Cellular and Molecular Life Sciences (2025) 82:239
https://doi.org/10.1007/s00018-025-05770-1

REVIEW

'Intelligent' proteins

Timir Tripathi[1] · Vladimir N. Uversky[2] · Alessandro Giuliani[3]

Received: 2 April 2025 / Revised: 20 May 2025 / Accepted: 25 May 2025

Abstract

We present an idea of protein molecules that challenges the traditional view of proteins as simple molecular machines and suggests instead that they exhibit a basic form of "intelligence". The idea stems from suggestions coming from Integrated Information Theory (IIT), network theory, and allostery to explore how proteins process information, adapt to their environment, and even show memory-like behaviors. We define protein intelligence using IIT and focus on how proteins integrate information (in terms of the parameter Φ coming from IIT) and balance their core (stable, ordered regions) and periphery (flexible, disordered regions). This balance allows proteins to remain stable while adapting to changes and operating in a critical state where order and disorder coexist. We summarize recent findings on conformational memory, allosteric regulation, protein intrinsic disorder, liquid-liquid phase separation, and critical transitions, and compare protein behavior to other complex systems like ecosystems and neural networks. While our perspective offers a unified framework to understand proteins, it also raises questions about applying intelligence concepts to molecular systems. We discuss how this understanding could advance protein engineering, drug design, and synthetic biology, while at the same time acknowledging the challenges of creating adaptive, "intelligent" proteins. This concept bridges the gap between mechanistic and systems-level views of proteins and offers a comprehensive understanding of their dynamic and adaptive nature. We have tried to redefine the traditionally metaphorical concept of "intelligence" in biochemistry as a measurable property while simultaneously establishing the material foundation of protein intelligence through the identification of fundamental elements such as memory and learning in molecular systems.

Keywords Protein intelligence · Integrated information theory · Allostery · Conformational memory · Core-periphery dynamics · Critical States · Liquid-liquid phase separation · Post-translational modifications · Intrinsically disordered proteins

Introduction

Proteins are often described as molecular machines that perform specific functions with precision and efficiency, driven by their specific structure [1]. This mechanistic view has been instrumental in advancing our understanding of protein function. However, this perspective has been increasingly seen as incomplete, as it fails to capture the dynamic, adaptive, and integrative nature of proteins. Recent advances in structural biology, network theory, information theory, etc., have begun to challenge the traditional view and suggest that proteins exhibit behaviors that can be described as minimally intelligent. We bring the concept of "intelligent proteins," which focuses on their ability to integrate information, adapt to environmental changes, and exhibit memory-like properties. Our goal is to bridge the gap between the traditional mechanistic view of proteins

✉ Vladimir N. Uversky
vuversky@usf.edu

Timir Tripathi
timir.tripathi@gmail.com

Alessandro Giuliani
alessandro.giuliani@iss.it

[1] Molecular and Structural Biophysics Laboratory, Department of Zoology, School of Life Sciences, North-Eastern Hill University, Shillong 793022, India

[2] Department of Molecular Medicine, Morsani College of Medicine, USF Health Byrd Alzheimer's Research Institute, University of South Florida, Tampa, FL 33612, USA

[3] Environment and Health Department, Istituto Superiore di Sanità, Viale Regina Elena 299, Roma 00161, Italy

Published online: 14 June 2025

at a systems-level perspective and to provide a more comprehensive and detailed framework for understanding these remarkable biological macromolecules. In order to dissipate any ambiguity, it is worth noting that the concept of intelligence extends far beyond our minimalist definition. In its broadest sense, intelligence is often associated with 'insight' [derived from the Latin words *intus* (inside) and *legere* (to read), which literally means 'to read inside'], i.e., the ability to discern implicit meanings not immediately evident in a given piece of information. However, we propose that recognizing a 'minimal' form of intelligence in proteins can provide valuable insights into their physiological behavior. This minimal form of intelligence corresponds to the behavior of a system that not only adapts to perturbations in its microenvironment (like a sensor returning to its original state once the stimulus is removed) but also integrates the 'experience' of that stimulus into its configuration. This 'incorporation' can manifest in various ways, ranging from receptor priming during immune responses [3] to post-translational modifications (PTMs), as seen in epigenetic memory encoded by covalent changes to histone proteins [2]. On a more general perspective, molecular intelligence involves hysteresis, i.e., the non-equivalence of the forward and reverse trajectories between naïve and stimulated states in the two opposite directions [4]. The presence of a hysteresis loop is one of the most fundamental indicators of learning.

The foundation of our analysis lies in Integrated Information Theory (IIT), a theoretical framework that was originally developed to explain consciousness in neurological systems. IIT posits that consciousness arises from the ability of a system to integrate information, which makes the whole greater than the sum of its parts [5–10]. While IIT was initially applied to the brain, its principles are generalizable to any complex system that is capable of integrating information. Using IIT, we can describe a basic level of intelligence in proteins by their ability to change their structure in response to external signals and incorporate these changes into their function. This approach allows us to move beyond the reductionist view of proteins as rigid entities and instead consider them as adaptive systems that can sense and react to their environment.

The traditional mechanistic view of proteins as molecular machines has been highly successful in explaining many aspects of protein function. For example, the lock-and-key model of enzyme-substrate interactions provides a clear explanation for the specificity and efficiency of enzymatic reactions [11]. Similarly, the induced-fit model accounts for the conformational changes that occur upon substrate binding and offers a more dynamic perspective on protein function [11]. However, these models are limited in their ability to explain the broader adaptive and integrative behaviors exhibited by proteins.

Among the key limitations of the induced-fit model, which primarily focuses on active site recognition and substrate binding, is the fact that it does not adequately account for allosteric regulation, wherein binding at one site modulates the dynamics at a distant site. Moreover, the model overlooks the chemical transformations that occur during catalysis and focuses instead on the structural adaptation of the binding site. It also tends to oversimplify the complexity of protein-ligand interactions by assuming a rigid, static representation of both partners. In reality, proteins often exist as ensembles of pre-equilibrated conformations, and ligand binding may select or stabilize specific conformers from this dynamic spectrum. This static view fails to capture the intrinsic flexibility of proteins, which can involve coordinated backbone motions, disorder-to-order transitions, and large-scale domain rearrangements [12]. These dynamic properties are fundamental to many biological processes and are often essential for ligand recognition and specificity. Additionally, the induced-fit model generally overlooks the substrate promiscuity observed in many enzymes, where a single active site can accommodate structurally diverse ligands by leveraging its conformational adaptability [13].

Another key limitation of the mechanistic view of proteins is its emphasis on a specific structure linked to a predefined function. Proteins are not rigid entities but are highly flexible and undergo conformational changes in response to environmental stimuli [14, 15]. This flexibility is crucial for their function and allows them to adapt to changing microenvironment conditions and to perform complex tasks [16, 17]. The dynamic and adaptive nature of proteins is evident in their ability to undergo conformational changes in response to external stimuli. For example, allosteric proteins can change their shape upon binding to a ligand, which alters their activity and enables them to regulate critical cellular processes [18]. These changes are not random but are highly coordinated and involve the integration of information across the protein structure. For example, the allosteric response of hemoglobin to oxygen partial pressure involves a structural reorganization that integrates the external stimulus into its functional repertoire [19–21]. This integration is quantified by the mutual information between the state of the system before and after the stimulus (Eq. 1, see below). This ability to adapt to environmental changes is a hallmark of intelligent behavior, yet it is not adequately captured by the traditional mechanistic view.

A significant challenge to the traditional mechanistic view of proteins comes from the discovery and characterization of intrinsically disordered proteins (IDPs) and intrinsically disordered regions (IDRs). Unlike proteins having a single well-defined 3D structure, IDPs/IDRs lack a fixed

conformation and exist as dynamic ensembles of interconverting states. Regions or entire sequences that do not fold into stable secondary or tertiary structures under physiological conditions characterize IDPs/IDRs. They remain highly flexible and disordered, but still they play critical roles in cellular processes, including signaling, regulation, and molecular recognition [22, 23]. The existence of IDPs challenges the notion that protein function is solely dependent on a well-defined structure. IDPs often exert their function thanks to their disordered state, using their conformational flexibility to interact with multiple binding partners and to adapt to different cellular contexts. For example, intrinsic disorder is frequently found in hub proteins within protein-protein interaction (PPI) networks, where their ability to adopt multiple conformations allows them to bind to diverse partners with high specificity and low affinity [24]. A systematic comparison of the interactomes of ordered and disordered proteins has shown that IDPs/IDRs tend to engage with significantly more binding partners than their ordered counterparts. On average, the number of protein-protein interactions per IDP/IDR is ~3.5 times higher than that observed for ordered proteins or regions [25]. This disorder-based binding promiscuity is further amplified by the remarkable versatility of IDPs/IDRs: a single disordered region can interact with multiple structurally unrelated partners, while conversely, multiple distinct IDPs/IDRs can target the same binding site [26]. Additionally, IDPs/IDRs can undergo partner-specific folding and adopt distinct conformations depending on the interaction context [27, 28] or even retain significant disorder upon binding by forming fuzzy complexes that allow for functional plasticity [29, 30]. This promiscuity enables IDPs to function as central hubs in signaling networks that are capable of integrating inputs from diverse pathways and modulating cellular decision-making processes. However, just as not all structural motifs in ordered proteins serve defined functional roles, it is important to note that not all disordered regions are functionally significant. In some cases, disorder may simply reflect evolutionary tolerance or structural flexibility without any functional consequence.

Integrated Information (Φ) represents or quantifies the capacity of an "intelligent" system to modify its structure (broadly defined as a set of constraints among its components) that allows it to have a real experience (and make memorization possible) of a stimulus. In contrast, a simple sensor merely detects a stimulus without undergoing any structural change, leaving no lasting trace of the interaction. A non-zero value of Φ indicates that the protein has 'experienced' the stimulus, which makes it a candidate for minimal intelligence [9]. The concept of protein intelligence is further supported by the observation that proteins can exhibit memory-like properties. For example, *E. coli* lactose permease retains a lipid-induced conformational change even after the lipid is removed. This phenomenon, which has been termed allokairy, suggests that proteins can 'remember' past stimuli, which influence their future behavior [31]. Similarly, prion-like proteins can adopt self-templating conformations that induce heritable traits, which highlight their role in information processing and storage [32, 33]. Beyond these examples, several well-characterized proteins demonstrate lipid-induced conformational changes that describe the dynamic interplay between lipid environments and protein structure. The protein ApoE is a key player in lipid metabolism that facilitates the clearance of lipoproteins from the plasma by binding to specific cell-surface receptors, such as members of the LDL receptor family. In its lipid-free state, the N-terminal domain of ApoE adopts a compact four-helix bundle conformation. Upon lipid binding, particularly with phospholipids like dimyristoylphosphatidylcholine (DMPC), this domain undergoes a significant conformational rearrangement. The helix bundle opens and exposes the receptor-binding region, which enhances its affinity for LDL receptors. This lipid-induced structural transition is crucial for the role of ApoE in lipid transport and receptor interaction [34–36]. Another protein, GlpG, a rhomboid protease, which is embedded within the cell membrane, exhibits activity that is modulated by its lipid environment. Studies have shown that specific lipid headgroups, such as phosphatidylglycerol (PG), can transiently bind near the active site of GlpG. These interactions influence the conformational dynamics of the protease and affect substrate access and catalytic efficiency. Molecular dynamics (MD) simulation results have revealed that lipid headgroup binding can alter the energy landscape of GlpG, highlighting the role of lipid-protein interactions in modulating enzymatic function [37, 38]. Such lipid-induced conformational dynamics are integral to the concept of protein intelligence.

However, it should be noted that our primary focus is on individual proteins as self-contained systems that are capable of processing information and adapting their behavior, with examples such as kinesin, hemoglobin, and allosteric enzymes illustrating this point. We acknowledge that protein collectives or networks may exhibit emergent behaviors as well, but our core argument is centered on the informational and functional complexity of single protein molecules.

Defining intelligence in proteins

The concept of "protein intelligence" can be seen as an evolutionary advancement in understanding protein behavior from the traditional mechanistic view, which treats proteins as static, pre-programmed molecular machines. Instead, it

posits that proteins exhibit a form of minimal intelligence, which is characterized by their ability to integrate information, adapt to environmental changes, and exhibit memory-like properties. We now explore the theoretical foundations of protein intelligence and focus on IIT and the core-periphery dynamics of protein structures to establish a framework for understanding protein intelligence. We explicitly acknowledge that the term "minimal intelligence" applies only where there is evidence of information integration, state-dependent memory, and non-trivial system dynamics (e.g., hysteresis), which are observed in certain protein behaviors. It should be noted that applying the same logic to other non-living or complex systems might either dilute the metaphor or demand alternative frameworks for interpretation. As a historical parallel, the "intelligence" metaphor has long been employed in physics, most famously in Maxwell's Demon, a thought experiment from 1867 that challenged the second law of thermodynamics. Like that example, our goal is not to assert literal intelligence, but to provoke productive rethinking of how molecular systems like proteins process information and respond over time.

Integrated information theory (IIT) and proteins

Integrated Information Theory (IIT) is a theoretical framework originally developed to explain consciousness in neurological systems. At its core, IIT posits that consciousness arises from the ability of a system to integrate information, making the whole greater than the sum of its parts [10]. This integration is quantified by a metric called Φ (phi), which measures the degree to which the components of a system interact in a way that generates a unified, irreducible experience [7, 39]. While IIT was initially applied to the brain, its principles are generalizable to any complex system capable of integrating information, including proteins.

In the field of neuroscience, where it was originally formulated, IIT is used to explain the relationship between consciousness and its physical substrate. IIT begins with a set of phenomenological axioms that are derived from the nature of conscious 'experience'. First, each experience is specific, i.e., it is defined by how it differs from other possible experiences. This corresponds to the 'Information' component of IIT. Second, each experience is integrated, i.e., it is unified and cannot be decomposed into independent parts. This principle of 'Integration' suggests that the state of a system as a whole contributes to experience, and no subset alone suffices. Applied metaphorically to proteins, integration implies that an experience (stimulus) leads to a global, coordinated reconfiguration of the molecular structure. A third principle, 'Exclusion', posits that each experience has distinct spatio-temporal boundaries. These axioms are formalized in IIT to determine the conditions under which a physical system (such as neurons or logic gates) can give rise to experience. Although it is not our intention to imply that proteins possess consciousness, we adopt the formalism of IIT as a metaphorical framework, particularly its core metric Φ (phi), which we interpret here as a measure of mutual information between a 'naïve' and 'experienced' states of a protein.

The integration of information in proteins can be quantified using the concept of mutual information, which measures the dependence between the state of a system before and after a stimulus. Mathematically, this is expressed as:

$$\mathrm{I}\left(\mathrm{X}^{\mathrm{t}-\tau};\mathrm{X}^{\mathrm{t}}\right)=\mathrm{H}\left(\mathrm{X}^{\mathrm{t}-\tau}\right)-\mathrm{H}\left(\mathrm{X}^{\mathrm{t}-\tau}\left|\mathrm{X}^{\mathrm{t}}\right.\right). \tag{1}$$

where $H(X^{t-\tau})$ represents the entropy of the state of the system before the stimulus, and $H(X^{t-\tau}|X^{t})$ represents the conditional entropy of the state of the system before the stimulus, given its state after the stimulus, with $X^{t-\tau}$ representing the state of X^{t} (an internal variable vector $X = \{X_1, X_2, \ldots, X_n\}$ at time t), τ steps before. A non-zero value of mutual information indicates that the protein has integrated the stimulus into its structure, making it a candidate for minimal intelligence.

Then, the system integration ability Φ can be expressed as [40]:

$$\Phi=\mathrm{I}\left(\mathrm{X}^{\mathrm{t}-\tau};\ \mathrm{X}^{\mathrm{t}}\right)-\mathrm{I}*\left(\mathrm{X};\ \tau,\ \pi\in\mathrm{P_S}\right) \tag{2}$$

where $I(X^{t-\tau}; X^{t})$ represents the mutual information between the current state X^{t} and past states $X^{t-\tau}$, S is the set of all nodes of a given system, P_S is the set of all bi-partitions (total $2^{|S|-1}-1$ partitions), and π is an element of the set P_S. Additionally, $I^*(X; \tau, \pi \in P_S)$ represents a 'hypothetical' mutual information, indicating the mismatched decoding in the partitioned probability distribution by π [41].

Since proteins are highly dynamic and adaptive systems, they are prime candidates for the application of IIT. Our key idea is that proteins can 'experience' their environment by integrating external stimuli into their structural and functional repertoire. However, the notion of proteins "experiencing" their environment refers to their ability to not only respond to external stimuli but also incorporate those interactions into persistent changes in their structural or functional state. As elaborated in our discussion of "minimal intelligence," this incorporation can take multiple forms, such as receptor priming during immune responses [3] or PTMs involved in epigenetic memory, such as histone modifications [2]. These examples support our broader interpretation that proteins can exhibit a primitive form of information integration, where past stimuli leave a trace that alters future responsiveness. We align this idea with IIT-inspired notions of state-dependent processing of information.

To illustrate the idea of minimal molecular intelligence in proteins, we present hemoglobin as a paradigmatic example. Traditionally described as a textbook case of allosteric regulation, hemoglobin displays several properties that extend beyond passive adaptation and align with our proposed framework of intelligent behavior at the molecular level. Hemoglobin, a tetrameric heme-bound protein, binds oxygen cooperatively, i.e., the binding of one oxygen molecule to a subunit increases the affinity of the remaining subunits for oxygen [19–21]. This property arises from a conformational transition between the low-affinity T (tense) state and the high-affinity R (relaxed) state. Crucially, this transition is not simply a switch but involves an asymmetric, history-dependent process. The pathway and energy landscape followed during oxygen binding (T → R) differs from that during oxygen release (R → T), which reflects hysteresis, a hallmark of systems with memory. This behavior suggests that the response of the molecule is shaped not only by the current external stimulus (oxygen concentration) but also by its prior state, which is a basic form of molecular 'learning'. Furthermore, hemoglobin exhibits distributed information integration: the binding of oxygen at one heme site propagates structural rearrangements across subunits, which modulates the dynamics of distal sites. This coordination represents an internal "decision-making" mechanism that cannot be localized to a single part of the protein. In this sense, the quaternary structure of hemoglobin supports an emergent form of integrated information processing, which is analogous in principle to systems considered in IIT, albeit at a minimal molecular scale. Another aspect consistent with our framework is the functional rewiring of the behavior of hemoglobin under different physiological contexts. For example, changes in pH (Bohr effect), CO_2 concentration, or the presence of 2,3-BPG further modulate the affinity of oxygen by stabilizing specific conformational states. These regulatory mechanisms reveal an ability to fine-tune responses dynamically, which enables the protein to adapt to environmental changes without requiring changes to its primary sequence. So, collectively, hemoglobin demonstrates: (i) Hysteretic behavior (trajectory-dependent conformational changes), (ii) Information integration across subunits, (iii) Adaptive tuning via external modulators, and (iv) Functional switching among multiple quasi-stable states. These features are consistent with our definition of minimal protein intelligence, where a system incorporates its past into its present state, integrates distributed information, and generates a coherent, goal-directed output, in this case, efficient transport of oxygen across diverse physiological conditions.

