of single-molecular methods and other innovative technologies, it demonstrates how biophysics deepens its understanding of biological mechanisms at the molecular level. The article systematically summarizes the research progress in biophysics, hoping to provide researchers with new insights to promote understanding of molecular interactions and promote further development in related fields.
Keywords Molecular interactions; Biophysics; Single-molecule techniques; Dynamic biomolecular processes; Innovative biophysical methods

1 Introduction

The interaction between molecules is an important basis for life activities. These effects include the connection between proteins and proteins, the binding of enzymes and substrates, and the movement of nucleic acids. They have a great influence on the stability of cellular structure, signal transmission, and metabolic response (Corrales-Guerrero et al., 2023). Especially those relatively weak interactions play an important role in protein folding, DNA replication and membrane movement. It is precisely because of these weak effects that cells can respond quickly and reversibly to changes in the environment. Understanding how these interactions occur will help us understand the basic principles of life activities and may also provide ideas for the development of new therapies.

Biophysics uses physics methods to study biological problems, which gives us a deeper understanding of how molecules interact. Over the past sixty years, these methods have helped us discover many structural and dynamic changes in proteins and nucleic acids, and can also link their physical properties with biological functions (Ren et al., 2012). For example, single-molecular biophysics technology has brought great changes to research. It allows us to see the behavior of individual molecules, which is often not visible when studying the overall system (Kim et al., 2022). In addition, the development of technologies such as super-resolution microscopy, optical tweezers and molecular dynamics simulation has greatly improved our ability to study complex biological systems (Miller et al., 2017; Haghizadeh et al., 2023).

This study mainly reviews the important contributions of biophysics in the study of molecular interactions. We focus specifically on the latest biophysical technologies and their applications in analyzing dynamic, complex molecular processes. At the same time, we also emphasized the unique role of new methods such as single-molecular technology, and wanted to show how biophysics can help us better understand life mechanisms at the molecular level.

2 Fundamentals of Molecular Interactions

2.1 Basic principles of molecular recognition

In biological systems, different molecules recognize each other. This is called "molecular recognition", which is a very important process. It refers to the combination between large molecules, or between large molecules and small molecules, through very specific and strong interactions, and combine into a stable complex. This process is related to many life activities, such as how enzymes and substrates bind, how receptors and ligands work, and how proteins and DNA pair. This recognition can occur because the molecular structures can cooperate well with each other and the physical and chemical properties can also complement each other (Du et al., 2016; Corrales-Guerrero et al., 2023). Scientists have proposed models to explain these processes, such as the "lock key model", "induced fit model" and "conformation selection model". These models show that molecular recognition is not rigid, but has some flexibility, and molecules will be adjusted according to the situation.

2.2 Physicochemical basis of intermolecular interactions

There are many kinds of forces between molecules. Common ones include hydrogen bonds, van der Waals forces, electrostatic effects, and hydrophobic effects. Together, they determine whether the molecules can bind stably and how strong the bond is. For example, relatively weak effects such as hydrogen bonding and van der Waals forces are actually particularly important in protein folding, enzyme catalysis and molecular recognition (Ardini et al., 2022). Moreover, these effects are not static. They can change rapidly according to the environment, which allows cells to flexibly cope with various external stimuli, which is very helpful for maintaining normal state. In addition, the cells are actually very crowded, and this environment can also affect the way molecules bind, such as slowing down the diffusion or making certain reactions more difficult to carry out (Haghizadeh et al., 2023).

2.3 Theoretical overview of free energy, entropy, and enthalpy in molecular interactions

In thermodynamics, we usually use "free energy" to describe whether two molecules can bind naturally. As long as the change in free energy is negative ($\Delta G < 0$), this process occurs spontaneously. Free energy (ΔG) is related to enthalpy (ΔH) and entropy (ΔS). The relationship between them is: $\Delta G = \Delta H - T\Delta S$ (Bronowska, 2011). Changes in enthalpy mainly reflect whether new chemical bonds are formed or broken between molecules; while changes in entropy refer to whether the degree of chaos in the system has changed. Sometimes enthalpy and entropy cancel each other out, which is called "enthalpy-entropy compensation". This situation makes it more difficult to predict the binding between molecules. To better understand these changes, scientists will use experimental techniques such as isothermal titration calorimetry (ITC) and nuclear magnetic resonance (NMR). These tools can help us accurately measure thermodynamic parameters, thereby analyzing the reasons behind molecular identification (Caro et al., 2017).

