Global Journal of Basic Science ISSN: 3049-3315

Review

Hallmarks of structural systems biology

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Citation: Mobashir, M et al. Hallmarks of structural systems biology. *Global Journal of Basic Science*. 2025, 1(5). 1-13.

Received: March 05, 2025
Revised: March 22, 2025
Accepted: March 25, 2025
Published: March 30, 2025

doi: 10.63454/jbs20000025
ISSN: 3049-3315

Abstract: Structural systems biology is an emerging interdisciplinary field that integrates the principles of structural biology with systems biology to provide a comprehensive understanding of biological systems. While traditional structural biology focuses on the three-dimensional (3D) structures of individual biomolecules, structural systems biology seeks to elucidate how these structures interact and function within the broader context of cellular and molecular networks. This approach aims to understand the dynamic and emergent properties of biological systems by considering the complex interplay of molecular components, from proteins and nucleic acids to cellular machinery. By combining structural data with omics technologies (genomics, proteomics, transcriptomics, and metabolomics), computational models, and dynamic experimental techniques, structural systems biology offers powerful insights into the functional roles of molecular structures in cellular processes, disease mechanisms, and therapeutic interventions. The future of structural systems biology lies in integrating real-time structural dynamics, multi-scale modeling, and personalized medicine, providing new opportunities for drug discovery, synthetic biology, and systems pharmacology. Despite challenges in data integration, high-resolution modeling, and computational prediction, the field holds great promise in transforming our understanding of biological complexity and advancing biotechnology and medicine.

Keywords: Structural systems biology; systems biology, modeling and simulation, signaling pathways, molecular docking; molecular simulations

1. Introduction

An emerging subject called structural systems biology aims to close the gap between biological macromolecules' intricate molecular structures and their functional roles in intricate biological systems. Structural systems biology combines the structural insights with the dynamic networks and interactions that control cellular processes, organismal physiology, and disease mechanisms. Traditional structural biology has concentrated on clarifying the three-dimensional (3D) structures of proteins, nucleic acids, and other macromolecules. In addition to attempting to comprehend particular biomolecular structures, this holistic approach explores the ways in which these structures impact and are impacted by systemic molecular interactions at a wider scale[1-4].

Whether it is a single protein, gene, or metabolic pathway, the study of components in isolation has frequently been the main emphasis of classical biology. However, because proteins, RNA, lipids, and metabolites all operate together in intricately controlled networks, biological systems are by nature interrelated. By examining individual components alone, it is impossible to fully comprehend the emergent behaviors that these networks produce. For example, the coordinated activity of several biomolecules that interact with one another in space and time is necessary for cellular functions like signal transmission, gene expression regulation, and metabolic balance[5-17].

The majority of biological functions are mostly carried out by proteins. They rarely function alone, though, as the majority of biological processes are controlled by intricate networks of protein-protein interactions and executed by macromolecular assemblies. Therefore, complexes, pathways, or even entire organisms are now the focus of modern molecular and cell biology rather than single macromolecules. A nearly comprehensive inventory of an organism's constituent parts has been made available by the numerous genome-sequencing programs, and post-genomic projects have sought to catalog the connections among them. Deciphering these linkages is currently the primary focus of the developing discipline of systems biology. All of these interaction maps, however, are devoid of chemical information; they just indicate which molecules interact with one another, not how. High resolution three-dimensional (3D) structures are the only method to fully comprehend how molecules interact because they offer essential atomic data regarding binding. Because of these details, experiments may be designed more logically to disturb an interaction and, consequently, any system that the interaction is a part of. The primary areas of scientific interest are in structural bioinformatics, namely the application of high-resolution 3D structures and protein sequences to uncover the molecular underpinnings of the functioning of cell networks and macromolecular complexes[5, 10, 18-28].