Beyond hemoglobin, this general principle extends to a broader class of proteins, such as G protein-coupled receptors (GPCRs). GPCRs are membrane-embedded sensors that undergo ligand-induced conformational changes that initiate intracellular signaling cascades. GPCRs exist in a dynamic equilibrium between inactive and active states, and the binding of a ligand shifts this equilibrium by stabilizing specific conformations. The conformational "memory" of prior activation can persist in the form of receptor desensitization or biased signaling, suggesting a primitive encoding of past events [42–44]. Another compelling example is viral fusion proteins, such as the influenza hemagglutinin or HIV-1 gp41, which undergo significant structural transitions in response to pH changes or receptor engagement [45, 46]. In the acidic environment of the endosome, hemagglutinin refolds from a metastable pre-fusion conformation into a stable post-fusion structure, driving membrane fusion. This pH-induced switch is a single-use, irreversible conformational memory encoded in the energy landscape of the protein. These examples illustrate how proteins use conformational plasticity not just for reactivity, but as a mechanism for encoding environmental information, integrating signals across spatial and temporal domains, and modulating future responses. When looked through the lens of IIT and network dynamics, these systems reveal the operational substrate for a minimal, non-conscious form of intelligence embedded within molecular architectures.

While the application of IIT to proteins is conceptually appealing, it comes with its own set of challenges that require attention. One major criticism is the difficulty of measuring Φ in complex systems [47]. Unlike the brain, where Φ can be estimated using neural activity data [48] proteins lack a direct analogue for such measurements. However, recent advances in computational modeling and experimental techniques, such as MD simulations and NMR spectroscopy, have made it possible to quantify the degree of integration in proteins [49]. These tools have enabled the mapping of the flow of information within protein structures and provided valuable insights into their dynamic and adaptive nature. Another criticism is the anthropocentric bias inherent in applying a theory of consciousness to proteins (discussed in detail in Sect. 8). Skeptics argue that intelligence, as defined by IIT, is a property of highly complex systems like the brain and cannot be meaningfully extended to simpler entities (in our case, proteins) [50]. However, proponents counter that intelligence is not a binary (all-or-nothing) phenomenon but exists on a continuum [51]. From this perspective, proteins exhibit a minimal form of intelligence, which is made evident by their ability to integrate information and adapt to environmental changes. We would like to emphasize that our criterion for distinguishing "minimal intelligence" from mere adaptation lies in the presence of hysteresis, i.e., the return of a system to its original state via a different trajectory than the one it followed in response to the stimulus. This asymmetry reflects not just a reversible adaptation but a history-dependent transformation, where

the system retains a trace of the stimulus beyond its presence. The area enclosed by the hysteresis loop provides a quantitative proxy for the persistence or "memory" of that prior stimulus. We argue that this behavior justifies the use of the term "minimal intelligence" because it implies more than passive adaptation: it involves a form of temporal integration and state-dependent processing. This shifts our understanding of proteins from static molecular machines to dynamic, history-sensitive systems. Such a perspective has meaningful implications, for example, a structurally symmetric homodimer can exhibit highly asymmetric dynamics, which can potentially influence its function in unexpected ways [52]. We frame this behavior within the broader lens of minimal intelligence to emphasize the nontrivial processing capabilities embedded in protein systems.

The application of IIT to proteins has profound implications for our understanding of protein function. It suggests that proteins are not merely passive executors of predefined tasks but active participants in their environment that are capable of 'learning' from experience and adapting their behavior accordingly. This perspective opens new avenues for research in protein engineering, drug design, synthetic biology, etc. We will discuss these applications in Sect. 7.

Core-periphery dynamics

The concept of core-periphery dynamics provides a structural basis for understanding protein intelligence [53, 54]. Proteins can be described as residue interaction networks, where nodes represent amino acids and edges represent interactions between them [55]. These networks exhibit a distinct core-periphery architecture, with densely connected, evolutionarily conserved residues forming the core and IDRs forming the periphery [56, 57].

The core of a protein is characterized by densely connected, evolutionarily conserved residues that facilitate fast energy transfer and signal transmission. These residues are typically located in the interior of a protein, where they are shielded from environmental fluctuations. The high degree of connectivity in the core ensures efficient communication between distant functional sites and enables the protein to respond rapidly to external stimuli. For example, in kinesin, a motor protein, the core consists of highly conserved residues that mediate ATP hydrolysis and microtubule binding. These residues are tightly packed and create a rigid structure that maintains the identity of the protein and ensures its functional integrity. However, the core is not static; it undergoes subtle conformational changes in response to external stimuli, which enable the protein to adapt its behavior to its microenvironment [58].

In contrast to the core, the periphery of a protein consists of IDRs that enable adaptability and conformational flexibility to the protein. IDRs allow the proteins to adopt multiple conformations in response to environmental changes [23, 59–63]. This flexibility is crucial for the ability of the protein to interact with binding partners and perform complex tasks. For example, in transcription factors, IDRs play a key role in mediating protein-DNA interactions [64]. Upon binding to DNA, these regions fold into specific conformations, which enable the protein to recognize and bind to specific DNA sequences. This process, known as conformational signaling, allows the protein to integrate external stimuli into its functional repertoire.

The interplay between the core and periphery is essential for protein intelligence. The core maintains the identity of the protein and ensures its functional integrity, while the periphery enables adaptability and responsiveness to environmental changes. This duality mirrors the balance between stability and adaptability observed in intelligent systems, such as the brain. For example, in allosteric proteins, the core and periphery work together to mediate the response of the protein to external stimuli. The core transmits signals between distant functional sites, while the periphery undergoes conformational changes that modulate the activity of the protein [65]. This coordinated response allows the protein to integrate information and adapt its behavior as a dynamic and adaptive system.

While the core-periphery model provides a useful framework for understanding protein intelligence, it has certain limitations. One key criticism can be that the distinction between core and periphery is often not well-defined. In some proteins, the boundaries between core and periphery are blurred, with residues exhibiting both ordered and disordered characteristics. This complexity challenges the traditional view of proteins as having a rigid core and a flexible periphery. Additionally, the model oversimplifies the complexity of protein dynamics. Proteins are highly dynamic systems that undergo continuous conformational changes, which makes it difficult to define a static core and periphery.

However, one should keep in mind that, despite their highly dynamic nature, all proteins exhibit at least some degree of structural heterogeneity, which is a feature that can be viewed as a logical extension of the core-periphery model of protein architecture. Even the most disordered proteins are not completely unstructured but contain regions of residual or transient structure, which function as dynamic cores and play a crucial role in mediating the interplay between structural stability and functional flexibility. An interesting example of this is the intrinsically

disordered kinase inhibitory domain (KID) of the cell cycle inhibitor protein $p27^{Kip}$ [1]. In its unbound state, p27-KID is largely disordered [66, 67]; however, upon binding to its partners Cdk2 and cyclin A, it undergoes a folding-upon-binding transition and adopts a well-defined p27-KID/Cdk2/cyclin A ternary complex conformation that includes an α-helix, a 3_{10}-helix, and β-strands [68]. Intriguingly, even in its disordered, unbound form, p27-KID harbors marginally stable helical structures that presage the α-helix observed in the p27-KID bound to cyclin A-Cdk2 complex [67]. These pre-structured motifs not only reduce the entropic cost associated with induced folding but also confer a kinetic advantage by facilitating rapid and regulated complex formation [67]. p27-KID is an illustrative example of how structural disorder and residual order coexist and exemplify the dynamic interplay between core and periphery, which is a hallmark of what we describe as protein intelligence. To further capture this complexity visually, Fig. 1 shows representative NMR solution structures of proteins with varying degrees of intrinsic disorder. It demonstrates that both core and peripheral regions can have different dynamics, structure, and spatial volume within a given protein molecule.

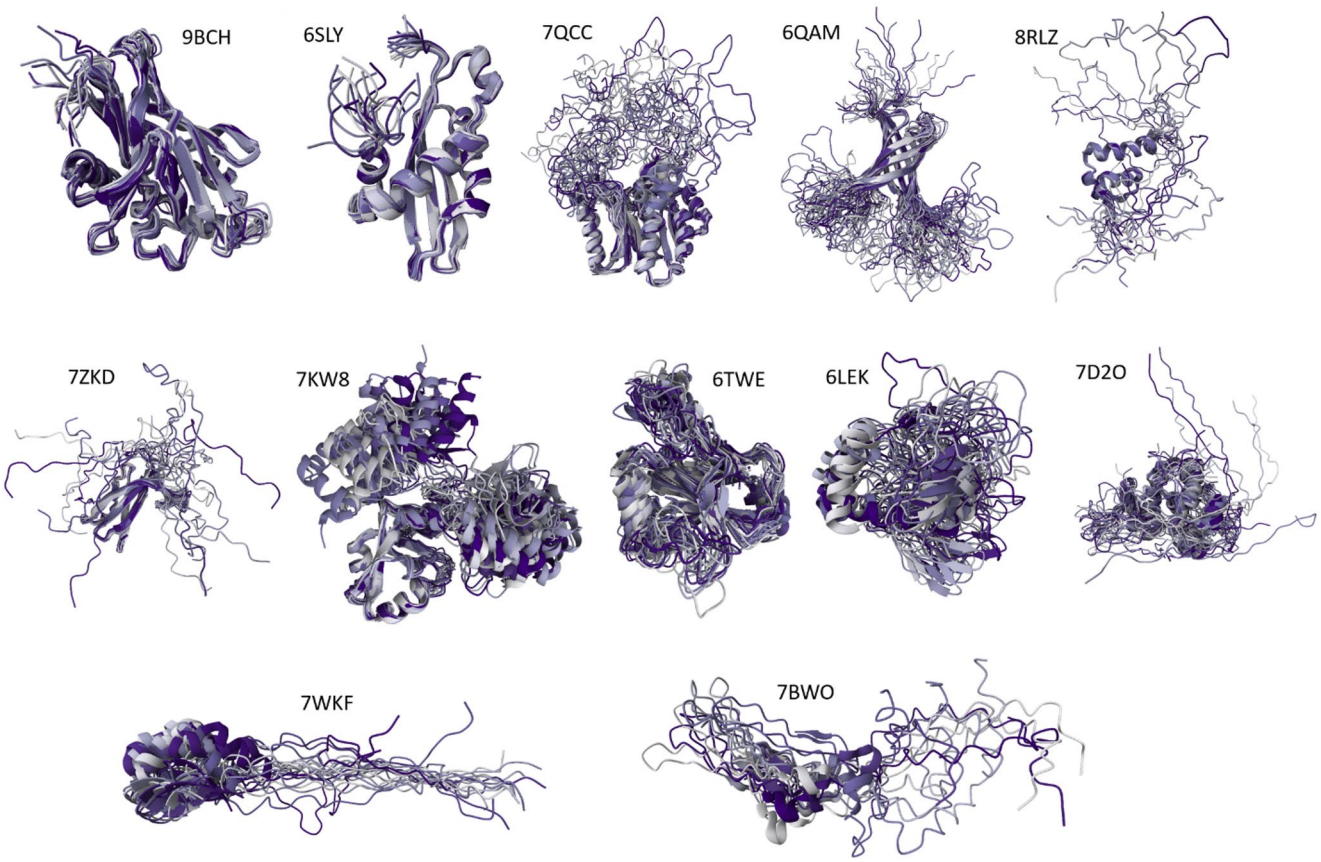


Fig. 1 Illustrative examples of proteins with varying levels of intrinsic disorder. Each panel displays an ensemble of structural models derived from solution NMR spectroscopy, capturing the conformational heterogeneity (or "fuzziness") present in different regions of the protein. This structural fuzziness reflects the dynamic nature of protein conformations and is typically more pronounced in the periphery than in the core. In all cases, the core regions exhibit comparatively lower flexibility (have lower fuzziness), reinforcing the concept of a dynamic core-periphery organization. Notably, even highly disordered proteins, such as the chitin-binding domain from the beak of the jumbo squid *Dosidicus gigas* (PDB ID: 7BWO), retain a partially ordered core, illustrating that complete structural disorder is rare. The figure includes examples spanning a broad structural continuum, from mostly ordered to predominantly disordered proteins. These include the hemoglobin receptor HbpA from *Corynebacterium diphtheriae* (PDB ID: 9BCH; [69]), the TonB C-terminal domain from *Helicobacter pylori* (residues 179–285; PDB ID: 6SLY; [70]), the Williams-Beuren syndrome-associated methyltransferase WBSCR27 (PDB ID: 7QCC; [71]), the outer membrane protein AlkL (PDB ID: 6QAM; [72]), the N-terminal cytoplasmic domain of the membrane antisigma factor DdvA (PDB ID: 8RLZ; [73]), the MAX47 effector from *Pyricularia oryzae* (PDB ID: 7ZKD; [74]), the tRNA 2′-phosphotransferase from *Runella slithyformis* (PDB ID: 7KW8; [75]), the chitin-active lytic polysaccharide monooxygenase BlLPMO10 A (PDB ID: 6TWE; [76]), the barnacle cement protein MrCP20 (PDB ID: 6LEK; [77]), *Gaussia* luciferase (PDB ID: 7D2O; [78]), the antimicrobial peptide LaIT2 (PDB ID: 7WKF; [79]), and the aforementioned chitin-binding domain (residues 163–223) from *D. gigas* (PDB ID: 7BWO; [80]). Together, these structures illustrate the wide spectrum of disorder in proteins and highlight the dynamic interplay between ordered cores and flexible peripheral regions

Structural and functional basis of protein intelligence

The concept of protein intelligence is deeply rooted in the structural and functional dynamics of proteins. Unlike synthetic machines, which are designed with modular, independently optimized components, proteins exhibit a global integration of structure and function. This integration enables proteins to adapt to environmental changes, integrate information, and exhibit memory-like properties.

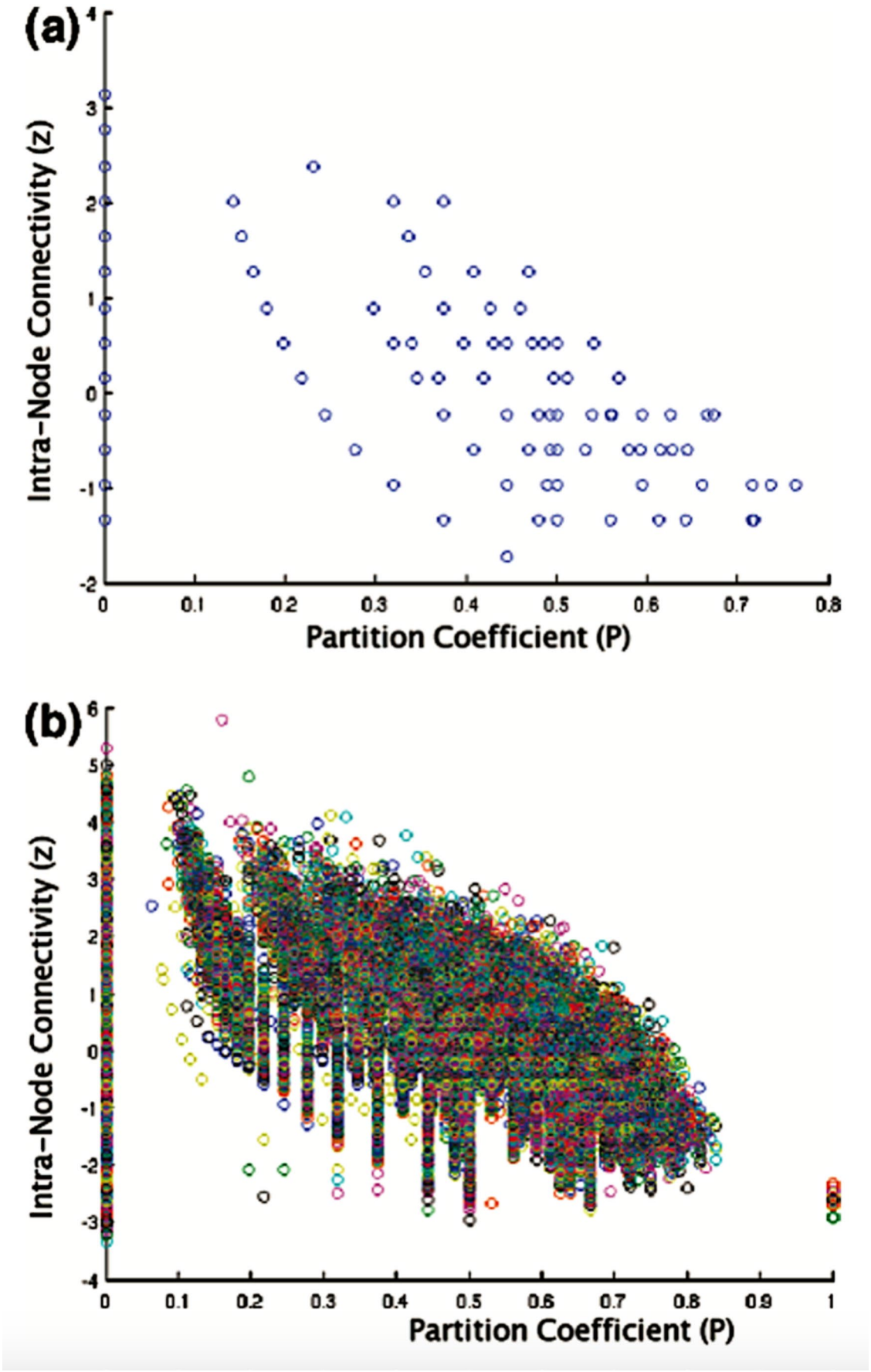
It is worth noting that the balance between a 'core' responsible for stability and a 'periphery' devoted to flexibility is a general feature of any protein molecule, even in the absence of IDRs. This balance becomes particularly evident when analyzing protein 3D structures through a network-based perspective. According to this framework, we can generate protein contact networks (PCNs) by filtering the distances between α-carbon atoms of any two residues by a threshold so that the distances are considered as 'contact' (below the threshold) and 'lack-of-contact' (above the threshold), respectively [81]. This threshold can be made more focused on 'elective' contacts (functionally relevant interactions) by eliminating the 'obliged' contacts (which arise solely due to primary sequence adjacency) [81]. This procedure transforms the 3D structure of a protein into a graph, where residues serve as nodes and pairwise contacts as edges. This allows the use of graph descriptors for investigating protein structures [81, 82].