3 Thermodynamic and Kinetic Principles of Molecular Interactions

3.1 Thermodynamic analysis of molecular binding

When two molecules combine, the energy changes. Thermodynamic analysis is about studying this energy change and the forces behind it. We usually use Gibbs free energy (ΔG) to determine whether molecules are prone to bond. If ΔG is a negative value, it is advantageous to indicate that this combination can occur on its own (Bronowska et al., 2011). The value of ΔG is affected by two factors: enthalpy (ΔH) and entropy ($-T\Delta S$). Enthelium is mainly related to the "binding forces" such as hydrogen bonding, van der Waals forces, and electrostatic action; while entropy is affected by changes in the flexibility of molecules and the rearrangement of water molecules. To measure these data, scientists use experimental tools such as isothermal titration calorimetry (ITC) and nuclear magnetic resonance (NMR). These methods can help us figure out how molecules bind (Terazima, 2021).

3.2 Kinetic analysis of molecular interactions

Kinetics studies how fast the two molecules bind and how fast they separate. We usually calculate two values: the binding rate (k_{on}) and the dissociation rate (k_{off}). They can tell us how stable a molecular complex is and how long it will last (Du et al., 2016). There are now some advanced experimental methods, such as time-resolved thermodynamics and molecular diffusion methods, which can help us see details that were not seen in the past. For example, some intermediate states are very short-lived and cannot be measured

by traditional methods, but can now be captured. In addition, a method called transient grating (TG) can measure the reaction speed in real time and draw a graph of energy changes, allowing us to see how the entire process is carried out step by step (Terazima, 2021).

3.3 Dynamic interactions and cooperative effects

Many molecules are not static when bound, but are constantly changing. This dynamic interaction is common in organisms. For example, in the interaction between proteins and nucleic acids, ions will move rapidly, and different ion combinations will change continuously. This "movement" binding method helps molecules recognize faster and more accurately (Yu et al., 2020). In addition, there is another phenomenon called synergistic effect. Simply put, the binding of one molecule will affect the binding of another molecule. If the two molecules cooperate well, the combination will be easier and the effect will be better. For example, when one ligand binds to a protein, it may make the other ligand more likely to bind to it. This effect also causes structural changes in proteins, thus helping them work better (Krapf, 2015; Juru et al., 2019). These dynamic and synergistic properties allow biomolecules to perform their functions well in complex environments.

4 Biophysical Techniques for Studying Molecular Interactions

4.1 Spectroscopic techniques

Spectroscopy technology is the basic tool for studying molecular structures and their interactions. In biophysics, it is used very widely. Commonly used methods include: nuclear magnetic resonance (NMR), electron paramagnetic resonance (EPR), and various fluorescence analysis technologies. These techniques can help us gain insight into how molecules bind. For example, NMR technology is particularly suitable for studying the interaction between protein and RNA. It provides very clear structural information, telling us where the molecules bind (Steinmetz et al., 2023). There is also a method called isothermal titration calorimetry (ITC), which also belongs to spectroscopy technology. It can directly measure the heat changes when two molecules bind without special treatment on the molecules, and it is fast and has high accuracy (Simon and Macdonald, 2018). These technologies, like "microscopes" and "thermometers", help us see and quantify the behavior of invisible molecules.

4.2 Microscopic imaging techniques

Microscopy technology allows us to "see" how molecules interact with each other, and even individual molecules. The development of this field has completely changed the way we study molecules. Now, scientists can use super-resolution microscopy, fluorescence microscopy combined with optical tweezers to observe very small and very complex molecular activities (Haghizadeh et al., 2023). To give a few examples: In gene editing studies, microscopy can observe how CRISPR/Cas9 binds to the target DNA. Its performance is also different under different conditions, which can help us determine whether it is accurate (Huang and Lin, 2024). In DNA tissue research, microscopy can show how the Cohesin complex changes the DNA junction state with the help of ATP, which is very helpful in understanding chromosomal structure. During DNA replication, these techniques can see how single-stranded DNA works with BLM proteins, telling us how replication begins and continues. In terms of DNA repair, confocal microscopy allows us to track how repair proteins like RAD-51 cooperate with other molecules, helping us to have a clearer understanding of the repair process (Figure 1) (Haghizadeh et al., 2023). In addition to these, electron microscopy and scanning probe microscopy are also important. They can help us quickly and accurately analyze the structure of proteins or other biological materials (Nezammahalleh et al., 2022).

4.3 Real-time detection techniques

The role of real-time detection technology is to directly observe the process of molecular action when it is happening. This is particularly important for understanding the behavior of molecules in the "real environment". Single-molecule technologies, such as force spectrum, can observe their reactions in real time by exerting force on the molecule. This method can see how molecules behave when they are stretched or compressed (Dobson, 2019). These techniques will be better if combined with mass spectrometry analysis. Especially when it comes to studying membrane proteins, they can help us discover details we didn’t know before. Nowadays, researchers

often combine these technologies with computer simulations. This allows for a more comprehensive understanding of the behavior of molecules in complex environments (Corrales-Guerrero et al., 2023).

