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Perspective

An updated viewpoint on the protein intramolecular network and protein-ligand interactions with the applications of AI and system science

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Abstract: The elucidation of structure-activity relationships of proteins and prediction of their binding sites for various agonists have been well depicted. However, there is still some mystery in this field. In this paper, we review some key properties of proteins from a systematic and networked perspective and then suggest their several intrinsic attributes, which have not been comprehensively explored. Specifically, we propose the "positive and negative activities" of various proteins based on their intramolecular organization and interplay with external environment, respectively. Furthermore, we suggest that the complicated protein conformations may be probably derived from their compromise strategies to coordinate the intramolecular and extramolecular requirements, synchronously. We use several representative proteins (G protein-coupled receptors, acetaldehyde dehydrogenase, and sweet-tasting protein monellin) as examples to delineate these attributes of proteins. These descriptions highlight the importance to dissect relationship between protein structure and activity from the system and network viewpoints, especially for reevaluating the intramolecular interaction forces of proteins with their ligands from these perspectives, and underline the necessity of collaboration among researchers in different areas. Lastly, we discuss the potential roles of artificial intelligence

technologies to aid the research in protein science and prospect their application in the future.

Keywords: protein; positive and negative activities; system and network; conformational state; artificial intelligence; structure-activity relationship

1. Introduction

The activities of proteins are essential for biological systems to maintain homeostasis and respond adaptively to environmental fluctuations [1]. In biomedical and biotechnological research, such as structure-based drug design and enzyme-catalyzed metabolism manipulation, elucidation of protein's full activities in living cells/organisms is obviously a central issue [2]. To date, numerous articles and data have depicted the details of various properties of different sorts of proteins, such as their motifs, domains, sectors, architectures and organizations; allosteric modulation; conformational transition; and targeted modification [3–7]. These meaningful insights have greatly enlarged our understanding of the structures and activities/functions relationships of different proteins.

In most cases, when the interactions between proteins and their partners are studied, no matter whether they are compounds, nucleic acids, peptides, or other bioactive elements, the main concerns of researchers are the interactive forces of amino acids in the proteins with the adjacent molecules of the partners (which are generally called ligands) in the binding pocket, such as residues of a peptide or chemical groups of a compound [8,9]. This framework sounds reasonable because it is generally deemed that connections and interaction forces between different molecules, such as hydrogen bonds, salt bonds (ionic bonds), and hydrophobic and van der Waals forces, are all restricted within certain distances. Indeed, this "close-range"-based protein-ligand interplay principle has been dominant in current structural biology studies for many years [10–12].

However, herein we argue that the aforesaid paradigm could be incomplete, as the role of an amino acid in a protein could be mainly responsible for the long-distance intramolecular forces to maintain structural integrity of the protein or long-range intra-protein communication, rather than accounting for the local interactions [13–15]. From this perspective, we outline a series of knowledge about the intramolecular communication within proteins, as well as their interactions with corresponding ligands, to support our standpoints and propose several novel insights in this field. Consequently, we suggest that the dichotomous positive and negative activities of proteins are two paramount properties of proteins. Based on this interpretation, we propose a hypothesis for protein conformation origin. Moreover, we propose that the lack of system- and network-based analysis in related areas could probably be a cause for the uncertainty or nonrepeatability of biological data of proteins' activities in published papers. For instance, a tiny variation in the chemical composition of the buffer or in the purity of the reagents, as well as the protein expression yield, might influence its activity.

2. Structural organization of proteins versus their interactions with environment

It has been well described that an individual protein can interact with other objects outside itself via various forces, but synchronously, the protein is subjected to its intramolecular interaction network organization to maintain its structural integrity [16–19]. Thus, for an amino acid residue in a protein,

it may have two distinct roles: to mediate the interplay of the protein with the external surroundings and to be involved in the intramolecular network organization. This division does not rule out that some residues of the protein are engaged in both of the roles. Obviously, this framework is based on the view that any protein can be seen as a system, while any of its external objects are excluded from this system [20,21]. This insight underlines that we should orchestrate the activities and properties of proteins from the viewpoint of system and network science rather than just focus on the interactions of residues of a protein with its adjacent surroundings.