A particularly useful approach to analyzing such networks is the so-called Guimerà-Amaral cartography [83]. This approach employs network spectral clustering [84] to partition the structure into clusters of strongly connected nodes. In this model, each node (i.e., amino acid residue in a PCN) is characterized by two key descriptors: z (intracluster connectivity), which represents the normalized number of contacts a node has within its own module (cluster), and P (partition coefficient), which quantifies the ratio of inter-cluster to intra-cluster links. Figure 2A illustrates a typical P-z diagram derived from a single protein structure, whereas Fig. 2B shows the superposition of P-z profiles of 1,420 structurally unrelated proteins [81]. Notably, despite the vast morphological diversity of these proteins, the general shape of the graph (in terms of intra-cluster and inter-cluster connectivity) remains remarkably consistent. This suggests a highly conserved wiring pattern in PCNs despite their huge morphological variability, highlighting the common fundamental organizational principles underlying protein structures. Residues with high P values play a crucial role in allosteric regulation and exhibit greater flexibility compared to others [85, 86]. On the contrary, residues with $P = 0$ and elevated values of z are those responsible for the global stability of the system. This dual nature, where structured (crystal-like) and flexible (liquid-like) phases coexist, is a hallmark of any self-organizing system that is capable of interacting with its environment [87, 88]. Such a balance is not only fundamental for biological function but is also considered a prerequisite for any minimal form of intelligence. Figure 2 also illustrates that these two phases do not align with any strict modular architecture. Instead, individual residues can establish effective topological connections with structural modules beyond their own. These 'extra-module' links play a key role in enabling the responsiveness of a protein to external stimuli and facilitating dynamic adaptations essential for function and regulation.

Fig. 2 P vs. z plot for (**a**) a single protein and (**b**) for 1420 proteins. Notably, the plots exhibit a striking similarity across all proteins, highlighting a conserved pattern. The dataset used in this study was obtained from the protein-culling server PISCES. The authors selected a subset of protein structures that share less than 20% sequence identity and at a resolution better than 2.0 Å. Only monomeric entries (single chains) were included. An initial set of 1757 structures was downloaded and subsequently filtered to exclude entries with missing residues, resulting in a final dataset of 1420 high-quality structures. The module detection algorithm was applied to this curated set, and the results are accessible via a dedicated web server (http://gandivaweb.iab.keio.ac.jp). A complete list of the PDB IDs included in the analysis is provided in the Supporting Information of the paper [89]. Figure adapted with permission from Krishnan et al. [89]

The concept of 'periphery' should be understood not in geometric terms but in a topological sense, representing the 'fluid phase' of the system as opposed to its 'crystal-like' phase in terms of connectivity. Lower connectivity corresponds to greater flexibility; thus, while peripheral regions do not necessarily overlap with IDRs, they tend to be enriched with unstructured patches. It is also important to emphasize that in reality, there is no strict boundary between ordered proteins and IDPs; instead, the structure-disorder landscape of a protein exists on a continuum [90]. In fact, regardless of their intrinsic disorder status, all proteins represent complex, heterogeneous systems with intricate spatiotemporal organization, where different regions of a protein molecule (even rather short ones) exhibit varying degrees of order and disorder [91–97]. As a result, a single protein can adopt multiple combinations of ordered and disordered states (Fig. 3). These combinations can be categorized as [91–97]:

1. **Mosaic architecture**: Comprising spontaneously folded regions (*foldons*) and regions that do not fold (*non-foldons*).
2. **Global semi-folded state**: Containing regions that remain in a semi-structured state (*semi-foldons*).
3. **Inducible foldons**: Folding (at least partially) upon interaction with binding partners.
4. **Morphing inducible foldons**: Adopting different folded states when binding to different partners.


(a)
Intra-Node Connectivity (z)
Partition Coefficient (P)
(b)
Intra-Node Connectivity (z)
Partition Coefficient (P)

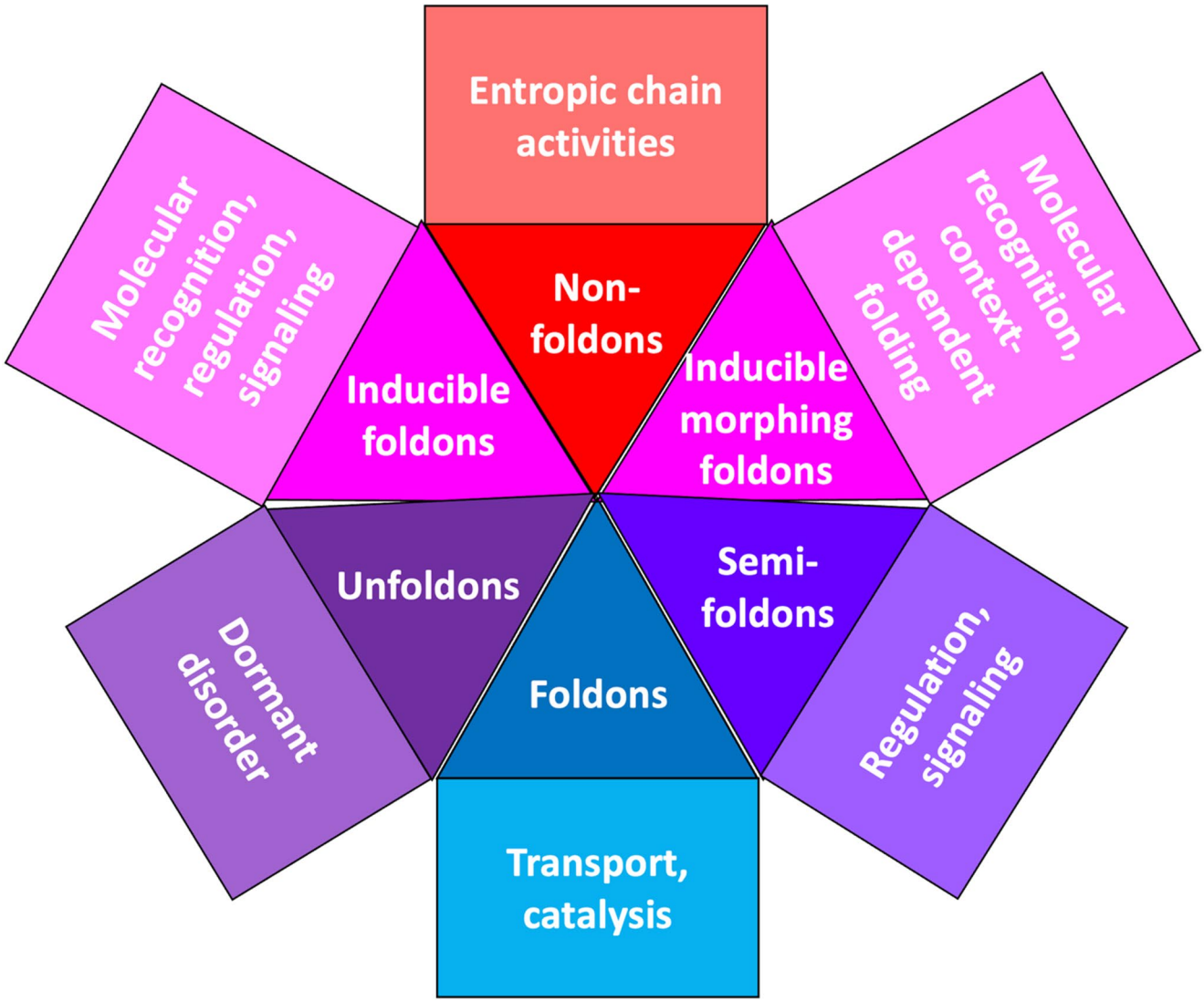


Fig. 3 Structure-function continuum of proteins. A single protein can adopt multiple combinations of ordered and disordered states, categorized as: (1) Mosaic architecture, comprising folded (foldons) and non-folded (non-foldons) regions; (2) Global semi-folded state, containing semi-structured regions (semi-foldons); (3) Inducible foldons, folding upon binding; (4) Morphing inducible foldons, adopting different folds with different partners; and (5) Unfoldons, requiring unfolding for activation. These dynamic states create a structural and functional continuum, and enable proteins to perform diverse roles over time

5. **Unfoldons**: Regions that must undergo partial or complete unfolding to activate the protein.

Beyond the intrinsic variability in order across different regions, the distribution of foldons, non-foldons, inducible foldons, morphing inducible foldons, semi-foldons, and unfoldons is highly dynamic over time. Consequently, a given protein segment can adopt different structures at different time points, resulting in an ever-changing, non-crystal-like overall protein structure. This dynamic structural mosaic underpins the multifunctionality of a protein, as each type of (dis)ordered region can serve distinct functional roles [91, 97–99]. In other words, protein function is best understood through a structure-function continuum model [100]where the structural continuum arises from the coexistence of differently (dis)ordered regions, and the functional continuum reflects their diverse functional contributions [91, 97–99]. Furthermore, this spatiotemporal organization, where even a single protein functions as a complex system composed of interdependent parts, each capable of dynamic change that influences the overall system behavior, forms the foundational basis of protein intelligence. Within the framework of complex adaptive systems, proteins exhibit hallmark features: “they are open, dynamic entities that are able to self-organize their structural configurations through continuous exchange of information, energy, and other resources with their environment. Importantly, they

are able to transform these resources in ways that enable context-dependent action and functional adaptation" [101].

Furthermore, beyond multifunctionality, the responsiveness of a protein is also rooted in its spatiotemporal heterogeneity. This heterogeneity, which is closely linked to intrinsic disorder, positions proteins at the edge of chaos (a state that enables rapid adaptation to fluctuating environmental conditions). Let us now explore the structural and functional basis of protein intelligence, using kinesin as a case study, and discuss the role of allostery and conformational signaling in protein dynamics.

Kinesin as a case study

Kinesin, a motor protein responsible for intracellular transport, serves as an exemplary model for understanding protein intelligence (Fig. 4) [58]. Kinesin moves along microtubules and transports cargo such as vesicles, organelles, and mRNA within the cell [102]. This process requires precise coordination between ATP hydrolysis, microtubule binding, and cargo recognition.

Unlike synthetic machines, which are designed with modular, independently optimized components, the structure-function relationship in kinesin is global and cannot be

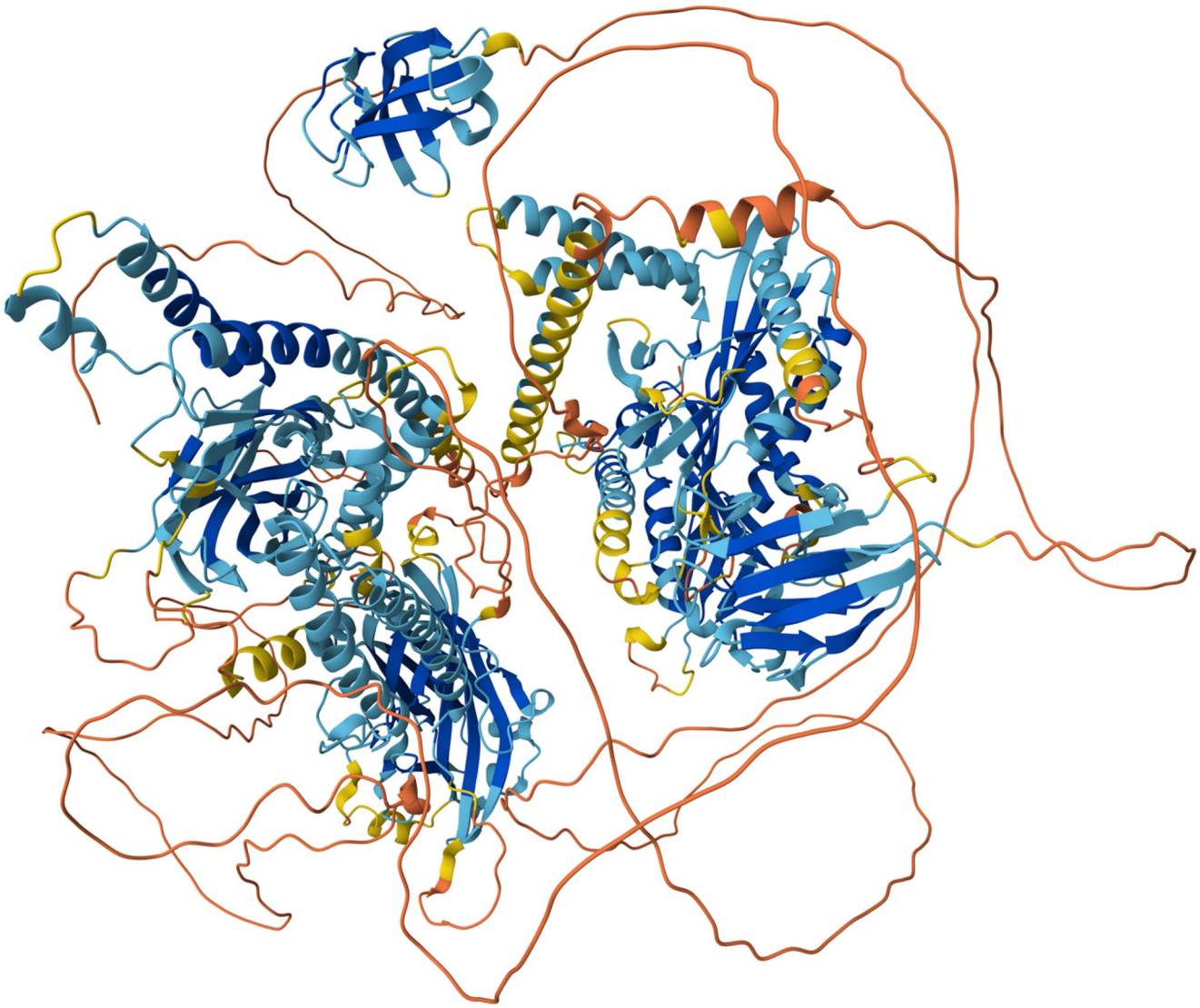


Fig. 4 Structural model of a kinesin protein. The ribbon diagram depicts the 3D structural model of a kinesin motor protein (containing 1815 amino acid residues), with different functional regions. The model has been generated using AlphaFold 2.0. The structure contains the motor domain (responsible for ATP hydrolysis and microtubule binding), the neck linker (involved in force generation and directional movement), and the coiled-coil stalk (mediating dimerization and cargo binding) [58]. Notably, there are no clear boundaries (and no macroscopic differences in structure) between these functional regions, which reflects the integrated nature of protein function. This lack of discrete partitioning contrasts sharply with the modular design of synthetic machines, which underscores the unique principles of biological engineering