Genome-sequencing programs have provided a nearly complete list of an organism's constituent parts, while post-genomic projects have attempted to catalog the connections among them. The main objective of systems biology is to make sense of these connections when viewed as a whole; for example, a full understanding of metabolic and signaling pathways or gene-regulatory networks requires a thorough understanding of protein–metabolite, protein–protein, and protein–nucleic acid interactions; three-dimensional (3D) structures are the only way to fully understand how molecules interact because they provide crucial atomic data regarding binding; knowing these details allows one to more rationally plan experiments to interfere with an interaction and, consequently, disturb any system of which the interaction is a part[13, 29-35].

Because of structural-genomics studies and the quick development of structural biology (Figure 1), it is becoming increasingly rare to find a single protein for which no structural information is available or for which structural information is difficult to obtain by straightforward homology modeling. It is anticipated that a virtually complete structural picture of most proteins in any particular organism will soon be available. The structures that are most crucial to systems biology, notably those that include the interaction of two or more macromolecules, continue to be problematic for structural biology, and its capabilities are still limited. To fully grasp the structure of huge protein complexes or complete systems, years of research are required. Many innovative techniques for simulating and forecasting the structures of interacting proteins have been created in an effort to address this problem. Here we revisit them and discuss how they are already affecting our understanding of complex biological systems.

Building on this insight, structural systems biology investigates how the behavior of entire systems can be explained by the three-dimensional (3D) structure of individual biomolecules, as well as their conformational variations, binding characteristics, and interactions. Structural systems biology produces a thorough map of molecular interactions and network dynamics by combining structural data—typically obtained from methods like X-ray crystallography, nuclear magnetic resonance (NMR) spectroscopy, cryo-electron microscopy (cryo-EM), and computational predictions—with omics data, including proteomics, metabolomics, and genomics.

Key concepts of structural systems biology[1, 5, 9, 36-40]:

- **Molecular interactions and network biology:** The study of how molecular interactions create intricate networks is at the heart of structural systems biology. Protein-protein interactions, enzyme-substrate dynamics, and even signaling networks that control cellular activity are examples of the several sizes at which these interactions take place. In order to comprehend these networks, one must be aware of both the individual component structures and the ways in which the components alter their conformation in response to external stimuli or cellular signals.
- **Dynamic nature of biological systems:** Biosystems are very dynamic, in contrast to static depictions of chemical structures. Conformational modifications allow proteins and other biomolecules to interact in controlled ways. Understanding processes like enzyme catalysis, molecule recognition, and receptor-ligand binding—all of which are essential for cellular functions like signal transduction and metabolic regulation—requires an understanding of these dynamic behaviors in structural systems biology.
- **Multi-scale modeling:** Integrating findings from the molecular level with higher-order biological phenomena is the goal of structural systems biology. Combining structural information at the atomic or molecular level with information at the cellular and organismal levels is known as multi-scale modeling. A protein's three-dimensional structure, for instance, can help explain how it interacts with other proteins or how it alters in response to cellular signaling pathways, both of which have an effect on how entire biological systems behave.
- **Computational tools and predictive modeling:** Researchers can now predict protein structures from sequences (e.g., using AlphaFold) and model their interactions within larger biological systems thanks to advancements in computational techniques like deep learning and artificial intelligence, which are completely changing the field. By simulating molecular dynamics over time, these methods aid in forecasting how a system will change or react to external events like medication side effects or genetic changes.
- **Integration of structural data with omics technologies:** Integrating structural data with extensive omics datasets is one of the hallmarks of structural systems biology. By mapping chemical structures onto biological networks, this integration enables researchers to better understand how genes, proteins, and metabolites interact to control cellular processes. For instance, combining genomic data—information about gene sequences and mutations—with proteomics, the study of protein expression, might show how variations in protein expression levels or structure lead to disease states.

From synthetic biology and systems pharmacology to drug development and personalized therapy, structural systems biology has a wide range of applications. Researchers can create more specialized treatments by comprehending how structural alterations in proteins or other macromolecules contribute to illness. For example, in cancer research, the discovery of highly specific inhibitors that restore normal cellular function might result from a detailed understanding of mutant proteins and their changed interactions within signaling networks. The construction of new biomolecular systems with desired functions, such biosensors for environmental monitoring or altered enzymes for biofuel synthesis, can be

facilitated by structural systems biology in synthetic biology. Likewise, in the process of developing new medications, structural systems biology can assist in locating protein-protein interaction surfaces or allosteric binding sites that are typically difficult to target with traditional small[41-48].