It is clear that proteins, the main executors of life processes, exist in a continuum of bound states between order and disorder [4]. This feature, as manifested by their considerably variable conformations, has been elaborately described and formalized as the "fuzzy protein theory" [16]. Besides their plasticity, on the contrary, proteins exhibit substantial rigidity [17]. It is acknowledged that rigidity (equal to regularity) is responsible for their structural stability maintained by various intramolecular interaction forces, while flexibility (equal to modifiability) with alterable conformations emerges as their responses to different environmental contexts [22,23]. The two opposite statuses and their intricate intermediates seem ubiquitous in proteins, giving rise to their uncertainty. Furthermore, the underlying driving forces for generating order/disorder uncertainty could be briefly interpreted as follows: if external surroundings have no influence on proteins, they tend to display a stationary and resting state (rigidity). In contrast, if external conditions have an impact on them, they tend to express a dynamic and active state (flexibility). This multidimensional and dynamic phenomenon has been widely demonstrated in multitudinous interactions between proteins and their external factors (e.g., substrate- or ligand-induced conformational transitions of enzymes or receptors) [24–28]. Therefore, two properties (i.e., interplay propensity with environment and self-stabilization nature excluding environment) can be attributed as two predominant characteristics of proteins, and an equilibrium of the two situations could lead to their specific states in the corresponding contexts.

Based on the above statement, we thereafter name the two distinct, extra-protein and intra-protein oriented activities of residues of proteins as their positive and negative activities, respectively. We searched the terminology "protein positive and negative activities" in the PubMed database and found that there was no such definition previously, except for one published article in which the HSV-1 alpha protein ICP27 was reported to possess two separable regulatory activities of ICP27, one positive and one negative, depending on its different splicing modes [29]. Thus, it is clear that the "positive/negative" property of ICP27 only refers to its own regulatory activity that is conceptually unrelated to our generic dichotomy of proteins' activities in this paper. Herein, we discriminate the two activities of residues of proteins for the first time, providing a framework to distinguish the two opposite activities in the protein-environment interaction context. This framework defines a functional differentiation of protein residues; however, it does not mean that the activity of a specific residue is fixed and unchangeable, as it may switch between positive and negative activities under certain environmental conditions. In some cases, it may exhibit both activities to keep structural integrity and adapt into surroundings simultaneously. Taken together, our dichotomy of protein activities establishes a two-sided insight to dissect protein activities, such as allostery, conformational dynamics, residue interaction networks, and protein stability, providing more comprehensive information for understanding the structure-activity relationships of various proteins.

To further illustrate this framework, we introduce an example, the acetaldehyde dehydrogenase (ALDH). ALDH is a widely distributed enzyme in metabolism that catalyzes the conversion of a wide variety of aldehyde substrates to respective carboxylic acids with reduction of coenzyme NAD or

NADP [30]. The catalytic mechanism of ALDH has been well elucidated based on extensive structural determination and mutagenesis analysis. Basically, with the aid of general base Glu, the essential nucleophile Cys forms a thiohemiacetal intermediate complex with the bound acetaldehyde substrate, which then undergoes a conversion of oxidation (hydride transfer), followed by the final deacylation step. Conformational transformations of the enzyme are synchronous in these catalytic processes [31–34]. Notably, some residues far from the substrate-binding pocket, are also essential for ALDH catalysis [35]. This scenario indicates that a portion of residues are responsible for the integrity of the intramolecular connection network and overall architecture of the enzyme, which exhibit primarily intramolecular negative activities, while other residues in the catalytic center region play crucial roles in responding to the interactive factors (the bound substrate and cofactor NAD or NADP) in its external surroundings, which display primarily extramolecular positive activities [36]. Obviously, an interplay between the enzyme protein system and its outside environment, as well as the derived positive and negative activities of key residues, mediates its conformational states and accounts for its functions, activities, and properties.