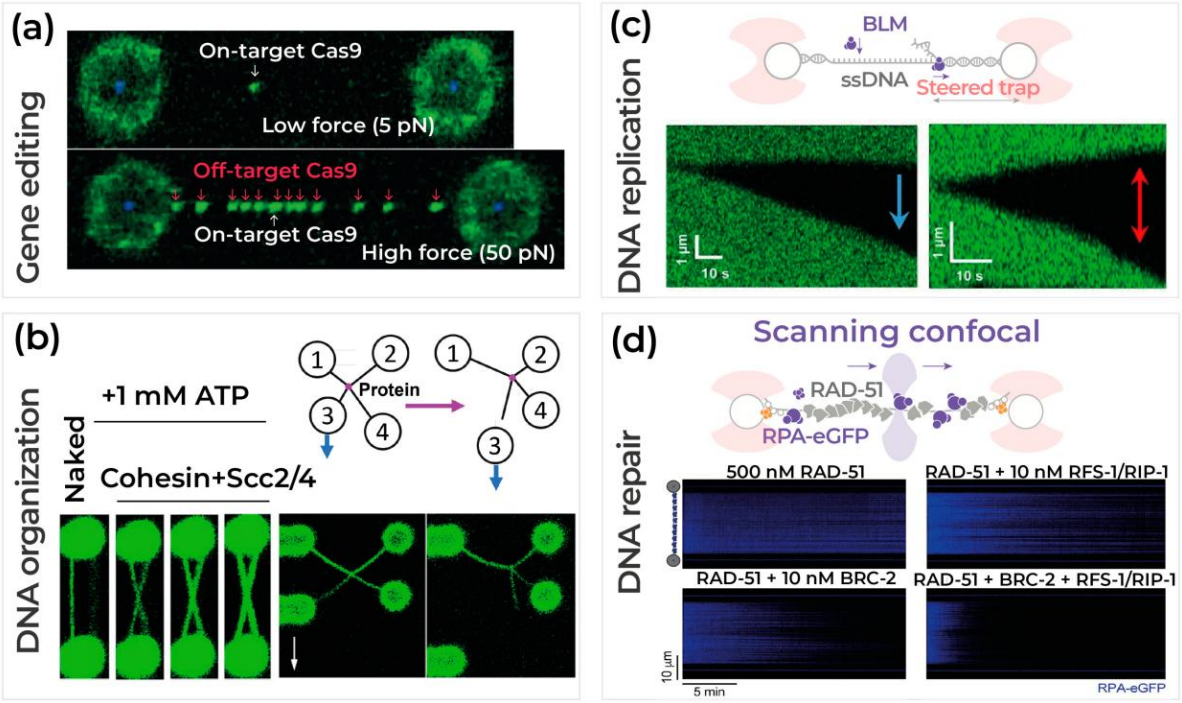

Figure 1 Understanding various DNA–protein interactions using correlated optical tweezers fluorescence microscopy (Adopted from Haghizadeh et al., 2023)

5 Biophysical Analysis of Protein-Protein Interactions

5.1 Structural and functional analysis of protein complexes

To figure out how proteins work together, we must first understand the structure and function of the "complex" they make up. Scientists have developed many biophysical methods to study these structures. For example, cryo-EM can take the structure of a protein very clearly and almost see atoms. This technology allows us to "see" directly how proteins are combined. There is a method called MarkovFit that accurately aligns different parts of a protein into cryo-EM images, which can be used even if the resolution is not high (Labrou et al., 2023). There is also matrix-assisted laser analytical ionization mass spectrometry (MALDI-MS), which can analyze the weak interaction between proteins that do not rely on chemical bonds, and can also see how their shapes change. This method has high sensitivity and few samples, which is very practical (Giampà and Sgobba, 2020). These tools can help us understand more comprehensively how proteins work together.

5.2 High-throughput screening techniques

In the past, it was very slow to study the interaction between proteins. But now with high-throughput screening technology, we can study the interactions of many proteins at one time, which is much faster. Such techniques include many proteomics and biophysical methods, which can help scientists quickly find which proteins are associated with each other and also draw a complete interaction “relationship map” (Schuck and Zhao, 2013). There is a tool called photoactivation localization microscopy (PALM) that can see how each individual protein molecule binds to other proteins in intact cells. This allows us to obtain very detailed space-time information. In addition, there is another method to use a simplified protein model, combining structure and energy information to perform computational simulations. This model can help us simulate how protein interactions change over a longer period of time, which is very helpful in studying complex cellular processes (Wang et al., 2018).