Structural systems biology has many obstacles in spite of its potential. The intricacy of biological systems is one of the main obstacles. Understanding the entire molecular network in its complete dynamic context is still challenging, despite the use of sophisticated techniques like cryo-EM and high-resolution NMR. Furthermore, complex computational techniques that may take into account the complex and occasionally chaotic nature of biological processes are frequently needed for the integration of data from many sources (structural, genomic, proteomic, etc.). Furthermore, in order to comprehend how molecular structures alter in response to signals or stimuli, real-time data that can record the dynamics of molecular interactions as they occur is required. Overcoming these constraints will require new tools, such as sophisticated computational modeling methods and experimental platforms like live-cell imaging or single-molecule fluorescence[10, 49-54].

One of the main objectives of structural systems biology is to forecast the behavior of biological systems. Therefore, understanding the interactions between these molecules is crucial for such endeavors. Despite the fact that hundreds of interactions are known to exist, only a small portion of them have precise chemical information. Prediction methods are essential to progress due to the difficulties in experimentally determining the atomic structures of interacting proteins. By adding structural components, abstract system representations can eventually be converted into models that more accurately mimic biological reality. Biological activities often rely on interactions between several molecular actors to generate systems-level emergent characteristics. To develop a predicted mechanistic knowledge of these interactions, we employ a systems-to-structure approach. Combining systems biology experimental approaches with quantitative and computational tools is necessary to understand how biological systems are controlled at the atomic level.

By serving as a link between molecular structures and the functional networks that govern cellular behavior, biology offers a revolutionary perspective on biology. Through the integration of structural data with computational modeling, network biology, and omics technologies, this discipline provides fresh perspectives on how biological systems are dynamic and interdependent. Future advances in biotechnology, medicine, and other fields will be made possible by the development of comprehensive, predictive models of biological systems made possible by the fusion of computational innovation and high-resolution experimental methodologies. This review provides an overview of structural systems biology, its key concepts, and its potential applications.

In order to comprehend how the intricate structures of biomolecules—such as proteins, nucleic acids, and other macromolecules—contribute to the operation of biological systems, the interdisciplinary field of structural systems biology integrates concepts from structural biology, systems biology, and computational biology.

To break it down:

- **Structural biology:** Understanding the three-dimensional structures of biological macromolecules, namely proteins, nucleic acids (DNA and RNA), and their complexes, is the main goal of structural biology. Understanding these molecules' structure is essential to comprehending how they work together and carry out biological functions. X-ray crystallography, NMR spectroscopy, cryo-EM, and computer modeling are examples of common methods.

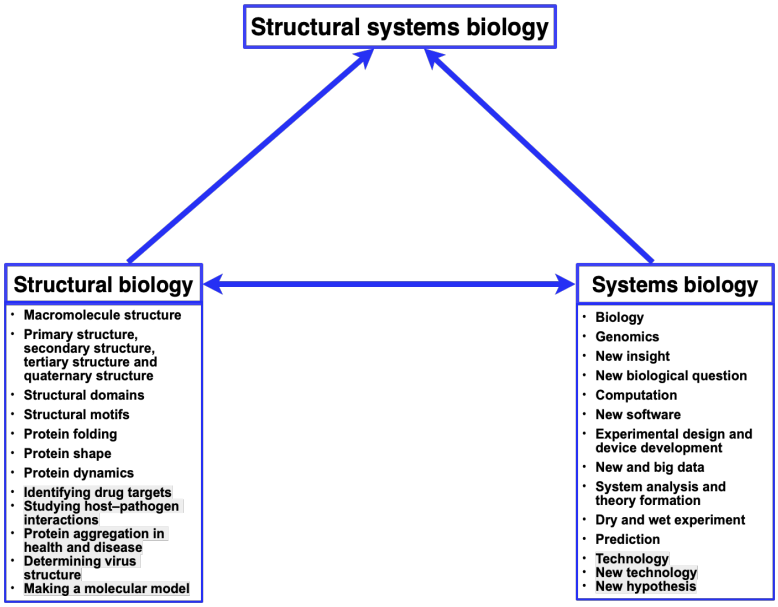

Figure 1. Structural systems biology *i.e.*, structural biology and systems biology.