3. The promiscuous conformational states of proteins could reflect their compromise strategies

Inspired by the diverse conformational states of proteins, we propose that since the two activities (positive and negative) are contrary to each other, proteins may adopt compromise strategies to respond to and cope with this circumstance, which is in both the intramolecular and extramolecular contexts. We suggest that, to some extent, this scheme could probably afford the derivation or diversification of complicated conformational states of a variety of proteins. In other words, depending on the change and fluctuation of external environment, proteins should accordingly adjust their responses for both the requirements of self-configuration and adaption into environment [37,38]. Although protein conformational behavior results from many interacting factors, including intramolecular energetics, entropy, solvent effects, ligand binding, temperature, membrane environment, and post-translational modifications, it could be imaged that both the positive and negative activities of proteins are involved and implicated in these processes [16,18,25–27]. Thus, based on the above analysis, we hypothesized that in a large proportion of conditions and most of realistic cases, the conformation states of proteins may reflect their compromise strategies for both the two requirements, which seemly are opposite.

A good example is the well-studied G protein-coupled receptor (GPCR) in our lab, the heterodimeric sweet taste receptor Tas1R2/Tas1R3, which mediates the sweetener-binding-evoked taste perception signal transduction. The structures of human Tas1R2/Tas1R3 with or without various agonists have been solved, enabling us to track their distinct conformational states in the corresponding situated environments [39,40]. Two typical conformational states, resting and active, have been identified based on the experimental, structural, and computational approaches. In the resting state without sweetener binding, the intramolecular negative activities of key receptor residues are predominant, as shown by the formation of ionic bonds between pincer residues K65 and D278 [41]. In contrast, at the active state upon sweetener binding, extramolecular positive activities of key receptor residues are predominant, as shown by the breakdown of ionic bonds between the two identical pincer residues. Besides the two states, there are other intermediate or desensitized states, which were identified for this receptor and other GPCRs, reflecting their promiscuous conformational states and the probable compromise strategies to coordinate the intramolecular and extramolecular requirements [21]. Overall, these results could explicitly support the concept of dichotomy distinction

of protein activities.

4. Reevaluating the interaction forces between proteins and ligands

On the basis of our interpretation above, especially the positive and negative activities of proteins and their system/network attribute, we propose that researchers could rethink the intramolecular interaction forces of proteins. This consideration does not mean that the "close-range"-based deduction of the intramolecular connection and protein-ligand interaction forces is completely wrong, but provides a more comprehensive perspective on this issue. Next, we use the sweet-tasting proteins, which have been well investigated in our lab for many years [42], to show how the positive and negative activities and long-range interaction mechanisms work.

The sweet-tasting protein monellin exhibits extraordinary sweetening power, which is around 3000 times than that of sucrose on the basis of molar weight [43,44]. The only known activity of this protein is its high-intensity sweetness and no other biological function has been found until now [45]. This protein (94 amino acids) consists of two chains, A and B, which are linked by intramolecular non-covalent forces. Interestingly, most residues of the protein displaying flexible conformations, which are located at the external surface plastic loop regions (e.g., E2, E50), do not tend to interact with other residues of the protein but are critical for its sweetening power, whereas residues linking different components of the protein, which are mostly internal within the protein (e.g., E23), are inclined to contribute to the overall folding and structural stability but not to be engaged in modulation of sweet taste [46,47]. Therefore, we could convincingly divide the activities of residues of monellin into two catalogues: the positive activity of the outside flexible residues and the negative activity of the inside non-flexible residues. Moreover, it could be proposed that the origin of conformation of this protein probably are mainly dependent on the flexibility of its surface "orphan residues", which are responsible for eliciting sweetness through binding and interactions with the sweet taste receptor.

In 2009, Halabi et al. raised the concept "protein sector", which refers to the cooperative action of amino acid residues that form an interactive architecture and physically connected networks, and each sector has a distinct functional role [48]. Specifically, they used several proteins as examples to reinforce their standpoints [49,50]. Previously, we have decoded the distribution of sectors in the sweet-tasting protein monellin. It is indicated that the molecular organization of monellin, as well as other sweet-tasting proteins, not only has local short-distance residue-residue interactions but also harbors long-range residue-residue communications [51]. Concretely, structural determination and network analysis revealed that a G16A mutation located in the core of sweet protein monellin could induce flexibility changes of protein surface via propagation effects mediated by hydrophobic interactions, which led to a disruption of a C-terminal distant poly-(L-proline) II helix and resulted in a 10-fold decrease in sweetness [52]. Similar interplay and arrangement can also be found in other structural and mutagenesis studies [53]. These findings illustrate the existence of long-range communication in proteins.