5.3 Role of protein interaction networks in cellular signal transduction

In cells, many signals are transmitted through interactions between proteins. These interactions form a system called protein interaction networks (PINs). This network is very critical and can regulate the activity of various

signal molecules. PINs have several characteristics, such as centrality, modularity and dynamic changes. By analyzing these characteristics, we can find out who the most important proteins in the network are, and we can also distinguish which proteins work together (Meng et al., 2021). The dynamic characteristics of the network are also important. It tells us that the connection between proteins is not fixed, but changes over time or space. These changes can affect the outcome of signaling. Modern high-throughput technology makes it easier for us to build and analyze these complex networks. This not only helps us understand how normal cells work, but also explains what exactly goes wrong in some complex diseases.

6 Biophysical Studies of Protein-Nucleic Acid Interactions

6.1 Mechanisms of DNA-binding proteins in nucleic acid recognition

DNA-binding proteins recognize and bind specific DNA sequences, which is a critical step in many life processes (such as transcription, replication, and repair). This binding process relies on several forces to work together: such as electrostatic action, hydrogen bonding and van der Waals force. Among them, electrostatic action is the most basic. There is negatively charged phosphoric acid on DNA, and some parts of the protein are positively charged, and they attract each other to form what is called "ionic pairs." These interactions are not static, but dynamic. There are many small ions moving around DNA, and when proteins bind, some ions are released, which helps maintain the balance of charge (Yu et al., 2020). Furthermore, certain side chains of proteins bind gently to DNA bases, and these weak interactions can also increase the specificity and stability of binding (Corrales-Guerrero et al., 2023). Understanding these processes can help us know more clearly how proteins “recognize” DNA.

6.2 Kinetics and regulation mechanisms of RNA-binding protein interactions

RNA-binding proteins (RBPs for short) recognize specific RNA molecules through their RNA-binding regions (RBDs). Some identify specific sequences, while others have special structures. Neither RNA nor RBP shape is static, and their conformational changes affect the speed and manner of the binding process. To understand these changes, scientists often use technologies such as nuclear magnetic resonance (NMR) and FRET (fluorescence energy transfer). These methods can observe in real time how proteins and RNA bind, and also see what changes in their structure after binding (Schlundt et al., 2017). These interactions are usually fast and reversible, which allows cells to flexibly regulate important processes such as gene expression. In addition, some thermodynamic factors during the binding process, such as the increase in entropy caused by the released counterions, will also affect the strength and specificity of the binding (Juru et al., 2019).

6.3 Structural analysis of protein-nucleic acid complexes

To figure out how proteins and nucleic acids bind, we have to figure out their structure first. Techniques like X-ray crystallography and cryo-EM can take very clear "still photos" of complexes. However, they are not very good at showing the dynamic behavior of molecules. So, to study how they change in solution, scientists also use other methods, such as NMR, small angle X-ray scattering (SAXS), and electron paramagnetic resonance (EPR) (Steinmetz et al., 2023). These techniques can help us see how molecules fold, stabilize, and even maintain bonding during movement. NMR can also tell us more specific things, such as the structural and morphological changes within the ribonucleoprotein complex (RNP), which is helpful in understanding how they behave in different environments (Schlundt et al., 2017). In addition to these, there is a technique called mass spectrometry (MS), which is now used to study RNA-binding proteins. It can accurately find where the protein and RNA bind. The entire experimental process includes: first "fix" the protein and RNA with ultraviolet rays or chemical crosslinking agents; then separate, enzymatically dissolve, and extract them; and finally analyze them by liquid chromatography-mass spectrometry (LC-MS/MS). This method allows us to not only know who is combined with whom, but also see how they come into contact with it, and which small fragment is involved in the combination (Figure 2).

7 Mechanisms of Membrane Protein-Lipid Interactions

7.1 Structural characteristics and binding sites of membrane proteins

Membrane proteins are an important part of cell membranes. They need to interact with the surrounding lipids in order to maintain normal structure and function. This interaction is sometimes direct, that is, lipids directly bind to

a certain position on the protein; sometimes indirectly, lipids affect the shape of the protein and thus change its function (Corey et al., 2019). Current structural analysis techniques, such as mass spectrometry, can help us see how this combination occurs and can also tell us how flexible it is. Studies have found that some specific lipids, such as phosphatidylinositol 4,5-diphosphate or cardiolipin, are very important in regulating protein structure (Agasid and Robinson, 2021).