- **Systems biology:** This method is more comprehensive since it stresses the study of biological systems as a whole as opposed to concentrating on its constituent parts. It entails the analysis of extensive networks, including metabolic, gene regulatory, and protein-protein interaction networks. Understanding how the elements interact in a dynamic and coordinated way is the aim.
- **Structural systems biology:** These two ideas are combined in this field. It examines how the behavior of biological systems at the level of the entire organism or cell is influenced by molecular structures (of proteins, enzymes, complexes, etc.). It seeks to comprehend how each biomolecule's structure influences its

function in more extensive, dynamic biological processes. It's about comprehending how molecules' intricate structural information affects their interactions, regulation, and overall biological function.

Key aspects of structural systems biology:

- **Multiscale Modeling:** This entails simulating molecular behaviors and interactions at many scales, ranging from atomic-level interactions to cellular-level processes. It simulates the behavior of biomolecules in a system-wide setting by combining information from computational systems biology and structural biology.
- **Integrating Structural Data with Biological Networks:** The goal of structural systems biology is to determine how structural characteristics (like conformational changes or post-translational modifications) impact a molecule's function within a network by fusing data about metabolic, signaling, and gene expression networks with structural data of individual proteins and other molecules.
- **Prediction of Protein Function and Interaction:** Predicting how certain chemical structures contribute to biological processes and how proteins interact to build bigger complexes or networks is one of the main objectives.
- **Applications in Drug Discovery:** Drug design requires an understanding of the intricate interactions and structures of proteins and other molecules inside a biological system. Drug discovery can be made more accurate and efficient by using structural systems biology to help build medications that target particular proteins or network connections.

2. Structural biology and the complexity

Determining the three-dimensional structures of proteins has been difficult from the beginning. It took decades to solve the first X-ray structures. However, a great deal has changed, and it is now possible to identify specific protein structures in a matter of days when sufficient material is available. Modern overexpression and purification procedures may usually yield sufficient material for structural research on a single protein, but gathering sufficient material for large complexes may prove to be a significant issue. The answers are really simple: complex assembly requires precise timing and control inside the cell, which is challenging to duplicate in a laboratory setting, despite its poor understanding. As a result, producing hundreds or thousands of liters of culture and gathering material from natural sources usually takes years of system tweaking when working with large complexes. This is necessary because it often takes milligram amounts of material to create crystals that will diffract to a high resolution, which is more difficult for complexes than for individual proteins[5, 10, 50, 51, 55, 56].

Fortunately, several advancements are beginning to tackle these problems. For example, attempts to express the subunits of a complex collectively in various animals have shown promise, while improvements in crystallization techniques and synchrotron radiation facilities enable the solution of large structures using less material. More recently, techniques such as cryo-electron microscopy, which can reconstruct structures from samples at very low temperatures, have made it possible to acquire lower-resolution structures for large complexes elsewhere using significantly less material. Still, there is a large difference between the number of complexes for which experimental 3D structures are available and the number that is thought to exist based on data from, instance, affinity-purification or two-hybrid techniques. This gap is growing since the first versions of the human interactome were released. The next generation of structure prediction has been essentially characterized by this; prediction techniques now need to address entire complexes or systems rather than simply individual proteins in order to have the most biological impact.

2.1. Structure prediction

Predicting interactions between proteins is a challenging field. Perhaps the most obvious is 'who interacts with whom'. The preliminary, still incomplete, drafts of whole-organism interactomes from high-throughput protein-interaction methods can be enhanced by computational predictions. In the late 1990s, a number of strategies with this objective started to emerge[18, 57-63].