Until now, many structures of the wild-type monellin, its single-chain variant, and many single-site and multiple-site mutants have been solved, demonstrating that some critical residues of this protein, which contact specific residues of the human sweet taste receptor via long-range surface charge complementation, mediate their interaction and receptor activation, thus determining the sweetness [54,55]. Indeed, the bulk volume of sweet-tasting proteins implies their inability to enter the orthosteric binding site of the sweet taste receptor, highlighting the importance of long-range

electrostatic interaction forces between them and the receptor for their sweetness [56]. Together, these findings indicate that researchers should pay more attention to the system/network-based long-range connections between residues of proteins in their studies.

Collectively, our discussions highlight the important roles of at least four types of long-range effects for the structures and activities of proteins, such as sweet-tasting proteins and GPCRs. First, long-range intramolecular communication, which is delineated as sectors of various proteins [48–51]. Second, allosteric coupling, as demonstrated by the multiple binding sites of the sweet taste receptor, in which an allosteric site at the transmembrane domain (TMD) of Tas1R3 can potently affect the actions of an orthosteric binding site located at the Venus flytrap domain (VFD) of Tas1R2 [57]. Third, correlated residue motions, as observed in the sophisticated molecular dynamics of both sweet-tasting proteins and sweet taste receptor [54,58]. Fourth, long-range intermolecular electrostatic interactions, which are the interactive mode between sweet-tasting proteins and the human sweet taste receptor, thereby determining receptor activation and elicitation of sweetness [53,55].

5. How system and network sciences aid the structural biology

System and network sciences have developed very quickly in recent years, which receive more and more attention. The most direct way to use system and network sciences to study structural biology is to transplant some principles or ideas of the former into the latter, such as hierarchy, modularity, self-organization, degree, hyperedge degree, and clustering coefficient [59]. We suggest that there are some commonalities between different systems because distinct networks are usually subjected to similar organizational patterns, that is, nodes form the system with specific connection modes [60,61]. Indeed, there has been some substantial progress in this research area, which has greatly enlarged our insight into understanding the deep structure and function relationships of various proteins [22,62].

Different methods or strategies have emerged to construct the networked systems of distinct proteins. Specifically, an amino acid is generally regarded as a node of the system, while their interactions (covalent or non-covalent), or connections between residues that are sequentially separated by N (> 1) residues along the protein backbone are defined as edges [63]. However, other elements, such as Cα, Cβ, center of mass of an amino acid residue, geometric center of the residue, and geometric center of the side chain of an amino acid residue, can also be appointed as nodes, respectively, and the corresponding settings for edge appointment vary according to those of the nodes, such as the distance between a pair of nodes that is within a threshold distance, or the interaction strength between two residues that is above a certain constant [64]. There are other different types of networks reported, which are generally modified or derived from the original ones, such as the updated node-weighted and edge-weighted networks [65], depending on the specific research requirement and context. Readers are encouraged to refer to concrete literature for more valuable information.

Using the constructed network model and system framework, principles leading to phenotypes and properties of proteins could be identified, and activities of specific mutations could be predicted. During these processes, certain algorithms (e.g., neural networks) were implemented, and the derived models can be further trained to improve their quality and accuracy. For instance, based on the amino acid network model, allosteric regulation and functional residues of proteins can be interpreted [65]. Residues with the co-evolution attribute can also be formalized as a network, where certain motifs and modules can be revealed, providing meaningful insight into the mechanistic and species diversity [66]. Furthermore, some web servers were constructed to quantitatively and qualitatively analyze residue-

residue interactions for a deeper understanding of the communications within proteins [63,64]. Moreover, on the basis of the multi-level organizational nature of proteins, the multiple-layer networks of networks have also been depicted [67].