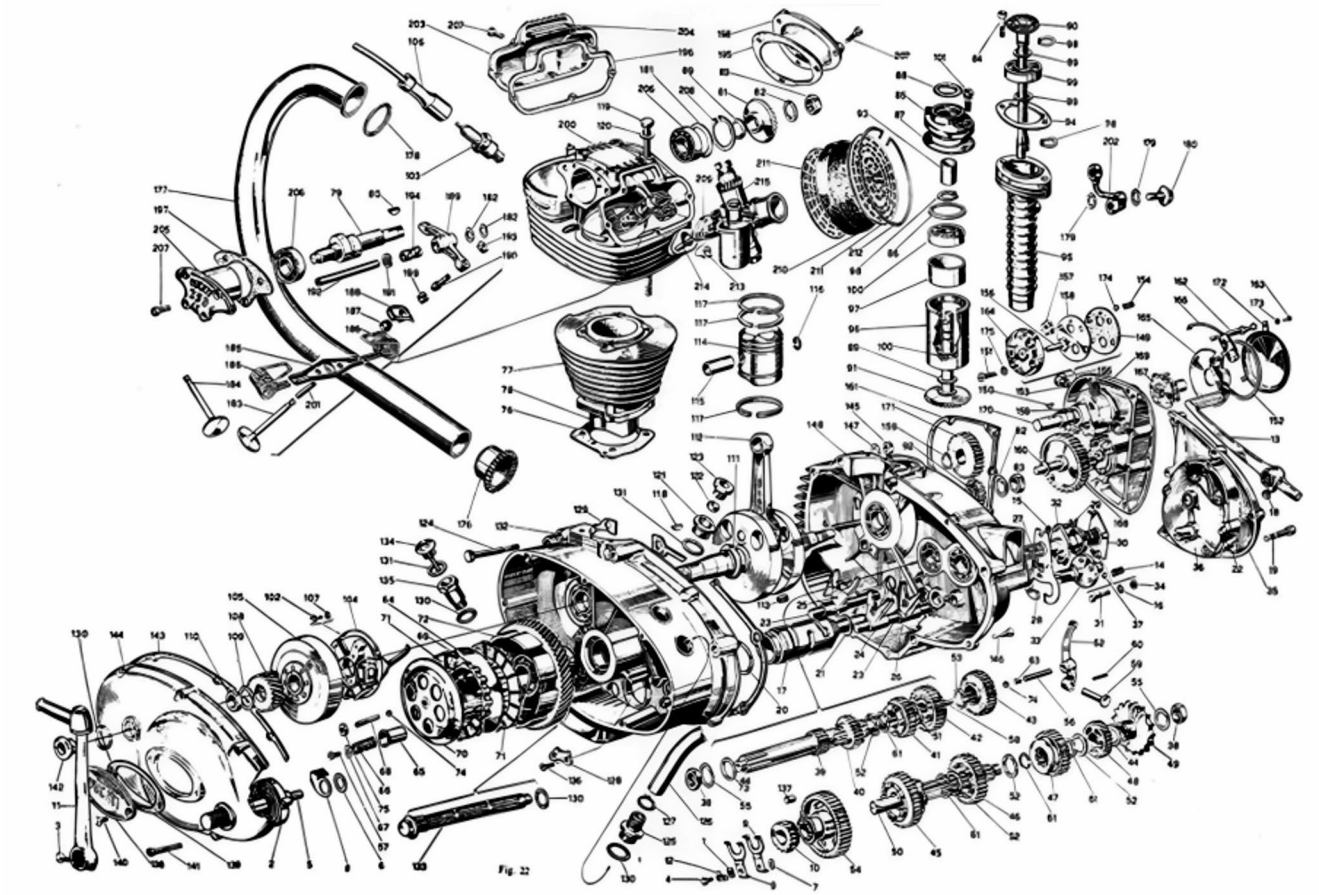


Fig. 5 Schematic of a Ducati 250 GT engine. The diagram illustrates the internal structure of a Ducati 250 GT race motorbike engine, 1966, a classic example of synthetic mechanical engineering. Key components, such as the pistons, crankshaft, and valves, are clearly delineated to highlight their distinct functionalities. Unlike the kinesin molecule (Fig. 4), the engine exhibits a modular and compartmentalized design, with well-defined boundaries between functional parts. The elements of the engine interact while at the same time maintaining their independent and unique forms; the structure of the engine remains invariant during operation. It is not by chance that each component has a distinct label, as there is no ambiguity regarding the borders between different parts. This contrast emphasizes the fundamental differences between biological and synthetic systems, even when both are designed to achieve controlled and regular motion. The rigid, predefined architecture of the engine stands in stark contrast to the dynamic and integrated nature of protein-based molecular machines. Figure adapted with permission from De Paola et al. [81]

factorized into independent parts. For example, the motor domain of kinesin, which binds to microtubules and hydrolyzes ATP, is intricately linked to its cargo-binding domain [103]. This integration ensures that changes in one domain (e.g., ATP hydrolysis) are transmitted to other domains (e.g., microtubule binding), which enables coordinated movement. The lack of clear boundaries between functional regions in kinesin contrasts sharply with the modular design of synthetic machines. In synthetic machines, such as car engines, each component (e.g., pistons, fuel injectors) is optimized independently and connected through rigid interfaces (Fig. 5). This modularity allows for easy repair and replacement, but limits the ability of the system to adapt to novel stimuli. In contrast, the global integration of kinesin enables it to 'learn' from its environment and adapt its behavior over time. The ability of kinesin to adapt to environmental changes is a hallmark of protein intelligence. For example, kinesin can adjust its stepping pattern in response to changes in microtubule structure or ATP availability. This adaptability is mediated by conformational changes that propagate across the protein and integrate information from multiple domains. These changes are not random but are highly coordinated, which enables kinesin to perform its transport function with remarkable efficiency. Furthermore, it is important to recognize that the step size of kinesin (typically 8.1 nm per ATP hydrolyzed, which corresponds to the distance between adjacent tubulin subunits on the microtubule lattice) [104] is not a fixed mechanical constant. Rather, it is modulated by several factors, including the structural properties of the microtubule, the presence of microtubule-associated proteins, and the nature of the mechanical load. Under increasing load, kinesin motors

have been observed to exhibit backstepping [105, 106] or to take smaller-than-normal steps [107]. Even more intriguingly, when multiple kinesin motors coordinate their movement, the resulting step sizes can deviate from the canonical 8 nm increments. In such collective scenarios, fractional steps of 4 nm and even sub-nanometer displacements as small as 0.73 nm have been recorded [108]. Crucially, kinesin is not merely a passive transporter that reacts to external cues. Recent findings suggest that it also acts as both a reader and a writer of the tubulin state within the microtubule lattice. As kinesin steps along the microtubule, it can induce conformational changes in the tubulin subunits [109]. These kinesin-induced alterations are not confined locally; they can propagate along the lattice and allow kinesin molecules to allosterically influence other proteins operating on the same track [109]. Such behavior transcends the boundaries of passive adaptation. It indicates that kinesin not only integrates cues from its environment but actively modifies that environment, which is an ability that aligns with the notion of a minimal form of learning or intelligence.

The concept of 'learning' in kinesin supports the idea that the protein can exhibit memory-like properties. Kinesin can retain information about past interactions with microtubules, which influences its future behavior. This functional "memory" is encoded not only in conformational changes within the kinesin molecule (stabilized through interactions between its structured core and more flexible peripheral regions), but also in the kinesin-induced modifications to the microtubule structure itself. As kinesin walks along microtubules, it can induce conformational changes that create high-affinity binding states, effectively marking the microtubule in a way that influences subsequent kinesin activity [110]. Thus, both the kinesin and the microtubule retain the resulting "memory" of previous interactions, which in turn shape future dynamics. In fact, kinesins can use this "memory" to guide polarized transport and selectively deliver cargo to specific subcellular locations such as axons or dendrites in neurons [110]. Importantly, kinesin does not merely follow predefined tracks, it actively shapes them. Since the stability, growth, and disassembly of microtubules can be modulated by kinesin, it seems that kinesin is building, fixing, and controlling the very paths they traverse [111]. This dual capacity to read the conformational state of the microtubule and to alter it suggests that kinesin can "read" the microtubule state, and it "knows" what specific cargos should be delivered to which specific destinations within the cell [109]. These insights challenge the view of kinesin-microtubule interaction as a simple, stimulus-driven process and do not represent a simple, one-time event. Instead, they reveal a complex, dynamic system where future behavior is influenced by past interactions. The ability of kinesin to "write" information onto the microtubule or store it within its kinesin itself and then "read" this information to inform future behavior suggests an elementary form of learning [109, 110].

While kinesin serves as a compelling example of protein intelligence, certain limitations must be considered. One key criticism is that, at present, the notion of 'learning' in proteins remains largely metaphorical and lacks a rigorous theoretical foundation. Unlike neural networks, which are explicitly designed to learn from data, proteins do not have a dedicated mechanism for learning. However, it is important to emphasize that learning in proteins emerges as a property of their dynamic and adaptive nature rather than a predefined function. Another potential concern is that the global integration of structure and function in kinesin may limit its evolvability. In contrast, modular systems, such as synthetic machines, are more amenable to evolutionary changes, as modifications to one component do not necessarily disrupt the entire system. In contrast, changes to the structure of kinesin could have far-reaching effects, which can potentially compromise its function [112]. However, this limitation may be offset by the ability of the protein to adapt to environmental changes, which provides a selective advantage in dynamic cellular environments.

In addition, the possibility of the presence of multiple quasi-equilibrium states that arise from the rich dynamics of frustrated systems (i.e., systems that lack a single minimal energy state) [113] enables proteins to rapidly adapt to evolutionary pressures. This structural frustration allows for a high degree of conformational flexibility, meaning that a specific mutational event can trigger a swift shift in the functional landscape of a protein [114]. In other words, a 'holistic' entity that does not rely on the separate optimization of individual 'pieces' can achieve a global and immediate adaptive response to external perturbations. This adaptability arises from the inherently frustrated nature of the energy landscape of a protein, where multiple configurations occupy local energy minima without a single optimal state (unlike artificial machines, which operate based on predefined, optimized configurations).

Allostery and conformational signaling

Allostery is a key mechanism underlying protein intelligence, which enables proteins to undergo conformational changes in response to ligand binding. These changes are not localized to the binding site but propagate across the protein and link distant functional sites. This integration of information allows proteins to regulate their activity

dynamically, adapt to environmental changes, and perform complex tasks.

IDRs play a crucial role in allostery by providing conformational flexibility. This flexibility enables IDRs to act as molecular switches that can modulate the activity of the protein in response to external stimuli [115, 116]. For example, in transcription factors, IDRs mediate protein-DNA interactions by folding into specific conformations upon binding to DNA. This conformational signaling allows the protein to recognize and bind to specific DNA sequences, which integrates external stimuli into its functional repertoire [117]. Similarly, the IDP 4E-BP1 (eukaryotic translation initiation factor 4E-binding protein 1), which regulates translation initiation, undergoes a disorder-to-order transition upon binding to its target, eIF4E (eukaryotic translation initiation factor 4E). This transition is modulated by phosphorylation, which alters the conformational ensemble of 4E-BP1 and regulates its binding affinity [118]. In kinases, IDRs regulate enzyme activity by modulating access to the active site, which enables the protein to respond to changes in cellular signaling pathways [119, 120]. Thus, conformational signaling is a hallmark of protein intelligence that enables proteins to integrate information from multiple sources and to adapt their behavior accordingly. As discussed earlier, in the case of hemoglobin, the integration of information is mediated by networks of interacting residues, which transmit signals between distant functional sites. These networks are not static but are dynamically rewired in response to environmental changes and enable the protein to adapt its behavior. Similarly, in GPCRs, ligand binding induces conformational changes that propagate across the protein and activate downstream signaling pathways [121]. This dynamic rewiring allows GPCRs to respond to a wide range of ligands and integrates information from multiple sources.

A key limitation of the allostery and conformational signaling framework is that the mechanisms underlying allostery are poorly understood, particularly in large, multi-domain proteins [122]. For instance, it is often unclear how conformational changes are transmitted across long distances or how multiple allosteric sites interact to modulate protein activity. However, advances in computational modelling and experimental techniques are providing new insights into these mechanisms [123]. Another challenge is that the concept of conformational signaling is often oversimplified, with proteins depicted as having a few discrete conformational states. In reality, proteins exist in a continuum of conformational states, which makes it difficult to define clear signaling pathways [62]. However, this complexity may not be a limitation but rather a functional advantage that enables proteins to respond to a wide range of stimuli and perform complex biological tasks.

Conformational memory and learning in proteins

The concept of protein intelligence extends beyond immediate responses to environmental stimuli and encompasses the ability of proteins to 'remember' past events and adapt their behavior accordingly. This phenomenon, known as conformational memory [124] is also a hallmark of protein intelligence. However, we would like to clarify that the form of "memory" we propose in proteins does not necessarily require evolutionary timescales for its expression. Rather, we suggest that certain proteins, by virtue of their conformational landscape and interaction networks, may act as associative memory systems that are capable of encoding transient or persistent changes in state in response to environmental stimuli. This is conceptually analogous to the Hopfield network model, where memory emerges from the dynamics of a complex system without requiring genomic changes [125]. Such systems can retain stimuli-specific conformational states or PTMs that bias future responses, which we term "minimal memory." A biological application of this concept has already been suggested in the context of cellular signaling and epigenetics, where persistent states are maintained without alteration to the genome [126]. Thus, the role of evolution is to give rise to the architecture of the protein, the "empty system", which is capable of such dynamic behavior. The actual encoding of memory can occur on much shorter timescales, within the lifetime of the cell or organism, as a product of biochemical interaction rather than gene acquisition.

There is a critical and foundational distinction between evolutionary encoding and real-time learning. Simply exhibiting a genetically encoded behavior does not in itself qualify as "learning." Our argument does not rest on the notion that proteins learn in the same sense that neural networks do, but rather that some proteins may exhibit behaviors consistent with minimal learning-like processes, such as plastic responses shaped by prior stimuli and stored as altered conformational states or molecular interaction patterns. As discussed earlier, the concept of associative memory in dynamical systems (exemplified by the Hopfield model) does not require evolutionary encoding for memory formation. In biological contexts, memory-like behavior can emerge from modulations in interaction strengths or conformational states that persist beyond the initial stimulus and influence future responses. The example in reference [126] illustrates this well: cellular architectures can be trained (by modifying the strength of cell-cell interactions) to produce

different tissue organizations from the same starting conditions. These modifications can occur on short timescales, and the resulting state represents a latent attractor within the phase space of the system. Importantly, these attractors are not hardwired by evolution; they become manifest through system dynamics triggered by external inputs. Analogously, we suggest that certain proteins (especially those involved in signaling, regulation, or epigenetic control) may access latent configurations that encode past environmental exposure without requiring new genetic information. Thus, while we do not argue that kinesin or other proteins literally "learn" in the cognitive sense, we propose that their conformational dynamics and context-sensitive behavior may constitute a minimal, molecular form of learning, as defined by the persistence of altered responses based on prior stimuli.

Kinetic allostery and allokairy

Kinetic allostery refers to the phenomenon where conformational changes induced by a stimulus persist long after the stimulus is removed [127]. This 'memory' of past events enables proteins to adapt their behavior based on prior experiences, which is a key feature of intelligent systems. The term allokairy (from the Greek *allos*, meaning 'other,' and *kairos*, meaning 'time') has been coined to describe this temporal aspect of allostery, where proteins retain information about past interactions and use it to modulate future activity [128]. Kinetic allostery is driven by the slow relaxation of protein conformations following a stimulus. Unlike classical allostery, where conformational changes are rapidly reversible, kinetic allostery involves metastable states that persist for extended periods [129]. These states are stabilized by interactions within the core and periphery of a protein and create a 'memory' of the stimulus. As discussed earlier, in *E. coli* lactose permease, a lipid-induced conformational change persists even after the lipid is removed [31]. This memory is encoded in the structure of the protein, which remains in a metastable state that influences its future interactions with lipids. Similarly, in human glucokinase, a hyper-activated state induced by substrate binding persists long after the substrate is released, modulating the activity of the enzyme over time [130].

The ability to retain information about past stimuli has important implications for protein function. For example, in signaling pathways, kinetic allostery enables proteins to integrate information over time and allows cells to respond to transient signals in a context-dependent manner [131]. This temporal integration is crucial for processes such as cell differentiation, where cells must 'remember' past signals to make fate decisions. In metabolic regulation, kinetic allostery allows enzymes to adapt their activity based on past substrate availability. For example, in the ATP binding cassette transporter BtuC2D2, a hyper-activated state induced by ATP binding persists long after ATP is hydrolyzed, which enables the transporter to efficiently import vitamin B12 under fluctuating energy conditions [132].

While some allosteric sites are readily accessible and observable in static structures, others are cryptic or transient, which become visible only under certain conformational states or environmental conditions [133, 134]. For example, the well-known allosteric site in HIV-1 integrase is exposed in the native structure and has been successfully targeted, whereas cryptic allosteric pockets in kinases or GPCRs often require conformational rearrangements for detection and targeting. Recent advances in experimental and computational methods are increasingly helping to identify such elusive sites. NMR spectroscopy has been used to detect dynamic regions and conformational exchanges that suggest the presence of allosteric sites [135]. Cryo-electron microscopy (cryo-EM) has provided unprecedented structural detail for large, dynamic protein complexes, such as GPCRs [136] and proteasomes [137]in multiple conformational states. Additionally, enhanced sampling MD simulations (such as metadynamics, accelerated MD, etc.) allow for the exploration of protein conformational landscapes and are able to reveal transient pockets that are not evident in crystallographic structures [138–140]. These methods are proving invaluable in mapping allosteric networks and in designing modulators that can access and stabilize specific protein conformations [141]. In parallel, machine learning (ML)-based techniques are being increasingly employed to predict allosteric sites and conformational transitions. However, a key bottleneck remains the limited availability and diversity of high-quality training datasets, particularly for underrepresented protein families and cryptic allosteric mechanisms. This limitation constrains the generalizability and robustness of current predictive models [142].

One criticism of kinetic allostery is that the mechanisms underlying metastable states are poorly understood. For example, it is often unclear how conformational changes are stabilized over long periods or how these states are eventually reset. Another criticism is that the concept of allokairy is often conflated with classical allostery, leading to confusion about its unique features. While both phenomena involve conformational changes, kinetic allostery is distinguished by its temporal persistence and functional implications. Clarifying these distinctions will be essential for advancing our understanding of protein memory.

Prion-like proteins and heritable traits

Prion-like proteins provide another example of protein memory, which exhibits self-templating conformations that

induce heritable traits. Prions are best known for their role in neurodegenerative diseases, such as Creutzfeldt-Jakob disease, where misfolded proteins propagate their conformation to normal proteins, leading to pathological aggregation [143]. However, recent studies have shown that prion-like behavior is not limited to disease states but is also involved in normal cellular processes that include memory storage and information processing. Prion-like proteins adopt self-templating conformations that are stable and heritable. These conformations are propagated through interactions with other proteins and create a 'memory' of past events. For example, in the yeast prion [PSI+], the misfolded form of the Sup35 protein propagates its conformation to normal Sup35 molecules, inducing a heritable change in protein function [144]. The stability of prion-like conformations is mediated by interactions within the core and periphery of the protein. In the mammalian prion protein PrP, the misfolded form (PrPSc) is stabilized by interactions between β-sheet-rich regions, which creates a template for further misfolding [145]. This self-templating behavior enables prion-like proteins to retain information about past events and propagate it to future generations.

Prion-like proteins also play a role in information processing and memory storage. For example, in neurons, prion-like proteins are involved in the formation and maintenance of synaptic connections, which underlie learning and memory [146]. The self-templating behavior of these proteins enables them to 'remember' past synaptic activity and influence future neuronal responses. In gene regulation, prion-like proteins modulate the expression of genes in response to environmental changes. For example, in yeast, the [PSI+] prion induces a heritable change in gene expression, which enables cells to adapt to fluctuating nutrient conditions. This epigenetic regulation provides a mechanism for cells to 'remember' past environmental conditions and adjust their behavior accordingly [147]. A recent study has identified amyloid-like protein structures that are stably inherited in wild-type *Caenorhabditis elegans* and influence phenotypic traits [148]. Disruption of these structures through genetic, environmental, or pharmacological interventions leads to developmental phenotypes that can be epigenetically transmitted to subsequent generations. Genetic and proteomic analyses further reveal that the 26 S proteasome and its conserved regulatory components are essential for maintaining these heritable amyloids across generations and ensure proper differentiation of germ cells.

While prion-like proteins offer a compelling example of protein memory, they also face significant criticism. One key concern is that the distinction between pathological and functional prion-like behavior is often unclear. While some prion-like proteins play a role in normal cellular processes, others are associated with disease states [149]. Additionally, the mechanisms underlying prion-like behavior remain poorly understood. Questions persist about how prion-like conformations are initiated and how they propagate within cells [150]. Gaining deeper insights into the factors that govern prion function and mechanisms will be essential for our understanding of protein memory.