The most well-known are probably those that focus on "genomic context." The common theme here is suggesting connections between proteins for which there is evidence of an association because of similarities in their expression profiles or in their relative positions among the hundreds of known genome sequences. For example, functionally related proteins are often encoded by genes located in the same bacterial operon. Functional associations that are established from a genetic context do not necessarily imply a direct physical contact between two molecules; proteins at opposite ends of a single route or complex can produce the same signal as those in close, direct physical contact. Additionally, errors in the underlying genome or expression data may lead to missed interactions or erroneous predictions. Further challenges include developing specific high-throughput quantitative assays to measure such constants directly or figuring out how to draw more biophysical conclusions from such a wide range of data sources, like by comparing association scores with actual physical measurements like dissociation constants. To address these issues, several organizations are developing ways to statistically mix multiple types of interaction data (genome context, expression, or other) while

accounting for the accuracy of each dataset. Each interaction is given an overall confidence score, with higher ratings indicating more likely direct physical contact.

The 'gold standard' for positive interactions (protein pairings known to interact) and, more importantly, for negative interactions (protein pairs known not to interact) is still missing, making it difficult to estimate rates for these. However, estimates of 30–60% false positives and 40–80% false negatives have been attributed to high-throughput investigations that have employed affinity-purification or two-hybrid methods employing defective benchmark interaction sets. When testing computational procedures, the same range of values applies, but these methods also suffer from the lack of a clear benchmark. The experimental techniques for detecting contacts and the previously stated methods offer little information about the molecular details of the relationship. However, in some cases, further details can be found, such as the protein segments or domains mediating the interaction. The interacting areas of two proteins can be empirically narrowed down by repeating research with smaller constructions and computationally detecting recurrent 'domain signatures' in pairs of interacting proteins. If a pair of domains is regularly present in protein pairs that interact, it is most likely mediating the interaction. Then, lists of these signatures can be used to predict interactions that have been found or to propose potential interactions. These kinds of techniques are useful for determining which parts of larger proteins are interacting, but they cannot give the atomic details of the interface needed for a more complete understanding of the process.

Many teams have developed methods to predict atomic details for a pair of interacting proteins. Conventional 'docking' methods search for the best docked complex based on electrostatic complementarity between protein surfaces or shape, and they usually require high-resolution structures of the interacting proteins to be accurate. Mutagenesis or other experiments are usually used to get a sense of the locations of the binding sites. This method was only occasionally used in the past due to the lack of understanding of both 3D structures and protein–protein interactions, but it is currently experiencing a sort of resurgence due to the growth of both structure and interaction databases, as well as techniques like NMR that may detect interaction surfaces on known structures. In addition to producing new approaches, combining docking with chemical-shift NMR studies (such as HADDOCK) and mutagenesis research has also produced encouraging outcomes. To be as applicable as possible in the future, docking approaches will need to operate with simulated protein structures. It will take several more decades until a full set of experimental structures is available, even if representative structures for many single globular proteins or domains are already available due to the accelerated pace of structure determination. Additionally, it would be advantageous if novel docking methods could predict protein interactions—that is, determine whether two proteins interact. It may not be able to predict interactions until the techniques can accurately quantify binding free energy, but current methods only search for the best fit between two proteins, without attempting to distinguish between protein pairings that interact and those that do not. To our knowledge, no attempt has been made to move in this direction, despite the community's perception that this is too difficult at the moment[18, 40, 57, 58, 64-81].