Next, we will elucidate the concrete applications of system and network science with several listed examples. A feasible method to measure the positive and negative activities of proteins is the determination of the distribution of degrees of the network, which is the number of connections from one node to other nodes [68,69]. Whether there is a ligand binding with the protein or not, the degree reflecting connections between all nodes in the protein and other elements outside the protein (because a protein is subjected to the influence of external solvent, so the outside elements could generally be divided into two cases: one ligand-free case refers to the solvent molecules, such as typical H_2O, but without ligand, and another ligand-binding case refers to the solvent and ligand molecules) can be regarded as the weight value of positive activity of the protein. It implies that in the ligand-free case, the positive degree still exists, although the interactions could be significantly weaker than those in the ligand-binding case. Conversely, the degree that reflects connections between all nodes within the protein can be attributed to the weight value of its negative activity. In addition, some parameters in protein networks can be used to predict the binding sites in the protein. It was revealed that residues in the binding sites tend to form local modules, thus having a high clustering coefficient, which reflects the extent of connections between nodes, so the quantitative clustering coefficient can serve as an indicator for the appointment of binding sites [70]. Similar approaches have been applied such as prediction of the active sites of proteins with the characteristic vector closeness [71]. Chang et al. found that the proper ligand-protein complexes have higher interface degree and lower path length values than those of improper ones. They then developed a multiple scoring function HPNCscore, which can improve the distinction power of RosettaDock by approximately 12% [69,70].

6. The implication of AI application in the protein science

Because artificial intelligence (AI) is a powerful tool to purify rules from a bulk of data, which are generally in a chaotic state; thus, it should also be applicable in the system- and network-based protein science [72]. Indeed, it has been a lot of successful AI and machine learning implementations until now. The most significant performance of AI in protein science should be the deep learning-based protein structure prediction, represented by AlphaFold, RoseTTAFold, and ProteinBERT [73]. AI can also be applied in protein-protein interactions using a graph neural network-based deep learning strategy, as well as in protein-peptide complex structure prediction, by integrating two machine learning models, AlphaFold 2 for structural prediction and ANI-2x for ab initio potential prediction, respectively [68,74]. Another important field of AI application is the ligand docking and binding site prediction, such as the scoring protein docking models with one physics-inspired deep learning framework and the energy-based graph convolutional networks [75]. The protein language models have also been generated in these processes, for example, the UniKP framework based on pretrained language models [76]. Besides, successful yields of ligands, which include compounds, peptides, proteins, and other biological elements (e.g., biosensors and plant-protein meat analogues) with AI-assisted design have also been reported [77–81]. All these outcomes underscore the essential roles of AI in network and system-based protein science research.

In practice, biologists usually have no background or experience to deal with AI-related network and system problems. Therefore, joint collaboration is crucial to bridge this gap and complete the task.

Nevertheless, we think that not all the results from AI technologies are fully correct, and researchers are suggested to use some other strategies and methods to verify their results. However, this process may last for a long time because not all the verifications are reasonable and, in some cases, results from other research groups could be more reliable than those of the original researchers.

7. Ending remarks

In this paper, we illuminate the positive and negative activities of proteins, highlighting that elucidation of the protein-ligand interactions deserves the inclusion of both short-distance and long-range forces. Our analysis implies that the order and disorder uncertainty of proteins probably originates from the complex short- and long-range communications and interactive networks within proteins, which are also subjected to the influence of external environments [82]. This updated viewpoint also proposes that the promiscuous conformational states of proteins could probably be derived from their adapted compromise strategies when they encounter multifarious external environments. On the basis of this analysis, it is indicated that system and network sciences are essentially involved in the protein structural biology and that AI could offer meaningful aid to this field. Thus, future cooperation among different researchers, especially chemists, biophysicists, mathematicians and information scientists, should produce fruitful achievements in this research area.

In summary, in this paper, we enumerate the established knowledge about protein behaviors, including intramolecular short-distance and long-range connections and communications, allostery, conformational dynamics, residues interaction networks, and protein stability. Furthermore, we interpreted this knowledge in the context of system and network science, proposing a dichotomy of protein activities (positive and negative). Moreover, we present a hypothesis that the promiscuous conformational states of proteins could probably originate from their compromise strategies to accommodate their external complicated environment and reconcile the intramolecular and extramolecular requirements. The novelty of this paper is the first proposal for a distinction between the positive and negative activities of all sorts of proteins, as well as an assumption of this framework implicated in the origin of protein conformation.

We hope that this essay can help readers develop a deeper insight into protein structure-activity relationship and accelerate the application of system and network science, as well as AI in various fields, including ligand modification, enzyme engineering, antibody generation, and drug design.

Use of generative-AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

Writing–original draft: Z.H., L.Y.; Writing–review & editing: S.Y., J.Y., X.W., B.L.; Conceptualization: B.L.; Funding: B.L.

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