Posttranslational modifications as means for memory imprinting

The fact that posttranslational modifications (PTMs, i.e., reversible or irreversible chemical changes of a polypeptide chain that occur after its translation from DNA) have multiple crucial roles in the regulation of protein structure and function is unquestionable [26, 151–153]. Numerous PTMs are known, with at least 300 occurring physiologically [154]. According to recent estimates, there are more than 400 different types of PTMs [155]whereas the UniProt database lists more than 650 PTMs [156]and the PTM inventory continues to increase [157].

PTMs are highly diverse and range from the enzymatic cleavage of peptide bonds to the covalent addition of specific chemical groups, lipids, carbohydrates, or even entire proteins to amino acid side chains, with some PTMs (e.g., phosphorylation) being reversible by the action of specific deconjugating (or de-modifying) enzymes. These chemical modifications of amino acid side chains extend the range of their structures and properties, thereby diversifying the structures and functions of proteins. Moreover, the interplay between modifying and de-modifying enzymes represents an important means for the rapid and economic control of the functions of many proteins [152]. Taking PTMs into account, we could estimate that proteins can use more than 140 chemically distinct residues, despite the fact that DNA typically encodes only 20 primary amino acids. As a result, the proteome size and complexity are dramatically increased well beyond what is expected from the analysis of encoding genomes [152, 158, 159].

While, at least in principle, all amino acid side chains can undergo various PTMs, most often protein PTMs are found at side chains that can act as either strong (C, M, S, T, Y, K, H, R, D, E) or weak (N, Q) nucleophiles, with the remaining residues (P, G, L, I, V, A, W, F) being rarely involved in covalent modifications of their side chains. PTMs can dynamically alter the properties of amino acids according to developmental and physiological requirements and allow proteins to rapidly adapt to changing cellular conditions [160, 161]. Furthermore, PTMs have been described not only for amino acid side chains but also for the protein backbone [152]. The importance of PTMs is further highlighted by the fact that in higher eukaryotes, up to 5% of the genome is estimated to encode enzymes dedicated to

the PTMs of the proteome [152]. Additionally, PTMs are closely linked to IDRs, as several types of modifications (such as phosphorylation, acetylation, protease digestion, ubiquitination, fatty acid acylation, and methylation) have been observed to preferentially occur within IDRs [151, 162–167]. Recently, by combining the comprehensive structural predictions from AlphaFold2 with large-scale proteomics data on PTMs, it was revealed that, except for ubiquitination and, to a lesser extent, acetylation, various PTMs such as phosphorylation, sumoylation, methylation, and O-GlcNAc/O-GalNAc glycosylation are significantly enriched in IDRs [168]. Interestingly, the association of ubiquitination and acetylation with ordered regions was observed almost exclusively at non-regulatory sites. When the analysis was restricted to PTM sites with known regulatory functions, this correlation disappeared for ubiquitination and was even reversed for acetylation [168]. Moreover, the study highlighted that short IDRs embedded within large ordered domains are particularly enriched in functionally relevant PTMs [168].

PTMs, which can occur at any stage of the lifecycle of the protein (i.e., before the final folding steps, shortly after biosynthesis, or after folding and localization are completed), are important regulatory agents that modulate protein folding and conformational stability. They play a crucial role in targeting proteins to specific subcellular compartments, mediating interactions with partners, and regulating functional states, such as catalytic activity in enzymes or signaling functions in proteins involved in signal transduction pathways [153, 158]. The functional significance of PTMs is further underscored by the fact that nearly all proteins are subject to modifications, with the vast majority undergoing some form of PTM [169].

Since any amino acid residue can undergo PTMs, it is not surprising that some proteins are regulated by multiple different types of PTMs, not only mediating individual functions but also acting in concert to modulate overall protein activity and stability, as well as fine-tune molecular interactions [170]. One of the most well-known examples of multi-PTM regulation is found in histones, a family of nuclear IDPs that undergo a diverse array of modifications, including acetylation, ADP-ribosylation, butyrylation, crotonylation, lactylation, malonylation, methylation, phosphorylation, propionylation, SUMOylation, and ubiquitination. These different modifications are collectively known as the 'histone code', which influences histone-DNA and histone-histone interactions, thereby controlling nucleosome stability and regulating the intra-nucleosomal interactions [171, 172]. While the N-terminal domains of core histones are known to contain an extraordinary number of PTM sites, over 30 modifications have been identified within their core domains [173]. The PTM regulatory machinery consists of three main components: 'Writers' are the enzymes that catalyze the addition of PTMs to protein substrates, 'Erasers' are the enzymes that remove PTMs and ensure their reversibility, and 'Readers' are the proteins that recognize specific PTMs and transduce PTM-dependent signals and functions [174, 175].

Beyond their well-known roles in protein regulation, PTMs also serve as a mechanism for protein memory imprinting, which provides a molecular means for encoding conformational memory. In psychology, memory imprinting refers to the rapid learning of the characteristics of a stimulus as a result of exposure. Analogously, PTMs modulate protein functionality and responsiveness by inducing specific conformational changes and influencing the dynamic behavior of structural ensembles in response to particular signals or stimuli. This enables proteins to 'remember' past events and adapt their behavior accordingly. Such conformational memory can be PTM-dependent, as PTMs incorporated by 'Writers' persist for a time, being recognized by specific 'Readers' before their removal by 'Erasers'. Thus, for "protein intelligence", PTMs represent a means of creating and maintaining conformational memory.

Furthermore, for multi-PTM proteins (i.e., proteins that are modified at multiple sites by various PTMs simultaneously), there is also a PTM crosstalk that plays a crucial role in defining the combinatorial action of multiple PTMs for higher-order regulation. This crosstalk adds an additional layer of functional regulation in a protein, which significantly expands the information content of the proteome [176]. PTM crosstalk can be either 'positive', where one PTM facilitates the regulation of another, or 'negative', where one PTM inhibits the function of another [177]. This phenomenon occurs at both intra-protein and inter-protein levels, with modifications taking place within the same protein or across separate proteins, respectively [174, 176–178]. From the perspective of protein intelligence, PTM crosstalk serves as a fundamental mechanism for enhancing, controlling, and regulating protein memory imprinting. For instance, intra-protein PTM crosstalk enables an individual protein to integrate multiple PTM signals, generating a complex, intertwined molecular memory that allows it to function as a signaling hub. Similarly, inter-protein PTM crosstalk facilitates a form of collective memory, where a PTM on one protein influences the regulation of a PTM on another, which enables proteins to coordinate responses within complex cellular networks.

Interestingly, PTM-driven protein memory imprinting can be directly linked to, or even serve as a defining factor in, memory formation during visual imprinting. Studies have shown that learning and memory formation are associated with dynamic changes in phosphorylation patterns of the non-receptor tyrosine kinase Src in the intermediate

medial mesopallium (IMM) of the domestic chick [179]. Src activity is tightly regulated by phosphorylation, with phosphorylation at Tyr-416 leading to activation (416P-Src) and phosphorylation at Tyr-527 resulting in inhibition (527P-Src). Notably, elevated levels of the active 416P-Src correlate with the predisposition of a chick to learn, whereas an increase in the inhibited 527P-Src form occurs as a consequence of learning [179]. These shifts in 416P-Src and 527P-Src levels during learning and imprinting show how interconnected intra-protein and inter-protein PTM crosstalk underpins both individual and collective protein memory imprinting.

Moonlighting and metamorphic proteins as a litmus test of the Idea that proteins have memory

A compelling conceptual demonstration of protein memory could be imagined in the form of a hypothetical IDP that folds into a helicase under conditions associated with DNA replication, but alternatively adopts an active kinase conformation in response to high salt stress. While this scenario is entirely speculative, nature offers multiple real-world parallels in the form of moonlighting proteins, which are proteins capable of switching between distinct, often unrelated functions depending on cellular context or environmental conditions [180–184]. Importantly, the multifunctionality of moonlighting proteins does not arise from mechanisms such as alternative RNA splicing, gene fusions, DNA rearrangements, PTMs generating isoforms, or the presence of multiple structural domains [185]. Initially thought to be rare exceptions, moonlighting proteins are now recognized as widespread across all domains of life, including bacteria, archaea, protozoa, fungi, insects, worms, fish, reptiles, birds, mammals, plants, and even viruses [184, 186]. For example, the MultifacetedProtDB database catalogs 1103 multifunctional human proteins [187]. Moonlighting proteins span a wide range of functional categories: some enzymes also serve as cytoskeletal components or proteasome subunits; others act as DNA stabilizers, receptors, secreted cytokines, structural proteins, or transcription factors [184]. A striking example is ε-crystallin in birds and crocodiles, which in the eye functions as a major structural protein essential for lens transparency and integrity, while it also performs the catalytic role of lactate dehydrogenase, an enzyme that mediates the reversible conversion of pyruvate to lactate [188]. Another example is the iron–sulfur enzyme aconitase, which catalyzes the interconversion of citrate to isocitrate via a cis-aconitate intermediate. In addition to its metabolic role, aconitase also functions as an iron-dependent regulator of mitochondrial oxidative metabolism and erythropoiesis [189]. Furthermore, in response to decreased cellular iron concentrations, the iron–sulfur cluster in its active site is lost, triggering conformational changes that convert aconitase into an RNA-binding protein. In this alternative form, it regulates the expression of genes encoding proteins involved in iron uptake [190–192]. Similarly, the moonlighting glycolytic enzyme rabbit phosphoglucose isomerase also performs diverse roles and can act as an autocrine motility factor, a differentiation mediator, and a neuroleukin [193]. Moonlighting is not limited to enzymes; other reported functional combinations among moonlighting proteins include chaperone and cytokine, ribosomal component and transcription factor, DNA-binding protein and extracellular matrix component, receptor and transcription factor, and transmembrane channel and regulator of other channels [184]. A notable example of moonlighting in highly disordered proteins is provided by alarmins, which, under conditions of stress, infection, or injury, shift from their normal physiological roles to functions associated with immune alert signaling, regulation of gene expression, maintenance of cellular homeostasis, wound healing, inflammation, allergy, autoimmunity, and oncogenesis [180, 194, 195]. Another protein, α-synuclein, is a highly disordered alarmin that has a remarkably broad functional spectrum and pronounced multipathogenicity, i.e., the ability to contribute to the pathogenesis of various disorders collectively known as synucleinopathies [196]. This protein serves as a stark counterexample of the classical "one protein-one function" model. Beyond its synaptic functions, α-synuclein exhibits molecular chaperone activity, binds a variety of interaction partners, and plays roles in lipid metabolism, membrane biogenesis, and neuroimmune regulation [196]. It is even implicated in modulating gastrointestinal immunity [197].

Metamorphic or fold-switching proteins represent another category of proteins that exhibit structural and functional memory. These proteins can adopt two or more distinct folded conformations and reversibly switch between them in response to cellular stimuli [198]. In this way, metamorphic proteins achieve moonlighting behavior through fold-switching [199]. For instance, under oxidizing conditions, glutathione oxidase undergoes a conformational change and functions as a chloride channel [198]. Similarly, the chemokine lymphotactin can exist in two structurally and functionally distinct forms: one as a monomer with the canonical chemokine fold, comprising a flexible N-terminus, a three-stranded β-sheet, and a C-terminal α-helix stabilized by a disulfide bond, which acts as an agonist of the GPCR XCR1; and another as a β-sandwich dimer, in which each monomer adopts a novel four-stranded β-sheet conformation that binds with high affinity to cell-surface glycosaminoglycans [200]. Notably, the transitions between these alternative folds are completely reversible and are tightly regulated by environmental cues [198, 199].

In conclusion, the multifunctionality of both moonlighting and metamorphic proteins is highly context-dependent, with their ability to switch between functions being directly triggered by changes in the cellular environment.

Liquid-liquid phase separation and collective intelligence of proteins

In his seminal review published in 2017, Simon Alberti pointed out: *"Evidence for the collective behavior of proteins has been around for many decades, but its significance for cell biology has only become clear in the past couple of years"* [201]. Indeed, recent years have seen a surge of interest in liquid-liquid phase separation (LLPS), coacervation, biomolecular condensates (BCs), and membrane-less organelles (MLOs). These topics have gained prominence in molecular and cellular biology as key players in intracellular space organization [201–211] and as a distinct mode of signal transduction [212]. It is now widely recognized that intrinsic disorder plays a central role in LLPS, as well as in the biogenesis of MLOs and BCs [213–218]. This is hardly surprising, given the fact that IDPs and IDRs are 'edge of chaos' systems that exhibit emergent behavior driven by complex self-organization processes and lead to the formation of novel structures, patterns, and functional properties [94, 219, 220]. In essence, MLOs, BCs, and colloids represent a manifestation of the collective behavior of protein crowds.

It is tempting to interpret LLPS and the related biogenesis of MLOs/BCs through the lens of protein intelligence. From this perspective, LLPS may be viewed as a process of selective assembly of complex intelligent proteins into MLOs, BCs, or colloidal structures, which, in turn, form a higher-order system that exhibits collective intelligence. In other words, this process aligns with the dialectical materialism concept of the 'transition of quantitative changes into qualitative ones', i.e., when the accumulation and interactions of individual intelligent proteins reach a critical threshold, a qualitative leap, LLPS, is triggered. This transition results in the emergence of MLOs/BCs with collective intelligence, a novel property that was absent at the level of individual proteins and may exceed the sum of the intelligences of its components.

MLOs, BCs, and colloids are not passive aggregates but dynamic systems that are capable of solving problems, adapting and learning from a changing environment, identifying patterns and interaction partners, and anticipating future changes. Moreover, they do not merely respond to external conditions, but they actively shape and modify their surroundings. These properties, which are inherent to intelligent biological systems, become further enhanced in MLOs/BCs due to the emergence of collective intelligence and amplify their capacity for functional adaptability and decision-making beyond what is achievable by single protein molecules.

For some proteins, the formation of condensates serves as a means to enhance functional efficiency, with condensates acting as biochemical reaction vessels where enzymatic reactions occur more efficiently than in bulk solution [201]. This concept of collective wisdom in cellular metabolism is exemplified by the metabolon model proposed in 1987 by Paul Srere [221, 222]which suggests that metabolic compartmentalization, i.e., the clustering of metabolic enzymes, dramatically increases enzymatic reaction efficiency [223–225]. A striking example of this phenomenon can be found in bacteria, where the selective sequestration of mRNA into bacterial ribonucleoprotein bodies (BR-bodies) that contain the RNA degradosome enhances RNA decay [226–228]. Similarly, bacterial RNA polymerase clusters [229] have been linked to nucleoid organization [230]while microdomains of the polar organizing protein PopZ, which are formed at both the stalk (old) and swarmer (new) poles of *Caulobacter crescentus*, serve as LLPS hubs for various cellular processes [231–234]. Additionally, the condensates of the divisome protein FtsZ play a critical role in bacterial cell division by forming the Z-ring structure at the bacterial midcell [235]initiating cytokinesis, while being actively excluded from the bacterial nucleoid [236].

Notably, many MLOs, BCs, and colloids appear in cells under stressful conditions [237]suggesting that their biogenesis represents a response of cellular intelligent proteins to stress and leads to the formation of novel entities that aid in stress mitigation. The most well-known example of this phenomenon is stress granules (SGs), which are MLOs formed in the cytoplasm of eukaryotic cells in response to various types of stress. SGs contain RNAs, RNA-binding proteins, and translation regulators [238–242]. They play key roles in cell survival under stress by carrying out functions such as translation arrest, RNA and protein protection, energy conservation, mRNA triage, and cell signaling [243–245].

The collective intelligence of MLOs, BCs, and colloids is further demonstrated by their ability to alter their microenvironment and selectively interact with new molecular partners. An example of this adaptability is the modulation of solvent properties within condensates, which influences the partitioning of various biomolecules (proteins, nucleic acids, small organic molecules, metal ions, etc.) between the condensate and its surroundings [246]. In other words, the unique microenvironment created by LLPS determines which molecules are preferentially incorporated into or excluded from the condensate. This principle is supported by findings that microenvironments formed through phase separation regulate the dynamic distribution of bacterial

division protein FtsZ, which influences its functional activity during cell division [236].

An important link between PTM-driven memory imprinting in individual proteins and the emergence of collective intelligence in condensates arises from the observation that LLPS efficiency and MLO/BC/colloid biogenesis are often controlled by PTMs [247–256]. In general, the formation and dissolution of BCs through LLPS, as well as the emergent properties of these condensates, are regulated by PTMs such as phosphorylation, acetylation, and ubiquitination [257]. Certain PTMs, including phosphorylation and methylation, can exert bidirectional effects on LLPS, either promoting or inhibiting phase separation depending on the context [256]. For example, the LLPS potential of the RNA-binding protein FUS (Fused in Sarcoma) is dramatically reduced by phosphorylation of its prion-like, low-complexity (LC) domain [258]. Similarly, in TDP-43, a single phosphorylation event within the globular N-terminal domain (NTD) significantly diminishes its ability to undergo LLPS [259]. In contrast, multisite phosphorylation of full-length tau protein, which increases the polarization of its charge distribution, has been shown to promote LLPS [260, 261]. Conversely, phosphorylation patterns that reduce charge polarization inhibit tau LLPS [260]. The LLPS potential of tau is also modulated by other PTMs: for example, hyperacetylation suppresses LLPS [262]while ubiquitination can either enhance or inhibit LLPS in a site- and cofactor-dependent manner [263]. Importantly, this regulation is bidirectional, i.e., LLPS can also influence PTMs [257]. For example, some ubiquitin ligase substrates, such as the substrate SPOP (Speckle-type POZ protein), which functions as a tumor suppressor, are activated within phase-separated condensates, leading to its ubiquitination and proteasomal degradation [264–266]. These connections suggest that the regulatory mechanisms governing protein memory at the individual level also play a role in shaping the behavior and intelligence of MLOs and BCs, further reinforcing the intricate interplay among PTMs, phase separation, and collective cellular decision-making.