However, docking is not always necessary. With structural data available for hundreds of interactions, it is increasingly possible to model protein interaction structures based on previously observed interactions. The degree of sequence identity between the target and the template has a significant impact on the accuracy, as it does in other modeling attempts. Selecting the appropriate template is even more crucial when modeling an interaction because employing the wrong one can produce results that demonstrate proteins interact through the wrong interface. This is similar to modeling one protein on another with a different fold. It is widely believed that proteins will interact similarly when their sequences are quite similar (for example, more than 25–30% sequence identity), while there may be exceptions. The challenging element is identifying structurally comparable interactions in the absence of sequence similarity. In recent years, a new family of techniques has arisen that use homology to model interacting structures (e.g., MULTIPROSPECTOR and InterPReTS). The idea is simple: use protein–protein complexes for which coordinate data are available to model interactions between their homologues. These approaches, which assess how well a homologous pair of sequences "fit" into a complex's previously established structure, are based on strategies borrowed from protein-fold recognition (or threading). We refer to these methods as empirical pair potentials. The notions of native interaction interfaces, which are learned from familiar structures, are used to test new interfaces that have been modeled based on homology. It is now feasible to predict connections on a genome size and specificities for large protein families, including those between fibroblast growth factors (FGFs) and their receptors, by applying these algorithms to all of the probable interacting proteins. However, these approaches are far from perfect, and they suffer if the interactions involve conformational changes at the interface or if the interfaces that are represented contain insertions or deletions that are not precisely modeled in relation to the template.

2.2. Complexes and the signaling pathways

The basis of biological activity in cells is macromolecular complexes, which are microscopic devices that carry out the majority of the tasks outlined in textbooks. For example, transcription, splicing, translation, replication, and metabolism are all carried out by various molecular machinery. While many complexes have been identified in the sense that

their component pieces have been identified, only a limited number have 3D structural information available. Thus, it makes sense to develop techniques that can recognize complex structures utilizing structural information on the individual subunits and their interactions, and to integrate these techniques with any available low-resolution structural information. Perhaps discouraged by the technological difficulties in determining the structures of large complexes, X-ray crystallographers often incorporate data from other sources to obtain the best structural model. These hybrid techniques have been used to clarify the architecture of the ribosome, actin-myosin fibers, RAD51, and the bac-teriophage-T4 baseplate. For example, the crystal structures of two subcomplexes from human small nuclear ribonucleoprotein particles (snRNPs) were determined in the previous work. However, a single model was constructed that was in agreement with the available protein-interaction, mutagenesis, and electron-microscopy data, which are now required when dealing with big complexities[19, 28, 82-94].

Since then, computational biologists have taken on the challenge of creating complexes from their component components. The relatively high proportion of structures available for individual subunits makes docking techniques an attractive choice. To give the most cohesive structures for a complex, for example, Nussinov, Wolfson, and colleagues have developed a multi-docking approach that pairwise combines docking results for the components. Our study's primary objective is to identify suitable 3D templates to simulate binary interactions on and then combine them in a comparable manner.

2.3. Structural pathways

In the last decade, several metabolic and signaling pathway databases have been developed, such as BioCyc, Kyoto Encyclopedia of Genes and Genomes (KEGG), BioCarta, Signal Transduction Knowledge Environment (STKE), and Reactome. These materials generally depict the interactions between molecules in a cell as either activation or inhibition events or reactions, and like other systems-biology data sets, they usually lack functional details about what an arrow between two proteins truly signifies, even though some of them try to record precise specifics of the interaction (e.g. phosphorylation sites). The goal of these databases is to summarize the results of hundreds of studies. Projected binding sites, expected interactions, and known structures can all greatly contribute in understanding a pathway. Crystal structures for the interactions of FGF1 and FGF2 with two of the three extracellular domains of the receptors FGFR1 and FGFR2a are available. Crystal structures are also given for FGF1–FGFR3c and FGF10–FGFR2b. This structural information covers only a fraction of the possible interactions between these ligand-receptor families. Although the specificities are still unknown, humans have around 30 FGF homologues and at least seven different receptors. Therefore, interaction modeling approaches are needed to predict the precise pairings[90, 95-107].

3. Systems biology: The goal of the multidisciplinary area of systems biology is to comprehend the intricate relationships that exist throughout biological systems. Systems biology examines how various parts interact and function as a whole to form a system, in contrast to traditional biology, which frequently isolates specific parts (such as proteins, genes, or cells). By combining information from several levels of biological organization, such as molecular interactions and organismal physiology, it seeks to explain how biological systems work, adapt, and evolve[108-110].