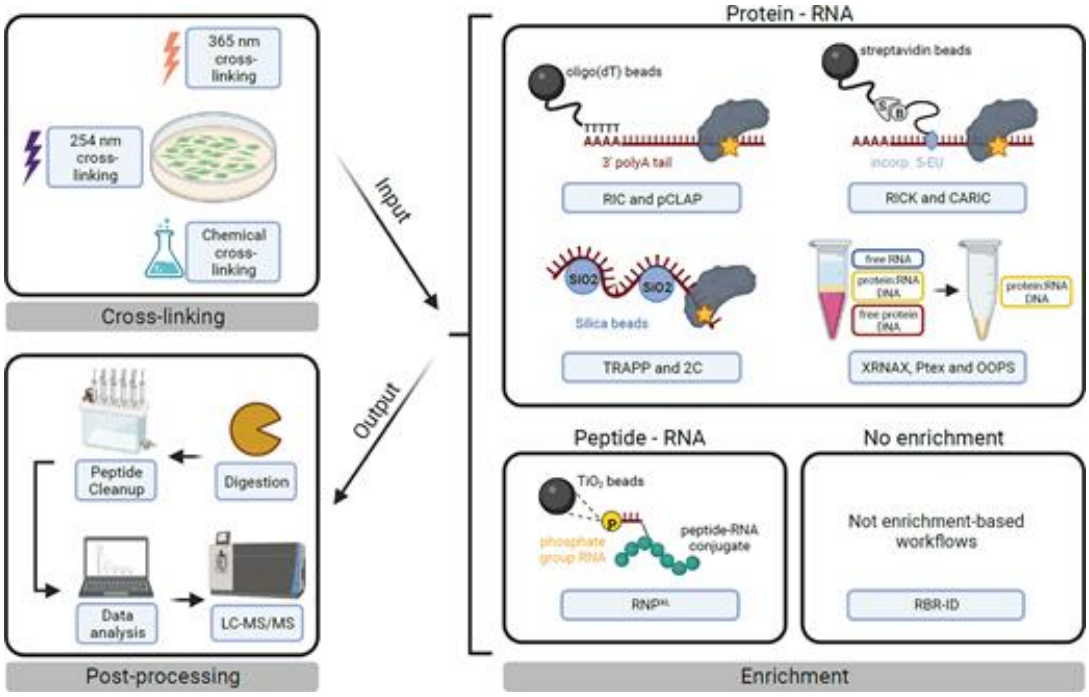

Figure 2 Protein-RNA UV crosslinking workflow (Adopted from Steinmetz et al., 2023)

7.2 Membrane protein interactions in signal transduction

Membrane proteins also play an important role in signaling. Their interaction with lipids can affect protein behavior, such as how they are combined, whether the shape has changed, and whether there is a linkage reaction (Jodaitis et al., 2021). For example: In a process called necrotic apoptosis, a membrane protein called MLKL binds to lipids. This binding triggers the functional changes of the protein, making the cell membrane "loopholes" and then triggers cellular responses (Ramirez et al., 2023). These membrane protein-lipid interactions are also involved in many important biological processes such as cell protection, material transport, and molecular recognition (Sarkis and Vié, 2020).

7.3 Biophysical detection techniques in membrane protein research

In order to figure out how membrane proteins and lipids interact, scientists have developed many biophysical technologies. For example, molecular dynamics simulation (MD) can simulate how lipids and proteins come into contact, move, and change their shape from the atomic level (Muller et al., 2019). There are also some experimental techniques such as circular dichromatic spectroscopy (CD), isothermal titration calorimetry (ITC) and fluorescence spectroscopy. These methods can measure how lipids and proteins bind, whether they bind strongly, and how they affect the proteins on the membrane (Lee, 2018). In addition, mass spectrometry is now also used to study the complexes formed by proteins and lipids. It can tell us what molecules are in the complex, and sometimes supplement the information provided by X-ray crystallography and cryo-EM (Bolla et al., 2019). Together, these techniques provide many useful clues for us to understand the complex interactions between lipids and proteins (Sych et al., 2022).

8 Applications of Biophysics in Drug Discovery and Design

8.1 Target identification and binding site prediction

At the beginning of drug research, we first need to find the target, that is, the protein that the drug wants to act on. This step is very critical. Scientists will use biophysical tools such as nuclear magnetic resonance (NMR), X-ray

crystallography and cryo-EM to determine the structure of these proteins. These tools can help us find the sites where the drug may bind, also called "binding sites" (Holdgate and Bergsdorf, 2021). With these detailed structural information, drug design can be more directional and drugs can act on target proteins more specifically. In addition, calculation methods such as molecular dynamics simulation (MD) and Markov state model (MSM) can also predict binding sites and help us understand the entire process of drug-target binding (Liu et al., 2018; Bernetti et al., 2019).

8.2 Energetic and kinetic analysis of drug-target interactions

To make the drug work well, you also need to know how strong it combines with the target and how fast it is. This requires analyzing the energy and dynamics between them.Scientists will use some experimental methods, such as isothermal titration calorimetry (ITC), surface plasmon resonance (SPR), and differential scanning fluorescence (DSF). These methods can measure energy changes when drugs and proteins bind, such as affinity, enthalpy and entropy. These parameters can help us understand how drugs bind (Winter et al., 2012). Especially ITC, it can directly measure the heat released or absorbed during bonding, and can also draw a clear combination curve, allowing us to understand the entire reaction process at a glance. In addition to doing experiments, researchers will also use MD simulations and free energy calculations to supplement the analysis. This can simulate how drugs and targets combine step by step from the atomic level, and can also see their "energy map" (Han, 2024). In RNA drug research, scientists will also use structural modeling, energy minimization and fragmentation methods to spell out the binding structure of RNA and small molecule compounds. These analyses combine structural biology and computational simulations, which are particularly helpful for drug optimization (Figure 3) (Shino et al., 2023; Miranda et al., 2017).