Parallels with critical States in complex systems

The behavior of intelligent proteins can be understood through the lens of critical states, a concept borrowed from physics and complexity science. Critical states represent a balance between order and disorder, where systems exhibit maximal adaptability and responsiveness to environmental changes [267]. In proteins, this balance is highlighted in the interplay between the ordered, crystalline phase (the core) and disordered, fluid phase (the periphery) [268]. This duality enables proteins to maintain their structural integrity while adapting to external stimuli, a hallmark of intelligent behavior. Proteins often undergo conformational transitions in response to environmental changes, such as ligand binding or changes in pH [269]. These transitions are not random but are highly coordinated and involve the propagation of conformational changes across the structure of the protein. This behavior is reminiscent of phase transitions in physical systems, where small changes in external conditions lead to large-scale reorganizations, such as in hemoglobin [19–21]. This cooperative behavior is a hallmark of criticality, where the system operates at the boundary between order and disorder. Similarly, in prion-like proteins, the transition from a normal to a misfolded state represents a critical transition, where small changes in environmental conditions lead to large-scale conformational changes [270].

In the following sub-sections, we aim to develop a unified framework for further understanding protein intelligence by drawing parallels between protein dynamics and critical states observed in other complex systems, such as ecosystems, gene regulatory networks, and neural networks.

Ecosystems

Ecosystems are complex systems that exhibit critical behaviour, which balances stability and adaptability. For example, in tropical rainforests, the interplay between diverse species and their environment creates a dynamic equilibrium, where small changes in environmental conditions can lead to large-scale reorganizations [271]. This behavior is reminiscent of core-periphery protein dynamics, which enables the protein to adapt to environmental changes while maintaining its structural integrity. The concept of ecological resilience (the ability of an ecosystem to recover from disturbances) provides a useful analogy for understanding protein intelligence [272]. Just as ecosystems rely on a balance between stability and adaptability to maintain their function, proteins rely on the interplay between order and disorder to integrate information and adapt their behavior.

Gene regulatory networks

Gene regulatory networks (GRNs) are another example of complex systems that exhibit critical behavior. GRNs consist of interconnected genes and regulatory elements that control gene expression in response to environmental changes [273]. The balance between stability and adaptability in GRNs is essential for maintaining cellular function and enabling developmental processes. For example, in stem cell differentiation, GRNs undergo critical transitions that allow cells to adopt different fates in response to environmental cues [274]. This behavior is reminiscent of

protein dynamics, where conformational transitions enable the protein to adapt its function in response to external stimuli. The parallels between GRNs and proteins highlight the universality of critical behavior in biological systems. To better ground this theoretical analogy, we can draw inspiration from computational models such as graph neural networks (GNNs), which are used to model complex molecular structures, including PPI networks. GNNs can capture the intricate relationships within biological systems, much like how GRNs regulate gene expression. Additionally, dynamic Bayesian networks (DBNs) can be applied to model signaling cascades within cellular networks, which can help to simulate the dynamic responses of proteins to external and internal stimuli.

Neural networks

Neural networks, both biological and artificial, exhibit critical behavior that enables them to process information and adapt to changing conditions. In the brain, the balance between excitatory and inhibitory signals creates a dynamic equilibrium, where small changes in input can lead to large-scale reorganizations [275]. This behavior is essential for learning and memory and enables the brain to integrate information and adapt its behavior accordingly. The parallels between neural networks and proteins highlight the universality of critical behavior in intelligent systems. Just as neural networks rely on the interplay between excitatory and inhibitory signals to process information, proteins rely on the interplay between order and disorder to integrate information and adapt their behavior. Computational approaches, such as deep learning models and reinforcement learning, can serve as analogs for protein systems, where artificial neural networks (ANNs) mimic the adaptability and decision-making processes that occur in biological systems. This can offer insights into how proteins might integrate information and adjust their conformation based on external signals.

Implications of protein intelligence for biotechnology and medicine

The concept of protein intelligence, where proteins are viewed as dynamic, information-processing entities that are capable of adapting to their environment, opens up exciting new directions in research. Proteins that can respond to signals, shift conformations, and perform context-dependent functions can offer powerful tools for solving complex biological problems. Researchers can rethink traditional approaches to protein engineering, drug development, synthetic biology, etc. We now briefly discuss how understanding proteins as intelligent systems can help create more selective and adaptable drugs, design proteins with customized properties for industrial or therapeutic use, as well as build synthetic biological systems that behave in more life-like, decision-making ways. These advances could potentially transform the way we diagnose, treat, and even prevent disease.

Protein engineering

The principles of protein intelligence can revolutionize protein engineering by helping in the design of synthetic proteins with better functionality [276]. Traditional protein engineering focuses on optimizing structures for specific tasks, such as enzyme catalysis or ligand binding. However, this approach often fails to account for the adaptive nature of proteins, which limits their performance in complex environments. The incorporation of core-periphery dynamics and conformational memory into protein design can help create proteins that adapt to novel environments and perform complex tasks. For example, synthetic proteins with IDRs could exhibit enhanced flexibility, which enables them to interact with diverse binding partners and respond to environmental changes. Similarly, proteins designed with allosteric networks could integrate information from multiple sources, which can enable them to perform context-dependent functions [277].

One of the major challenges in using protein intelligence for protein engineering is the difficulty of predicting and controlling the dynamic behavior of proteins. Since proteins exist in a continuum of conformational states, designing them to exhibit specific, predictable behaviors will be a complex task [278]. Another challenge is the inherent trade-off between stability and adaptability. Proteins with high conformational flexibility may be more adaptable but less stable, which limits their practical applications. Balancing these issues will demand a deeper understanding of the principles underlying protein intelligence, as well as advances in computational and experimental techniques. Despite these challenges, the basic principles of protein intelligence (without explicitly using the term) are already being applied in industry and medicine. For instance, enzyme engineering has been used to create enzymes with enhanced catalytic activity and substrate specificity for their use in industrial processes such as biofuel production and waste degradation [279]. Similarly, therapeutic proteins designed with allosteric networks could exhibit enhanced efficacy and specificity, which can enable their use in targeted therapies for cancer and other diseases [280].

Drug design and discovery

Understanding the fundamentals of protein intelligence can also improve drug design by helping in the development of allosteric modulators (drugs that target sites other than the active site) [281]. Allosteric modulators offer several advantages over traditional drugs, such as higher specificity and fewer side effects. For example, allosteric inhibitors of kinases have been developed to treat cancer that targets conformational changes that regulate enzyme activity [282]. Similarly, allosteric modulators of GPCRs are being explored for the treatment of neurological disorders, which target conformational changes that modulate receptor signaling [283]. The principles of protein intelligence are particularly relevant for precision medicine, where treatments are tailored to individual patients based on their genetic profiles [284]. For example, allosteric modulators could be designed to target specific conformational states of proteins associated with disease, which can enable more precise and effective treatments [285]. Similarly, drugs that exploit conformational memory could be used to modulate long-term protein behavior. This may offer new approaches for chronic diseases such as diabetes and neurodegenerative disorders.

However, allosteric modulators are difficult to design and optimize. One major challenge is the complexity of allosteric networks, which involve multiple interacting residues and conformational states. Predicting how a drug will interact with these networks will require a detailed understanding of protein dynamics. Another challenge is the lack of structural data available for allosteric sites [286].

Synthetic biology

The concept of protein intelligence has important implications for synthetic biology, where researchers aim to design and construct new biological systems with novel functions. The incorporation of the principles of protein intelligence into synthetic systems can help create proteins and pathways that exhibit emergent properties, such as self-organization and adaptability. For example, synthetic proteins with allosteric networks could be used to create biosensors that respond to environmental changes in real-time [287]. Similarly, proteins with conformational memory could be used to create biological circuits that store and process information, which can help in the development of synthetic cells with intelligent behaviors [288].

One challenge of the use of protein intelligence in synthetic biology is the complexity of designing and constructing synthetic systems that exhibit intelligent behaviors. Unlike traditional synthetic biology, which focuses on optimizing individual components, intelligent systems require a holistic approach that considers the dynamic interactions between components. Another challenge is the unpredictability of synthetic systems, which can exhibit emergent behaviors that are difficult to control [289]. For example, synthetic proteins with high conformational flexibility may exhibit unintended interactions, leading to off-target effects. Despite these existing challenges, the principles of protein intelligence are already being applied in synthetic biology. For example, synthetic enzymes with allosteric networks have been used to create metabolic pathways for the production of biofuels and pharmaceuticals [277]. Similarly, synthetic regulatory networks with conformational memory have been used to create genetic circuits that respond to environmental changes, which enable the development of smart materials and biosensors [290].

Protein intelligence and anthropomorphic considerations

Protein intelligence, as discussed in this article, suggests that proteins possess the ability to adapt and learn from a changing environment, memorize, anticipate future changes, solve problems, identify patterns, recognize partners, actively shape or modify their environment when necessary, and control and modulate the behavior of their interaction partners. All these features are clearly anthropomorphic, and they have been present in the scientific literature for decades. The anthropomorphic nature of protein function can be traced back to Hermann Emil Louis Fischer (1852–1919) and his "lock-and-key" model of enzyme-substrate interaction, proposed in 1894, which was based on the concept of specific recognition. It was the idea that an active site of an enzyme precisely fits its substrate, akin to a key fitting into a lock [291]. Later, in 1969, Peter H. von Hippel emphasized the central role of molecular recognition in protein function, stating that extensive experimental evidence had proven "beyond a doubt that there *is* specificity and that there *is* recognition and we hope eventually to come to grips with the structural bases of the interactions upon which the observed specific recognition processes must ultimately depend" [292].

Shortly thereafter, structural and mechanistic principles of protein-protein recognition began to emerge from studies on the insulin dimer, the trypsin-PTI complex, and the α-β oxyhemoglobin dimer, which provide deeper insight into how proteins recognize and interact with each other [293]. Since then, an overwhelming body of research has explored various aspects of protein recognition (as of May 19, 2025, there were 161492 scientific papers containing the term "protein recognition" in PubMed). A similar trend is observed for other anthropomorphic attributes of proteins, such as their ability to control and regulate

cellular processes, modify their partners, and transmit signals. Each of these functions has been extensively studied and described in thousands of research papers, underscoring the long-standing scientific acceptance of proteins as dynamic, decision-making molecular entities.

The ability of a protein to adapt is well illustrated by the induced-fit model of substrate-protein interaction, proposed in 1958 by Daniel E. Koshland Jr. (1920–2007) [294]. This model expanded on Fischer's lock-and-key hypothesis by emphasizing the importance of structural flexibility and suggesting that the active site of an enzyme and its substrate do not necessarily have complementary shapes prior to binding. Instead, the active site of an enzyme undergoes a conformational change upon substrate binding, optimizing the interaction and enhancing catalytic efficiency [12].

A logical extension of this idea was the binding-induced folding concept, in which a disordered protein or protein region folds upon interaction with a specific binding partner. Although this model gained widespread recognition at the turn of the century (i.e., after the subsequent acceptance of the protein intrinsic disorder concept), its conceptual foundation dates back much earlier. In 1969, Peter H. von Hippel had already proposed that *"a protein that exists in solution in a random coil or 'structureless' form might be induced into a specific conformation in order to fit into a specific groove, or to optimize interaction with the sequence of charges on the nucleic acid backbone."* He further suggested that the precise structural adaptation of a "structureless" protein to a specific DNA groove could depend on the sequence of amino acids along its polypeptide backbone [292].

And, of course, for an organism to function properly, all its proteins must behave appropriately, as their misbehavior and dysfunction (manifesting as misrecognition, deregulation, mislabeling, misfolding, or pathological aggregation) are directly implicated in a wide range of human diseases [295–303]. To maintain normal protein behavior and combat proteinopathies caused by misfolded or malfunctioning proteins, nature has evolved an elaborate proteostasis network. This protein-based quality control system includes specialized proteinaceous machines responsible for protein biogenesis, folding, conformational maintenance, and degradation [304–308]. Through this intricate regulatory framework, cells ensure proteome integrity and prevent the accumulation of dysfunctional proteins and mitigate the risks of disease.

Although in all these and many other anthropomorphic actions commonly described in the scientific literature, proteins have been considered active players, these actions were generally not explicitly linked to protein intelligence, apart from a largely metaphorical usage of the term. We hope that the arguments presented in this article offer a new perspective on proteins and their activities by introducing measurable quantities grounded in the mathematical theory of information. In mathematical terms, mutual entropy (a fundamental concept in information theory) is essentially a nonlinear correlation coefficient. Its applicability in protein science extends to various domains, where it can be quantified and computed in biologically relevant contexts such as MD simulations [309] and protein interaction networks [310, 311]. Using these quantitative approaches, we move beyond metaphorical descriptions and establish a rigorous framework for understanding protein intelligence. This framework allows objective assessment of how proteins encode, process, and transmit information in biological systems.

What might constitute a hypothetical "super-intelligent" protein?

While it is not possible to identify a single "most intelligent" protein in a strict empirical sense, especially given the fact that we are proposing a conceptual framework rather than a quantitative scale of intelligence, we can outline characteristics that a hypothetical "highly intelligent" protein might exhibit as part of a thought experiment. Such a "super-intelligent" protein would likely possess a rich landscape of quasi-stable conformational states, which would allow it to encode and integrate multiple environmental cues over time. Crucially, its transition matrix between states would exhibit full reachability, i.e., it could access a wide range of configurations in response to different stimuli, while also retaining memory of previous states through hysteresis or other path-dependent behaviors. Moreover, these transitions would need to strike a delicate balance: they should be robust enough to resist random thermal fluctuations, at the same time finely tuned to respond specifically to biologically relevant stimuli. This would allow the protein not only to adapt, but to modulate its behavior based on prior "experience," satisfying our definition of minimal intelligence. While we do not currently have a concrete, experimentally validated example that fulfills all these criteria, certain allosteric proteins, molecular chaperones, or even transcriptional regulators with known conformational plasticity and memory-like behaviors offer useful preliminary analogs for such exploration. Future work aimed at systematically identifying proteins that approach this theoretical ideal will be highly useful.

General conclusions

Universality is a fundamental pillar of the statistical mechanics of critical phenomena [312, 313]. It enables the formulation of 'Network Thermodynamics', a theoretical framework based solely on the mutual relationships among the components of a system, independent of the constitutive laws that define the specific nature of the system [314]. This universality provides the conceptual bridge necessary to transcend disciplinary boundaries and allows concepts and methods developed in chemical physics to be applied to molecular biology, economics, computer science, or ecology [315]. The elucidation of general principles governing the behavior of mesoscopic systems has been recognized as one of the forefront challenges of 21 st-century science [316]which serves as the primary motivation for applying IIT to protein science. This theoretical approach enables us to discuss "protein intelligence", a concept that may appear paradoxical within conventional definitions of intelligence.

As a closing remark, it is important to emphasize that the concept of 'cell intelligence' (even in non-neural tissues and bacterial life forms) has been explored for decades across diverse biological phenomena, ranging from biofilm formation to cancer dormancy. This concept follows a similar line of reasoning as presented in our work. A model of cell intelligence that places IDP dynamics at its core is elaborated in Csermely et al. [317]. Here, the authors discuss molecular mechanisms underlying cellular learning and demonstrate that conformational memory in IDPs adheres to classical Hebbian learning principles, namely, the progressive strengthening of responses upon repeated stimulation. This molecular Hebbian learning, as well as its counterpart, 'anti-Hebbian' desensitization (forgetting), has been shown to play critical roles in processes such as cancer progression and allergic responses [318]. This body of work further supports our proposition of a minimal form of intelligence based on molecular and conformational memory mechanisms.

Our deliberate effort to present both supporting ('pro') and opposing ('contra') perspectives on this idea is intended to direct the attention of researchers to the systemic nature of our proposal. While our approach offers a broad, unifying framework, it also acknowledges its limitations when addressing finer mechanistic details, which remain within the realm of specific constitutive laws [314]. Nonetheless, we are convinced that defining protein molecules as "intelligent" could open new and productive avenues of research. Shifting the focus of protein science toward emergent phenomena such as ordered/disordered phase transitions and exploring the potential role of 'entropic reservoirs' [319] in structural and MD studies may deepen connections between protein structure and biological function. Our primary goal in this work is to transform the traditionally metaphorical use of "intelligence" in biochemistry into a quantifiable property, while simultaneously proposing the material basis of protein intelligence by identifying fundamental elements such as memory and learning in molecular systems.

Authors' contributions Conceptualization: Timir Tripathi, Vladimir N. Uversky, and Alessandro Giuliani; Literature Search: Timir Tripathi, Vladimir N. Uversky, and Alessandro Giuliani; Data Analysis: Timir Tripathi, Vladimir N. Uversky, and Alessandro Giuliani; Writing – original draft: Timir Tripathi, Vladimir N. Uversky, and Alessandro Giuliani; Writing – review, and editing: Timir Tripathi, Vladimir N. Uversky, and Alessandro Giuliani.

Funding TT acknowledges the Indian National Science Academy (INSA), New Delhi, for INSA Associate Fellowship.