3.1. Key areas of systems biology include:

- **Network biology:** This examines the network interactions between genes, proteins, and other substances. These connections create networks and pathways that control biological processes. Signaling networks, for instance, regulate gene expression, metabolism, and cell division.
- **Omics Technologies:** Large datasets that depict the condition of different molecular entities in cells or tissues are produced by the fields of genomics, proteomics, transcriptomics, and metabolomics. Models of biological systems can then be produced by analyzing these datasets.
- **Mathematical and Computational Modeling:** In order to model biological systems, systems biology mostly uses computer techniques. These models can be used to forecast how a system will react to various circumstances, including modifications in gene expression, external influences, or medication regimens. Modeling approaches include:
    - **Dynamic modeling** (to represent time-dependent changes in biological processes)
    - **Network modeling** (to represent interactions among biomolecules)
    - **Predictive modeling** (to forecast how changes will affect system behavior)
- **Feedback Loops and Regulation:** Numerous biological processes are controlled by feedback loops, in which a process's output can either positively or negatively affect its own activity. Comprehending these loops is essential to comprehending homeostasis, stability, and adaptability in cells and organisms.
- **Integration of Data:** Integrating data from several sources, including proteomic, transcriptomic, and genomic data, is a key component of systems biology. Systems biology seeks to create a more comprehensive understanding of biological processes by integrating these various informational levels.

3.2. Applications of Systems Biology:

- **Personalized Medicine**: Tailoring medical treatments to individuals based on their unique molecular profile.
- **Drug Discovery**: Identifying new drug targets by understanding disease mechanisms at the system level.
- **Synthetic Biology**: Designing new biological systems or organisms with custom functions.
- **Cancer Research**: Investigating the complex interactions that drive cancer and how to interrupt those processes.
- **Metabolic Engineering**: Optimizing microbial systems for the production of biofuels, pharmaceuticals, or other chemicals.

3.3. Challenges in Systems Biology:

- **Complexity**: Biological systems are highly complex, and capturing all the interactions accurately can be daunting.
- **Data Integration**: Combining large-scale data from different technologies (e.g., genomics and proteomics) in meaningful ways is still an ongoing challenge.
- **Predictive Accuracy**: While models are helpful, they don't always predict biological behavior accurately due to the stochastic (random) nature of biological systems.

4. Future Perspectives of Structural Systems Biology: Structural systems biology examines how these structures interact in intricate networks to form molecular machines, pathways, and systems, as opposed to traditional structural biology, which focuses on characterizing the 3D structures of individual biomolecules using techniques like X-ray crystallography, NMR spectroscopy, and cryo-EM.

4.1. Integration of Structural Data with Omics Information:

- Large volumes of data regarding the constituents of biological systems have been produced by omics techniques (such as genomics, proteomics, transcriptomics, and metabolomics); nevertheless, incorporating structural data is necessary to comprehend how these constituents interact at the molecular level.
- It is anticipated that structural data would be seamlessly integrated with proteomics and genomes in future studies. To forecast how molecular interactions (such protein-protein interactions or protein-DNA binding) impact cellular functions and system behaviors, for instance, structural data could be incorporated into network biology models.
- For example: Transcriptomic information and accurate 3D structures of the interacting proteins are necessary for the study of the network of protein-protein interactions in diseases such as cancer in order to comprehend how mutations may interfere with these interactions.

4.2. Computational Methods for Predicting Molecular Structures:

- Structural biology is undergoing a revolution thanks to developments in computational biology, such as deep learning and AI-driven prediction models. The ability to predict protein structures directly from amino acid sequences with previously unheard-of accuracy has already advanced significantly thanks to programs like AlphaFold.
- Extending these techniques to forecast not just the architecture of individual proteins but also their evolution within the broader biological system will be the next stage. Multi-scale modeling will become more and more significant when molecular-level structural features are linked to whole-cell or even organism-level dynamics.