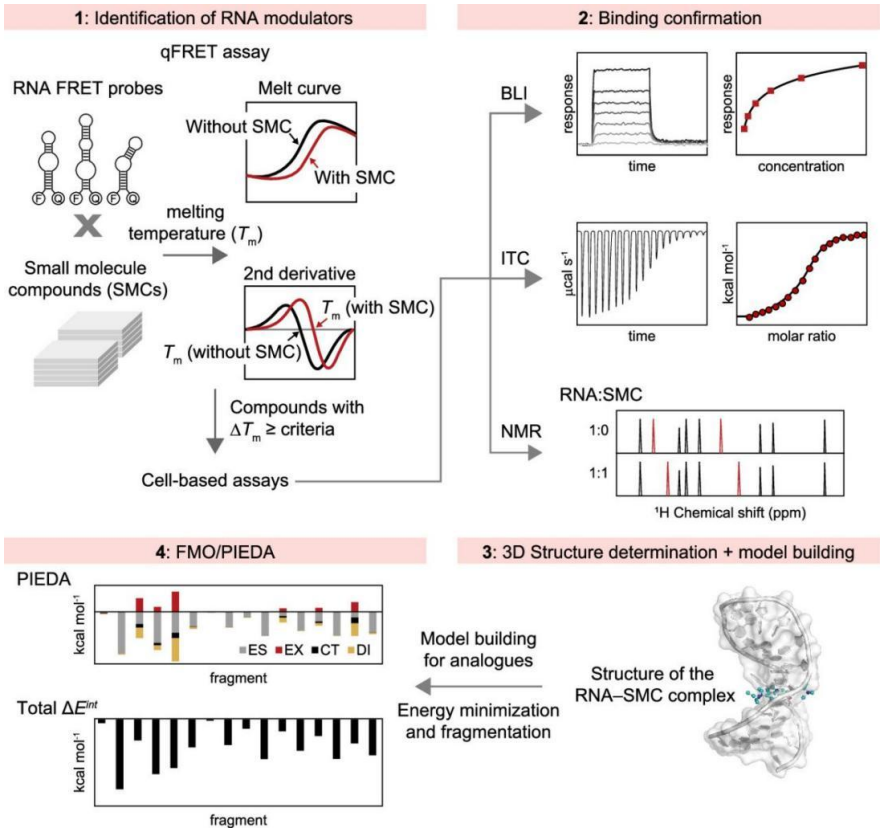

Figure 3 Our workflow for probing intermolecular interactions between RNA and small molecule compounds (SMCs) (Adopted from Shino et al., 2023)

8.3 Successful case studies of biophysical techniques in drug development

Many successful drug projects use biophysical methods. For example, some studies used thermal transition detection to screen more than 400,000 compounds and finally found multiple SMYD3 inhibitors, which shows that this method is very suitable for high-throughput screening. There are also studies that use NMR reporter

molecules to detect weak binding forces, which is particularly useful for "fragment drug discovery" and also provides a data reference for comparisons between different detection methods. Another example is that scientists combined MD simulations, Markov models (MSMs) and pathway variables (PCVs) to reconstruct how the drug "Apronore" was step by step bound to the β2 adrenaline receptor. This study also computes its binding free energy and the most energy-saving path (Bernetti et al., 2019). These examples illustrate: Biophysical methods not only help us find potential drugs, but also help us understand how it works, providing a lot of help in developing new drugs.

Acknowledgements

The author is very grateful to the biological science research expert Jiang Y. for carefully reading the initial draft of the paper and providing detailed revision suggestions; At the same time, we would like to express our sincere gratitude to the two anonymous peer reviewers for their valuable feedback on the initial draft of this study.

Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

References

Agasid M., and Robinson C., 2021, Probing membrane protein-lipid interactions, Current Opinion in Structural Biology, 69: 78-85.
https://doi.org/10.1016/j.sbi.2021.03.010

Ardini M., Baiocco P., Matteo A., Giardina G., and Miele A.E., 2022, Editorial: tailored modulation of interactions between biomolecules: fundamentals and applications, Frontiers in Molecular Biosciences, 9: 961452.
https://doi.org/10.3389/fmolb.2022.961452

Bernetti M., Masetti M., Recanatini M., Amaro R., and Cavalli A., 2019, An integrated markov state model and path metadynamics approach to characterize drug binding processes, Journal of Chemical Theory and Computation, 15(10): 5689-5702.
https://doi.org/10.1021/acs.jctc.9b00450

Bolla J., Agasid M., Mehmood S., and Robinson C., 2019, Membrane protein-lipid interactions probed using mass spectrometry, Annual Review of Biochemistry, 88: 85-111.
https://doi.org/10.1146/annurev-biochem-013118-111508

Bronowska A., 2011, Thermodynamics of ligand-protein interactions: implications for molecular design, IntechOpen, 2011.
https://doi.org/10.5772/19447

Caro J., Harpole K., Kasinath V., Lim J., Granja J., Valentine K., Sharp K., and Wand A., 2017, Entropy in molecular recognition by proteins, Proceedings of the National Academy of Sciences, 114: 6563-6568.
https://doi.org/10.1073/pnas.1621154114

Corey R., Stansfeld P., and Sansom M., 2019, The energetics of protein–lipid interactions as viewed by molecular simulations, Biochemical Society Transactions, 48: 25-37.
https://doi.org/10.1042/BST20190149

Corrales-Guerrero L., Prischi F., and Díaz-Moreno I., 2023, Editorial: weak interactions in molecular machinery volume II, Frontiers in Molecular Biosciences, 10: 1284353.
https://doi.org/10.3389/fmolb.2023.1284353

Dobson C., 2019, Biophysical techniques in structural biology, Annual Review of Biochemistry, 88: 25-33.
https://doi.org/10.1146/annurev-biochem-013118-111947

Du X., Li Y., Xia Y.L., Ai S.M., Liang J., Sang P., Ji X.L., and Liu S.Q., 2016, Insights into protein–ligand interactions: mechanisms models and methods, International Journal of Molecular Sciences, 17(2): 144.
https://doi.org/10.3390/ijms17020144

Giampà M., and Sgobba E., 2020, Insight to functional conformation and noncovalent interactions of protein-protein assembly using MALDI mass spectrometry, Molecules, 25(21): 4979.
https://doi.org/10.3390/molecules25214979

Haghizadeh A., Iftikhar M., Dandpat S.S., and Simpson T., 2023, Looking at biomolecular interactions through the lens of correlated fluorescence microscopy and optical tweezers, International Journal of Molecular Sciences, 24(3): 2668.
https://doi.org/10.3390/ijms24032668

Han L.Z., 2024, Harnessing the power of PGPR: unraveling the molecular interactions between beneficial bacteria and crop roots, Molecular Soil Biology, 15(1): 8-16.
https://doi.org/10.5376/msb.2024.15.0002

Holdgate G., and Bergsdorf C., 2021, Applications of biophysics in early drug discovery, SLAS Discovery, 26: 945-946.
https://doi.org/10.1177/24725552211035123

Huang Y.P., and Lin H.M., 2024, Syntenic relationships and chromosomal evolution in the legume family, Legume Genomics and Genetics, 15(4): 151-162.
https://doi.org/10.5376/lgg.2024.15.0016

Jodaitis L., Oene T., and Martens C., 2021, Assessing the role of lipids in the molecular mechanism of membrane proteins, International Journal of Molecular Sciences, 22(14): 7267.
https://doi.org/10.3390/ijms22147267

Juru A., Patwardhan N., and Hargrove A., 2019, Understanding the contributions of conformational changes thermodynamics and kinetics of RNA-small molecule interactions, ACS Chemical Biology, 14(5); 824-838.
https://doi.org/10.1021/acschembio.8b00945

Kim S.H., Ray S., and Li I.S.T., 2022, Editorial: surveying life one molecule at a time: single molecule methods dig deeper into contemporary biology, Frontiers in Molecular Biosciences, 9: 967434.
https://doi.org/10.3389/fmolb.2022.967434

Krapf D., 2015, Dynamic fluctuations in single-molecule biophysics experiments: comment on "extracting physics of life at the molecular level: a review of single-molecule data analyses" by W. Colomb and S.K. Sarkar, Physics of life reviews, 13: 148-149.
https://doi.org/10.1016/j.plrev.2015.04.019

Labrou N.E., Kwok H.F., and Zhang Q., 2023, Editorial: insights in protein biochemistry: protein biophysics, 2022, Frontiers in Molecular Biosciences, 10: 1207184.
https://doi.org/10.3389/fmolb.2023.1207184

Lee M.T., 2018, Biophysical characterization of peptide–membrane interactions, Advances in Physics, 3(1): 1408428.
https://doi.org/10.1080/23746149.2017.1408428

Liu X., Shi D., Zhou S., Liu H., Liu H., and Yao X., 2018, Molecular dynamics simulations and novel drug discovery, Expert Opinion on Drug Discovery, 13: 23-37.
https://doi.org/10.1080/17460441.2018.1403419