Data availability Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Bruce A, Rebecca H, Alexander J, David M, Martin R, Keith R, Peter W (2022) Molecular biology of the cell: seventh international student edition with registration card. W.W. Norton & Company
2. Zhang X, Zhang J, Wang Y, Wang M, Tang M, Lin Y, Liu Q (2022) Epigenetic modifications and neurodegenerative disorders: A biochemical perspective. ACS Chem Neurosci 13(2):177–184. https://doi.org/10.1021/acschemneuro.1c00701
3. Schmaier AA, Zou Z, Kazlauskas A, Emert-Sedlak L, Fong KP, Neeves KB, Maloney SF, Diamond SL, Kunapuli SP, Ware J, Brass LF, Smithgall TE, Saksela K, Kahn ML (2009) Molecular priming of Lyn by GPVI enables an immune receptor to adopt a

hemostatic role. Proc Natl Acad Sci U S A 106(50):21167–21172. https://doi.org/10.1073/pnas.0906436106
4. Xu D, Phillips JC, Schulten K (1996) Protein response to external electric fields: relaxation, hysteresis, and echo. J Phys Chem 100(29). https://doi.org/10.1021/jp960076a
5. Balduzzi D, Tononi G, Qualia (2009) The geometry of integrated information. PLoS Comput Biol 5(8):e1000462. https://doi.org/10.1371/journal.pcbi.1000462
6. Albantakis L, Barbosa L, Findlay G, Grasso M, Haun AM, Marshall W, Mayner WGP, Zaeemzadeh A, Boly M, Juel BE, Sasai S, Fujii K, David I, Hendren J, Lang JP, Tononi G (2023) Integrated information theory (IIT) 4.0: formulating the properties of phenomenal existence in physical terms. PLoS Comput Biol 19(10):e1011465. https://doi.org/10.1371/journal.pcbi.1011465
7. Oizumi M, Albantakis L, Tononi G (2014) From the phenomenology to the mechanisms of consciousness: integrated information theory 3.0. PLoS Comput Biol 10(5):e1003588. https://doi.org/10.1371/journal.pcbi.1003588
8. Tononi G (2012) Integrated information theory of consciousness: an updated account. Arch Ital Biol 150(2–3):56–90. https://doi.org/10.4449/aib.v149i5.1388
9. Tononi G (2008) Consciousness as integrated information: A provisional manifesto. Biol Bull 215(3):216–242. https://doi.org/10.2307/25470707
10. Tononi G (2004) An information integration theory of consciousness. BMC Neurosci 5:42. https://doi.org/10.1186/1471-2202-5-42
11. Koshland DE Jr (1995) The Key–Lock theory and the induced fit theory. Angewandte Chemie Int Ed Engl 33(23–24):2375–2378. https://doi.org/10.1002/anie.199423751
12. Gupta MN, Tripathi T, Uversky VN (2025) Chapter 3 - binding of a substrate (Lock and Key) and conformational adaption (Induced Fit) are different stages of Enzyme action. In: Tripathi T, Uversky VN (eds) The three functional states of proteins. Academic, pp 31–43. https://doi.org/10.1016/B978-0-443-21809-5.00017-X
13. Redhair M, Atkins WM (2021) Analytical and functional aspects of Protein-Ligand interactions: beyond induced fit and conformational selection. Arch Biochem Biophys 714:109064. https://doi.org/10.1016/j.abb.2021.109064
14. Papaleo E, Saladino G, Lambrughi M, Lindorff-Larsen K, Gervasio FL, Nussinov R (2016) The role of protein loops and linkers in conformational dynamics and allostery. Chem Rev 116(11):6391–6423. https://doi.org/10.1021/acs.chemrev.5b00623
15. Skjærven L, Reuter N, Martinez A, Dynamics (2011) Flexibility and Ligand-Induced conformational changes in biological macromolecules: A computational approach. Future Med Chem 3(16):2079–2100. https://doi.org/10.4155/fmc.11.159
16. Teague SJ (2003) Implications of protein flexibility for drug discovery. Nat Rev Drug Discov 2(7):527–541. https://doi.org/10.1038/nrd1129
17. Teilum K, Olsen JG, Kragelund BB (2009) Functional aspects of protein flexibility. Cell Mol Life Sci 66(14):2231–2247. https://doi.org/10.1007/s00018-009-0014-6
18. McCullagh M, Zeczycki TN, Kariyawasam CS, Durie CL, Halkidis K, Fitzkee NC, Holt JM, Fenton AW (2024) What is allosteric regulation?? Exploring the exceptions that prove the rule! J Biol Chem 300(3):105672. https://doi.org/10.1016/j.jbc.2024.105672
19. Eaton WA, Henry ER, Hofrichter J, Mozzarelli A (1999) Is cooperative oxygen binding by hemoglobin really understood?? Nat Struct Biol 6(4):351–358. https://doi.org/10.1038/7586
20. Szczesny-Malysiak E, Dybas J, Blat A, Bulat K, Kus K, Kaczmarska M, Wajda A, Malek K, Chlopicki S, Marzec KM (2020) Irreversible alterations in the hemoglobin structure affect oxygen binding in human packed red blood cells. Biochim Biophys Acta Mol Cell Res 1867(11):118803. https://doi.org/10.1016/j.bbamcr.2020.118803
21. Ahmed MH, Ghatge MS, Safo MK, Hemoglobin (2020) Structure, function and allostery. Subcell Biochem 94:345–382. https://doi.org/10.1007/978-3-030-41769-7_14
22. N Uversky V (2019) Intrinsically disordered proteins and their mysterious (Meta)Physics. Front Phys 7. https://doi.org/10.3389/fphy.2019.00010
23. Dunker AK, Lawson JD, Brown CJ, Williams RM, Romero P, Oh JS, Oldfield CJ, Campen AM, Ratliff CM, Hipps KW, Ausio J, Nissen MS, Reeves R, Kang C, Kissinger CR, Bailey RW, Griswold MD, Chiu W, Garner EC, Obradovic Z (2001) Intrinsically disordered protein. J Mol Graph Model 19(1):26–59. https://doi.org/10.1016/s1093-3263(00)00138-8
24. Haynes C, Oldfield CJ, Ji F, Klitgord N, Cusick ME, Radivojac P, Uversky VN, Vidal M, Iakoucheva LM (2006) Intrinsic disorder is a common feature of hub proteins from four eukaryotic interactomes. PLoS Comput Biol 2(8):e100. https://doi.org/10.1371/journal.pcbi.0020100
25. Perovic V, Sumonja N, Marsh LA, Radovanovic S, Vukicevic M, Roberts SGE, Veljkovic N, IDPpi (2018) Protein-Protein interaction analyses of human intrinsically disordered proteins. Sci Rep 8(1):10563. https://doi.org/10.1038/s41598-018-28815-x
26. Uversky VN (2013) Intrinsic Disorder-Based protein interactions and their modulators. Curr Pharm Des 19(23):4191–4213. https://doi.org/10.2174/1381612811319230005
27. Hsu W-L, Oldfield CJ, Xue B, Meng J, Huang F, Romero P, Uversky VN, Dunker AK (2013) Exploring the binding diversity of intrinsically disordered proteins involved in One-to-Many binding. Protein Sci 22(3):258–273. https://doi.org/10.1002/pro.2207
28. Oldfield CJ, Meng J, Yang JY, Yang MQ, Uversky VN, Dunker AK (2008) Flexible nets: disorder and induced fit in the associations of P53 and 14-3-3 with their partners. BMC Genomics 9 Suppl 1 (Suppl 1):S1. https://doi.org/10.1186/1471-2164-9-S1-S1
29. Fuxreiter M (2024) Context-dependent, fuzzy protein interactions: towards sequence-based insights. Curr Opin Struct Biol 87:102834. https://doi.org/10.1016/j.sbi.2024.102834
30. Tompa P, Fuxreiter M (2008) Fuzzy complexes: polymorphism and structural disorder in Protein-Protein interactions. Trends Biochem Sci 33(1):2–8. https://doi.org/10.1016/j.tibs.2007.10.003
31. Jung H, Jung K, Kaback HR (1994) A conformational change in the lactose permease of Escherichia Coli is induced by ligand binding or membrane potential. Protein Sci 3(7):1052–1057. https://doi.org/10.1002/pro.5560030707
32. Brown JCS, Lindquist SA (2009) Heritable switch in carbon source utilization driven by an unusual yeast prion. Genes Dev 23(19):2320–2332. https://doi.org/10.1101/gad.1839109
33. Alberti S, Halfmann R, King O, Kapila A, Lindquist SA (2009) Systematic survey identifies prions and illuminates sequence features of prionogenic proteins. Cell 137(1):146–158. https://doi.org/10.1016/j.cell.2009.02.044
34. Weisgraber KH, Pitas RE, Mahley RW, Lipoproteins (1994) Neurobiology, and alzheimer's disease: structure and function of Apolipoprotein E. Curr Opin Struct Biol 4(4):507–515. https://doi.org/10.1016/S0959-440X(94)90212-7
35. Fisher CA, Ryan RO (1999) Lipid Binding-Induced conformational changes in the N-Terminal domain of human Apolipoprotein E. J Lipid Res 40(1):93–99
36. Narayanaswami V, Szeto SS, Ryan RO (2001) Lipid Association-Induced N- and C-Terminal domain reorganization in human Apolipoprotein E3. J Biol Chem 276(41):37853–37860. https://doi.org/10.1074/jbc.M102953200

37. Mohr S, Aldakul YK, Sun H, Sawczyc H, Lange A. Mechanistic studies of membrane proteins using integrated solid-state NMR and computational approaches
38. Bondar A-N (2019) Mechanisms by which lipids influence conformational dynamics of the GlpG intramembrane protease. J Phys Chem B 123(19):4159–4172. https://doi.org/10.1021/acs.jpcb.8b11291
39. Mediano PAM, Rosas FE, Bor D, Seth AK, Barrett AB (2022) The strength of weak integrated information theory. Trends Cogn Sci 26(8):646–655. https://doi.org/10.1016/j.tics.2022.04.008
40. Niizato T, Sakamoto K, Mototake Y, Murakami H, Tomaru T (2024) Information structure of heterogeneous criticality in a fish school. Sci Rep 14(1):29758. https://doi.org/10.1038/s41598-024-79232-2
41. Vicsek T, Czirók A, Ben-Jacob E, Cohen I, Shochet O (1995) Novel type of phase transition in a system of Self-Driven particles. Phys Rev Lett 75(6):1226–1229. https://doi.org/10.1103/PhysRevLett.75.1226
42. Zhang M, Chen T, Lu X, Lan X, Chen Z, Lu SG (2024) Protein-Coupled receptors (GPCRs): advances in structures, mechanisms, and drug discovery. Signal Transduct Target Ther 9(1):88. https://doi.org/10.1038/s41392-024-01803-6
43. Méndez-Couz M, Manahan-Vaughan D, Silva AP, González-Pardo H, Arias JL, Conejo NM (2021) Metaplastic contribution of neuropeptide Y receptors to Spatial memory acquisition. Behav Brain Res 396:112864. https://doi.org/10.1016/j.bbr.2020.112864
44. Su J, Song Y, Zhu Z, Huang X, Fan J, Qiao J, Mao F (2024) Cell-Cell communication: new insights and clinical implications. Signal Transduct Target Ther 9(1):196. https://doi.org/10.1038/s41392-024-01888-z
45. Gao J, Gui M, Xiang Y (2020) Structural intermediates in the low pH-Induced transition of influenza hemagglutinin. PLoS Pathog 16(11):e1009062. https://doi.org/10.1371/journal.ppat.1009062
46. Mair CM, Ludwig K, Herrmann A, Sieben C (2014) Receptor binding and pH Stability - How influenza A virus hemagglutinin affects Host-Specific virus infection. Biochim Biophys Acta 1838(4):1153–1168. https://doi.org/10.1016/j.bbamem.2013.10.004
47. Cerullo MA (2015) The problem with phi: A critique of integrated information theory. PLoS Comput Biol 11(9):e1004286. https://doi.org/10.1371/journal.pcbi.1004286
48. Mathis MW, Perez Rotondo A, Chang EF, Tolias AS, Mathis A (2024) Decoding the brain: from neural representations to mechanistic models. Cell 187(21):5814–5832. https://doi.org/10.1016/j.cell.2024.08.051
49. Son A, Kim W, Park J, Lee W, Lee Y, Choi S, Kim H (2024) Utilizing molecular dynamics simulations, machine learning, Cryo-EM, and NMR spectroscopy to predict and validate protein dynamics. Int J Mol Sci 25(17):9725. https://doi.org/10.3390/ijms25179725
50. Farisco M, Evers K, Changeux J-P (2024) Is artificial consciousness achievable?? Lessons from the human brain. Neural Netw 180:106714. https://doi.org/10.1016/j.neunet.2024.106714
51. Falandays JB, Kaaronen R, Moser C, Rorot W, Tan J, Varma V, Williams T, Youngblood M (2022) All intelligence is collective intelligence. https://doi.org/10.31234/osf.io/jhrp6
52. Minicozzi V, Giuliani A, Mei G, Domenichelli L, Parise M, Di Venere A, Di Paola L (2025) The dynamical asymmetry in SARS-CoV2 protease reveals the exchange between catalytic activity and stability in homodimers. Molecules 30(7):1412. https://doi.org/10.3390/molecules30071412
53. Luo F, Li B, Wan X-F, Scheuermann RH (2009) Core and periphery structures in protein interaction networks. BMC Bioinformatics 10(4):S8. https://doi.org/10.1186/1471-2105-10-S4-S8
54. Csermely P, London A, Wu L-Y, Uzzi B (2013) Structure and dynamics of core/periphery networks. J Complex Networks 1(2):93–123. https://doi.org/10.1093/comnet/cnt016
55. del Sol A, Carbonell P (2007) The modular organization of domain structures: insights into Protein-Protein binding. PLoS Comput Biol 3(12):e239. https://doi.org/10.1371/journal.pcbi.0030239
56. Csermely P (2018) The wisdom of networks: a general adaptation and learning mechanism of complex systems: the network core triggers fast responses to known stimuli; innovations require the slow network periphery and are encoded by core-remodeling. BioEssays 40(1). https://doi.org/10.1002/bies.201700150
57. Yehorova D, Di Geronimo B, Robinson M, Kasson PM, Kamerlin SCL (2024) Using residue interaction networks to understand protein function and evolution and to engineer new proteins. Curr Opin Struct Biol 89:102922. https://doi.org/10.1016/j.sbi.2024.102922
58. Ren J, Wang S, Chen H, Wang W, Huo L, Feng W (2018) Coiled-Coil 1-Mediated fastening of the neck and motor domains for Kinesin-3 autoinhibition. Proc Natl Acad Sci U S A 115(51):E11933–E11942. https://doi.org/10.1073/pnas.1811209115
59. Tompa P (2002) Intrinsically unstructured proteins. Trends Biochem Sci 27(10):527–533. https://doi.org/10.1016/S0968-0004(02)02169-2
60. Trivedi R, Nagarajaram HA (2022) Intrinsically disordered proteins: an overview. Int J Mol Sci 23(22):14050. https://doi.org/10.3390/ijms232214050
61. van der Lee R, Buljan M, Lang B, Weatheritt RJ, Daughdrill GW, Dunker AK, Fuxreiter M, Gough J, Gsponer J, Jones DT, Kim PM, Kriwacki RW, Oldfield CJ, Pappu RV, Tompa P, Uversky VN, Wright PE, Babu MM (2014) Classification of intrinsically disordered regions and proteins. Chem Rev 114(13):6589–6631. https://doi.org/10.1021/cr400525m
62. Wright PE, Dyson HJ (1999) Intrinsically unstructured proteins: Re-Assessing the protein Structure-Function paradigm. J Mol Biol 293(2):321–331. https://doi.org/10.1006/jmbi.1999.3110
63. Uversky VN (2002) Natively unfolded proteins: A point where biology waits for physics. Protein Sci 11(4):739–756. https://doi.org/10.1110/ps.4210102
64. Miao J, Chong S (2025) Roles of intrinsically disordered protein regions in transcriptional regulation and genome organization. Curr Opin Genet Dev 90:102285. https://doi.org/10.1016/j.gde.2024.102285
65. Del Sol A, Tsai C-J, Ma B, Nussinov R (2009) The origin of allosteric functional modulation: multiple Pre-Existing pathways. Structure 17(8):1042–1050. https://doi.org/10.1016/j.str.2009.06.008
66. Lacy ER, Filippov I, Lewis WS, Otieno S, Xiao L, Weiss S, Hengst L, Kriwacki RW (2004) P27 binds Cyclin-CDK complexes through a sequential mechanism involving Binding-Induced protein folding. Nat Struct Mol Biol 11(4):358–364. https://doi.org/10.1038/nsmb746
67. Bienkiewicz EA, Adkins JN, Lumb KJ (2002) Functional consequences of preorganized helical structure in the intrinsically disordered Cell-Cycle inhibitor P27(Kip1). Biochemistry 41(3):752–759. https://doi.org/10.1021/bi015763t
68. Russo AA, Jeffrey PD, Patten AK, Massagué J, Pavletich NP (1996) Crystal structure of the p27Kip1 Cyclin-Dependent-Kinase inhibitor bound to the Cyclin A-Cdk2 complex. Nature 382(6589):325–331. https://doi.org/10.1038/382325a0
69. Mahoney BJ, Lyman LR, Ford J, Soule J, Cheung NA, Goring AK, Ellis-Guardiola K, Collazo MJ, Cascio D, Ton-That H, Schmitt MP, Clubb RT (2025) Molecular basis of hemoglobin binding and Heme removal in Corynebacterium Diphtheriae.