4.3. Dynamic and Functional Structural Studies:

- Biological molecules are dynamic by nature and act through conformational changes, although traditional structural biology frequently takes static pictures of them. Time-resolved structural methods (such as cryo-EM, single-molecule fluorescence, or NMR relaxation) will be the main focus of future structural systems biology research.
- To comprehend disease mechanisms or therapeutic action, it will be essential to comprehend how proteins and other macromolecules go through dynamic changes, such as allosteric transitions (in enzymes or receptors), and how these changes affect biological processes in real-time.
- Example: New therapeutic approaches may become possible if it is better understood how the structural flexibility of the enzyme kinase may influence its role in cell signaling or its malfunction in conditions like cancer.

4.4. Personalized and Precision Medicine:

- Personalized medicine will probably heavily rely on structural systems biology. Treatments can be customized to target certain structural alterations in proteins or pathways by fusing structural data about a person's genetic mutations and protein expression profiles with a systems-level comprehension of their biological networks.

- Additionally, biomarker panels based on structural alterations may be developed in the future, enabling more accurate prognostics and diagnoses.
- For instance, tailored medication development that targets specific protein alterations brought on by genetic mutations, as observed in some cancers (e.g., targeting specific structural abnormalities in EGFR in lung cancer).

4.5. Synthetic Biology and Drug Development:

- A thorough understanding of the molecular structure and systems-level interactions that these molecules participate in is essential for designing novel biological systems in synthetic biology, whether for the production of industrial chemicals, medicines, or biofuels.
- Designing next-generation therapies in drug development will require an understanding of how medicines interact structurally with their target proteins and how these interactions spread via biological networks.
- For instance, a better knowledge of dynamic protein structures could be very helpful in the development of allosteric modulators, which change a protein's function by attaching to a place other than the active site, in drug design.

4.6. Systems Pharmacology:

- Pharmacology will adopt a systems-based approach in the future, where the effects of medications on the entire biological network will be examined in addition to the drug and its target. Mapping how medications impact the connectivity of molecular networks in cells and how drug binding impacts broader pathways can be aided by structural systems biology.
- For instance, a deeper comprehension of how drugs alter protein networks may help detect adverse effects or off-target effects prior to clinical trials. For diseases like cancer or neurological disorders, focusing on protein-protein interactions instead of conventional enzyme inhibition may result in more effective and targeted treatments.

5. Conclusions: Structural systems biology has a bright future ahead of it as we continue to learn more about the molecular complexity of life. Researchers can learn how molecular interactions lead to the behavior and function of entire biological systems by incorporating structural data into systems biology methodologies. This has the potential to result in revolutionary breakthroughs in a number of domains, such as systems pharmacology, synthetic biology, customized medicine, and drug discovery.

However, challenges remain. There is the need for:

- High-resolution tools that can capture real-time, dynamic molecular structures.
- Integration of diverse datasets from genomics, proteomics, metabolomics, and structural biology in a meaningful way.
- Improved computational models that can predict the behavior of entire molecular systems based on structural information.

The capacity to forecast intricate biological behaviors from structure will only grow stronger as computer techniques advance. In addition to shedding light on how biological systems function at the molecular level, structural systems biology will open up new avenues for disease treatment, biological function engineering, and biotechnology advancement. Finally, a comprehensive and predictive understanding of biology may be possible through the combination of structure and systems, propelling advancements in biotechnology, medicine, and other fields.

Institutional Review Board Statement: Not Applicable

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Author Contributions: Conceptualization, M.M.; methodology, M.M.; validation, M.M.; formal analysis, M.M.; investigation, M.M.; resources, M.M.; data curation, M.M.; writing—original draft preparation, M.M.; writing—review and editing, M.M.; visualization, M.M.; supervision, M.M.; project administration, M.M.; funding acquisition, M.M. The author has read and agreed to the published version of the manuscript.

Funding: Not Applicable.

Acknowledgments: We acknowledge Department of Biomedical Laboratory Science, Norwegian University of Science and Technology, Trondheim - 7491 Norway for providing us the facility and resource to carry out the study.

Conflicts of Interest: The author declare no conflict of interest.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

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