Meng X., Li W., Peng X., Li Y., and Li M., 2021, Protein interaction networks: centrality modularity dynamics and applications, Frontiers of Computer Science, 15(6): 156902.
https://doi.org/10.1007/s11704-020-8179-0

Miller H., Zhou Z., Shepherd J., Wollman A.J.M., and Leake M.C., 2017, Single-molecule techniques in biophysics: a review of the progress in methods and applications, Reports on Progress in Physics, 81(2): 024601.
https://doi.org/10.1088/1361-6633/aa8a02

Miranda W.E., Ngo V.A., Perissinotti L.L., and Noskov S., 2017, Computational membrane biophysics: From ion channel interactions with drugs to cellular function, Proteins and Proteomics, 1865(11): 1643-1653.
https://doi.org/10.1016/j.bbapap.2017.08.008

Muller M., Jiang T., Sun C., Lihan M., Pant S., Mahinthichaichan P., Trifan A., and Tajkhorshid E., 2019, Characterization of lipid-protein interactions and lipid-mediated modulation of membrane protein function through molecular simulation, Chemical Reviews, 119(9): 6086-6161.
https://doi.org/10.1021/acs.chemrev.8b00608

Nezammahalleh H., Ghanati F., Rezaei S., Badshah M.A., Park J., Abbas N., and Ali A., 2022, Biochemical interactions through microscopic techniques: structural and molecular characterization, Polymers, 14(14): 2853.
https://doi.org/10.3390/polym14142853

Ramirez R.X., Campbell O., Pradhan A.J., Atilla-Gokcumen G.E., and Monje-Galvan V., 2023, Modeling the molecular fingerprint of protein-lipid interactions of MLKL on complex bilayers, Frontiers in Chemistry, 10: 1088058.
https://doi.org/10.3389/fchem.2022.1088058

Ren P., Chun J., Thomas D., Schnieders M., Marucho M., Zhang J., and Baker N., 2012, Biomolecular electrostatics and solvation: a computational perspective, Quarterly Reviews of Biophysics, 45: 427-491.
https://doi.org/10.1017/S003358351200011X

Sarkis J., and Vié V., 2020, Biomimetic models to investigate membrane biophysics affecting lipid–protein interaction, Frontiers in Bioengineering and Biotechnology, 8: 270.
https://doi.org/10.3389/fbioe.2020.00270

Schlundt A., Tants J.N., and Sattler M., 2017, Integrated structural biology to unravel molecular mechanisms of protein-RNA recognition, Methods, 118: 119-136.
https://doi.org/10.1016/j.ymeth.2017.03.015

Schuck P., and Zhao H., 2013, Biophysical methods for the study of protein interactions, Methods, 59(3): 259-260.
https://doi.org/10.1016/j.ymeth.2013.03.003

Shino A., Otsu M., Imai K., Fukuzawa K., and Morishita E.C., 2023, Probing RNA-small molecule interactions using biophysical and computational approaches, ACS Chemical Biology, 18(11): 2368-2376.
https://doi.org/10.1021/acschembio.3c00287

Simon A., and Macdonald J., 2018, Basic techniques probing molecular structure and interactions, Cambridge University Press, 2018: 500-534.
https://doi.org/10.1017/9781316677056.016

Steinmetz B., Smok I., Bikaki M., and Leitner A., 2023, Protein–RNA interactions: from mass spectrometry to drug discovery, Essays in Biochemistry, 67: 175-186.
https://doi.org/10.1042/EBC20220177

Sych T., Levental K.R., and Sezgin E., 2022, Lipid-protein interactions in plasma membrane organization and function, Annual Review of Biophysics, 51(1): 135-156.
https://doi.org/10.1146/annurev-biophys-090721-072718

Terazima M., 2021, Spectrally silent protein reaction dynamics revealed by time-resolved thermodynamics and diffusion techniques, Accounts of Chemical Research, 54(9): 2238-2248.
https://doi.org/10.1021/acs.accounts.1c00113

Wang B., Xie Z., Chen J., and Wu Y., 2018, Integrating structural information to study the dynamics of protein-protein interactions in cells, Structure, 26(10): 1414-1424.
https://doi.org/10.1016/j.str.2018.07.010

Winter A., Higueruelo A., Marsh M., Sigurdardottir A., Pitt W., and Blundell T., 2012, Biophysical and computational fragment-based approaches to targeting protein–protein interactions: applications in structure-guided drug discovery, Quarterly Reviews of Biophysics, 45: 383-426.
https://doi.org/10.1017/S0033583512000108

Yu B., Pettitt B., and Iwahara J., 2020, Dynamics of ionic interactions at protein-nucleic acid interfaces, Accounts of Chemical Research, 53: 1802-1810.
https://doi.org/10.1021/acs.accounts.0c00212