Proc Natl Acad Sci USA 122(1):e2411833122. https://doi.org/10.1073/pnas.2411833122
70. Ciragan A, Backlund SM, Mikula KM, Beyer HM, Samuli Ollila OH, Iwaï HNMR (2020) Structure and dynamics of TonB investigated by Scar-Less segmental isotopic labeling using a Salt-Inducible split intein. Front Chem 8:136. https://doi.org/10.3389/fchem.2020.00136
71. Mariasina SS, Chang C-F, Navalayeu TL, Chugunova AA, Efimov SV, Zgoda VG, Ivlev VA, Dontsova OA, Sergiev PV, Polshakov VI (2022) Williams-Beuren syndrome related methyltransferase WBSCR27: from structure to possible function. Front Mol Biosci 9:865743. https://doi.org/10.3389/fmolb.2022.865743
72. Schubeis T, Le Marchand T, Daday C, Kopec W, Tekwani Movellan K, Stanek J, Schwarzer TS, Castiglione K, de Groot BL, Pintacuda G, Andreas LB (2020) A β-Barrel for oil transport through lipid membranes: dynamic NMR structures of AlkL. Proc Natl Acad Sci USA 117(35):21014–21021. https://doi.org/10.1073/pnas.2002598117
73. Bernal-Bernal D, Pantoja-Uceda D, López-Alonso JP, López-Rojo A, López-Ruiz JA, Galbis-Martínez M, Ochoa-Lizarralde B, Tascón I, Elías-Arnanz M, Ubarretxena-Belandia I, Padmanabhan S (2024) Structural basis for regulation of a CBASS-CRISPR-Cas defense Island by a transmembrane Anti-σ factor and its ECF σ partner. Sci Adv 10(43):eadp1053. https://doi.org/10.1126/sciadv.adp1053
74. Lahfa M, Barthe P, de Guillen K, Cesari S, Raji M, Kroj T, Le Naour-Vernet M, Hoh F, Gladieux P, Roumestand C, Gracy J, Declerck N, Padilla A (2024) The structural landscape and diversity of pyricularia oryzae MAX effectors revisited. PLoS Pathog 20(5):e1012176. https://doi.org/10.1371/journal.ppat.1012176
75. Alphonse S, Banerjee A, Dantuluri S, Shuman S, Ghose RNMR (2021) Solution structures of Runella Slithyformis RNA 2'-Phosphotransferase Tpt1 provide insights into NAD+Binding and specificity. Nucleic Acids Res 49(17):9607–9624. https://doi.org/10.1093/nar/gkab241
76. Courtade G, Ciano L, Paradisi A, Lindley PJ, Forsberg Z, Sørlie M, Wimmer R, Davies GJ, Eijsink VGH, Walton PH, Aachmann FL (2020) Mechanistic basis of Substrate-O2 coupling within a Chitin-active lytic polysaccharide monooxygenase: an integrated NMR/EPR study. Proc Natl Acad Sci USA 117(32):19178–19189. https://doi.org/10.1073/pnas.2004277117
77. Mohanram H, Kumar A, Verma CS, Pervushin K, Miserez A (2019) Three-Dimensional structure of Megabalanus Rosa cement protein 20 revealed by Multi-Dimensional NMR and molecular dynamics simulations. Philos Trans R Soc Lond B Biol Sci 374(1784):20190198. https://doi.org/10.1098/rstb.2019.0198
78. Wu N, Kobayashi N, Tsuda K, Unzai S, Saotome T, Kuroda Y, Yamazaki T (2020) Solution structure of Gaussia luciferase with five disulfide bonds and identification of a putative coelenterazine binding cavity by heteronuclear NMR. Sci Rep 10(1):20069. https://doi.org/10.1038/s41598-020-76486-4
79. Tamura M, Tatsushiro C, Morita EH, Ohki S (2022) Structural and functional studies of LaIT2, an antimicrobial and insecticidal peptide from Liocheles australasiae. Toxicon 214:8–17. https://doi.org/10.1016/j.toxicon.2022.04.015
80. Heymann D, Mohanram H, Kumar A, Verma CS, Lescar J, Miserez A (2021) Structure of a consensus Chitin-Binding domain revealed by solution NMR. J Struct Biol 213(2):107725. https://doi.org/10.1016/j.jsb.2021.107725
81. Di Paola L, De Ruvo M, Paci P, Santoni D, Giuliani A (2013) Protein contact networks: an emerging paradigm in chemistry. Chem Rev 113(3):1598–1613. https://doi.org/10.1021/cr3002356
82. Csermely PC, Elements (2008) Network-Based predictions of active centres in proteins and cellular and social networks. Trends Biochem Sci 33(12):569–576. https://doi.org/10.1016/j.tibs.2008.09.006
83. Guimerà R, Amaral LAN (2005) Cartography of complex networks: modules and universal roles. J Stat Mech 2005(P02001):nihpa35573. https://doi.org/10.1088/1742-5468/2005/02/P02001
84. Ding L, Li C, Jin D, Ding S (2024) Survey of spectral clustering based on graph theory. Pattern Recogn 151:110366. https://doi.org/10.1016/j.patcog.2024.110366
85. Uversky VN, Giuliani A (2021) Networks of networks: an essay on multi-level biological organization. Front Genet 12. https://doi.org/10.3389/fgene.2021.706260
86. Di Paola L, Giuliani A (2015) Protein contact network topology: A natural Language for allostery. Curr Opin Struct Biol 31:43–48. https://doi.org/10.1016/j.sbi.2015.03.001
87. Raeymaekers L (2002) Dynamics of boolean networks controlled by biologically meaningful functions. J Theor Biol 218(3):331–341. https://doi.org/10.1006/jtbi.2002.3081
88. Kauffman S, Peterson C, Samuelsson B, Troein C (2003) Random boolean network models and the yeast transcriptional network. Proc Natl Acad Sci U S A 100(25):14796–14799. https://doi.org/10.1073/pnas.2036429100
89. Krishnan A, Giuliani A, Zbilut JP, Tomita M (2007) Network scaling invariants help to elucidate basic topological principles of proteins. J Proteome Res 6(10):3924–3934. https://doi.org/10.1021/pr070162v
90. Gupta MN, Tripathi T, Uversky VN (2025) Chapter 2 - ordered proteins and structure–function relationship: a classical view. In: Tripathi T, Uversky VN (eds) The three functional states of proteins. Academic Press, pp 17–30. https://doi.org/10.1016/B978-0-443-21809-5.00023-5
91. Uversky VN, Functional, Unfoldomics (2024) Roles of intrinsic disorder in protein (Multi)Functionality. Adv Protein Chem Struct Biol 138:179–210. https://doi.org/10.1016/bs.apcsb.2023.11.001
92. DeForte S, Uversky VN, Order (2016) Disorder, and everything in between. Molecules 21(8):1090. https://doi.org/10.3390/molecules21081090
93. Uversky VNA (2013) Decade and a half of protein intrinsic disorder: biology still waits for physics. Protein Sci 22(6):693–724. https://doi.org/10.1002/pro.2261
94. Uversky VN (2013) Unusual biophysics of intrinsically disordered proteins. Biochim Biophys Acta 1834(5):932–951. https://doi.org/10.1016/j.bbapap.2012.12.008
95. Uversky VN (2016) Dancing protein clouds: the strange biology and chaotic physics of intrinsically disordered proteins. J Biol Chem 291(13):6681–6688. https://doi.org/10.1074/jbc.R115.685859
96. Uversky VN (2016) Paradoxes and wonders of intrinsic disorder: complexity of simplicity. Intrinsically Disord Proteins 4(1):e1135015. https://doi.org/10.1080/21690707.2015.1135015
97. Uversky VN (2019) Protein intrinsic disorder and Structure-Function continuum. Prog Mol Biol Transl Sci 166:1–17. https://doi.org/10.1016/bs.pmbts.2019.05.003
98. Uversky VN (2015) Functional roles of transiently and intrinsically disordered regions within proteins. FEBS J 282(7):1182–1189. https://doi.org/10.1111/febs.13202
99. Uversky VN (2016) P53 proteoforms and intrinsic disorder: an illustration of the protein Structure-Function continuum concept. Int J Mol Sci 17(11):1874. https://doi.org/10.3390/ijms17111874
100. Gupta MN, Uversky VN (2024) Protein structure–Function continuum model: emerging nexuses between specificity, evolution, and structure. Protein Sci 33(4):e4968. https://doi.org/10.1002/pro.4968

101. Larson C (2016) Evidence of shared aspects of complexity science and quantum phenomena. Cosmos History: J Nat Social Philos 12(2):160–171
102. Welte MA (2004) Bidirectional transport along microtubules. Curr Biol 14(13):R525–R537. https://doi.org/10.1016/j.cub.2004.06.045
103. Hirokawa N, Nitta R, Okada Y (2009) The mechanisms of Kinesin motor motility: lessons from the monomeric motor KIF1A. Nat Rev Mol Cell Biol 10(12):877–884. https://doi.org/10.1038/nrm2807
104. Coy DL, Wagenbach M, Howard J (1999) Kinesin takes one 8-Nm step for each ATP that it hydrolyzes. J Biol Chem 274(6):3667–3671. https://doi.org/10.1074/jbc.274.6.3667
105. Toleikis A, Carter NJ, Cross RA (2020) Backstepping mechanism of Kinesin-1. Biophys J 119(10):1984–1994. https://doi.org/10.1016/j.bpj.2020.09.034
106. Clancy BE, Behnke-Parks WM, Andreasson JOL, Rosenfeld SS, Block SM (2011) A universal pathway for Kinesin stepping. Nat Struct Mol Biol 18(9):1020–1027. https://doi.org/10.1038/nsmb.2104
107. Carter NJ, Cross RA (2005) Mechanics of the Kinesin step. Nature 435(7040):308–312. https://doi.org/10.1038/nature03528
108. Leduc C, Ruhnow F, Howard J, Diez S (2007) Detection of fractional steps in cargo movement by the collective operation of Kinesin-1 motors. Proc Natl Acad Sci U S A 104(26):10847–10852. https://doi.org/10.1073/pnas.0701864104
109. Verhey KJ, Ohi R, Causes (2023) Costs and consequences of Kinesin motors communicating through the microtubule lattice. J Cell Sci 136(5):jcs260735. https://doi.org/10.1242/jcs.260735
110. Shima T, Morikawa M, Kaneshiro J, Kambara T, Kamimura S, Yagi T, Iwamoto H, Uemura S, Shigematsu H, Shirouzu M, Ichimura T, Watanabe TM, Nitta R, Okada Y, Hirokawa N (2018) Kinesin-Binding-Triggered conformation switching of microtubules contributes to polarized transport. J Cell Biol 217(12):4164–4183. https://doi.org/10.1083/jcb.201711178
111. Marceiller J, Drechou A, Durand G, Perez F, Poüs C (2005) Kinesin is involved in protecting nascent microtubules from disassembly after recovery from nocodazole treatment. Exp Cell Res 304(2):483–492. https://doi.org/10.1016/j.yexcr.2004.12.007
112. Wang W, Cao L, Wang C, Gigant B, Knossow M, Kinesin (2015) 30 years later: recent insights from structural studies. Protein Sci 24(7):1047–1056. https://doi.org/10.1002/pro.2697
113. Castellana M, Parisi G (2010) Renormalization group computation of the critical exponents of hierarchical spin glasses. Phys Rev E 82(4):040105. https://doi.org/10.1103/PhysRevE.82.040105
114. Kauffman SA (1992) The origins of order: self-organization and selection in evolution. In *S*pin Glasses and Biology; Series on Directions in Condensed Matter Physics. World SCientific 6:61–100. https://doi.org/10.1142/9789814415743_0003
115. Zanzoni A, Ribeiro DM, Brun C (2019) Understanding protein multifunctionality: from short linear motifs to cellular functions. Cell Mol Life Sci 76(22):4407–4412. https://doi.org/10.1007/s00018-019-03273-4
116. Moses D, Ginell GM, Holehouse AS, Sukenik S (2023) Intrinsically disordered regions are poised to act as sensors of cellular chemistry. Trends Biochem Sci 48(12):1019–1034. https://doi.org/10.1016/j.tibs.2023.08.001
117. Brodsky S, Jana T, Barkai N (2021) Order through disorder: the role of intrinsically disordered regions in transcription factor binding specificity. Curr Opin Struct Biol 71:110–115. https://doi.org/10.1016/j.sbi.2021.06.011
118. Bah A, Vernon RM, Siddiqui Z, Krzeminski M, Muhandiram R, Zhao C, Sonenberg N, Kay LE, Forman-Kay JD (2015) Folding of an intrinsically disordered protein by phosphorylation as a regulatory switch. Nature 519(7541):106–109. https://doi.org/10.1038/nature13999
119. López-Palacios TP, Andersen JL (2023) Kinase regulation by Liquid–Liquid phase separation. Trends Cell Biol 33(8):649–666. https://doi.org/10.1016/j.tcb.2022.11.009
120. Dyla M, Kjaergaard M (2020) Intrinsically disordered linkers control tethered kinases via effective concentration. Proc Natl Acad Sci USA 117(35):21413–21419. https://doi.org/10.1073/pnas.2006382117
121. Zhang M, Chen T, Lu X, Lan X, Chen Z, Lu SG (2024) Protein-Coupled receptors (GPCRs): advances in structures, mechanisms and drug discovery. Sig Transduct Target Ther 9(1):1–43. https://doi.org/10.1038/s41392-024-01803-6
122. Wodak SJ, Paci E, Dokholyan NV, Berezovsky IN, Horovitz A, Li J, Hilser VJ, Bahar I, Karanicolas J, Stock G, Hamm P, Stote RH, Eberhardt J, Chebaro Y, Dejaegere A, Cecchini M, Changeux J-P, Bolhuis PG, Vreede J, Faccioli P, Orioli S, Ravasio R, Yan L, Brito C, Wyart M, Gkeka P, Rivalta I, Palermo G, McCammon JA, Panecka-Hofman J, Wade RC, Pizio AD, Niv MY, Nussinov R, Tsai C-J, Jang H, Padhorny D, Kozakov D, McLeish T (2019) Allostery in its many disguises: from theory to applications. Structure 27(4):566–578. https://doi.org/10.1016/j.str.2019.01.003
123. Isogai S, Deupi X, Opitz C, Heydenreich FM, Tsai C-J, Brueckner F, Schertler GFX, Veprintsev DB, Grzesiek S (2016) Backbone NMR reveals allosteric signal transduction networks in the B1-Adrenergic receptor. Nature 530(7589):237–241. https://doi.org/10.1038/nature16577
124. Schörner M, Beyer SR, Southall J, Cogdell RJ, Köhler J (2015) Conformational memory of a protein revealed by Single-Molecule spectroscopy. J Phys Chem B 119(44):13964–13970. https://doi.org/10.1021/acs.jpcb.5b07494
125. Muezzinoglu MK, Guzelis C, Zurada JM (2003) A new design method for the Complex-Valued multistate Hopfield associative memory. IEEE Trans Neural Netw 14(4):891–899. https://doi.org/10.1109/TNN.2003.813844
126. Gigante G, Giuliani A, Mattia MA (2023) Novel network approach to multiscale biological regulation. Cell Syst 14(3):177–179. https://doi.org/10.1016/j.cels.2023.02.004
127. Manley LJ, Lin MM (2023) Kinetic and thermodynamic allostery in the Ras protein family. Biophys J 122(19):3882–3893. https://doi.org/10.1016/j.bpj.2023.08.010
128. Hilser VJ, Anderson JA, Motlagh HN (2015) Allostery vs. Allokairy. Proc Natl Acad Sci USA 112(37):11430–11431. https://doi.org/10.1073/pnas.1515239112
129. Ghosh DK, Ranjan A (2020) The metastable States of proteins. Protein Sci 29(7):1559–1568. https://doi.org/10.1002/pro.3859
130. Liu S, Ammirati MJ, Song X, Knafels JD, Zhang J, Greasley SE, Pfefferkorn JA, Qiu X (2012) Insights into mechanism of glucokinase activation. J Biol Chem 287(17):13598–13610. https://doi.org/10.1074/jbc.M111.274126
131. Wu N, Barahona M, Yaliraki SN (2024) Allosteric communication and signal transduction in proteins. Curr Opin Struct Biol 84:102737. https://doi.org/10.1016/j.sbi.2023.102737
132. Weng J, Ma J, Fan K, Wang W (2008) The conformational coupling and translocation mechanism of vitamin B12 ATP-Binding cassette transporter BtuCD. Biophys J 94(2):612–621. https://doi.org/10.1529/biophysj.107.110734
133. Bowman GR, Geissler PL (2012) Equilibrium fluctuations of a single folded protein reveal a multitude of potential cryptic allosteric sites. Proc Natl Acad Sci U S A 109(29):11681–11686. https://doi.org/10.1073/pnas.1209309109
134. Vajda S, Beglov D, Wakefield AE, Egbert M, Whitty A (2018) Cryptic binding sites on proteins: definition, detection, and druggability. Curr Opin Chem Biol 44:1–8. https://doi.org/10.1016/j.cbpa.2018.05.003

135. Goričan T, Golič Grdadolnik S (2024) Insights into the allosteric regulation of human Hsp90 revealed by NMR spectroscopy. Biomolecules 15(1):37. https://doi.org/10.3390/biom15010037
136. Russell IC, Lee D, Wootten D, Sexton PM, Bumbak F (2025) Cryoelectron microscopy as a tool for illuminating activation mechanisms of human class A orphan G Protein-Coupled receptors. Pharmacol Rev 77(3):100056. https://doi.org/10.1016/j.pharmr.2025.100056
137. Zhang S, Zou S, Yin D, Zhao L, Finley D, Wu Z, Mao Y (2022) USP14-Regulated allostery of the human proteasome by Time-Resolved Cryo-EM. Nature 605(7910):567–574. https://doi.org/10.1038/s41586-022-04671-8
138. Ali AAAI, Dorbath E, Stock G (2024) Allosteric communication mediated by protein contact clusters: A dynamical model. J Chem Theory Comput 20(23):10731–10739. https://doi.org/10.1021/acs.jctc.4c01188
139. Zhu R, Wu C, Zha J, Lu S, Zhang J (2025) Decoding allosteric landscapes: computational methodologies for enzyme modulation and drug discovery. RSC Chem Biology 6(4):539–554. https://doi.org/10.1039/D4CB00282B
140. Vithani N, Zhang S, Thompson JP, Patel LA, Demidov A, Xia J, Balaeff A, Mentes A, Arnautova YA, Kohlmann A, Lawson JD, Nicholls A, Skillman AG, LeBard DN (2024) Exploration of cryptic pockets using enhanced sampling along normal modes: A case study of KRAS G12D. J Chem Inf Model 64(21):8258–8273. https://doi.org/10.1021/acs.jcim.4c01435
141. Zhang L, Mobbs JI, May LT, Glukhova A, Thal DM (2023) The impact of Cryo-EM on determining allosteric Modulator-Bound structures of G Protein-Coupled receptors. Curr Opin Struct Biol 79:102560. https://doi.org/10.1016/j.sbi.2023.102560
142. Li K, DeCost B, Choudhary K, Greenwood M, Hattrick-Simpers JA (2023) Critical examination of robustness and generalizability of machine learning prediction of materials properties. Npj Comput Mater 9(1):1–9. https://doi.org/10.1038/s41524-023-01012-9
143. Soto C, Satani N (2011) The intricate mechanisms of neurodegeneration in prion diseases. Trends Mol Med 17(1):14–24. https://doi.org/10.1016/j.molmed.2010.09.001
144. Saibil HR, Seybert A, Habermann A, Winkler J, Eltsov M, Perkovic M, Castaño-Diez D, Scheffer MP, Haselmann U, Chlanda P, Lindquist S, Tyedmers J, Frangakis AS (2012) Heritable yeast prions have a highly organized Three-Dimensional architecture with interfiber structures. Proc Natl Acad Sci U S A 109(37):14906–14911. https://doi.org/10.1073/pnas.1211976109
145. Poggiolini I, Saverioni D, Parchi P (2013) Prion protein misfolding, strains, and neurotoxicity: an update from studies on mammalian prions. Int J Cell Biol 2013:910314. https://doi.org/10.1155/2013/910314
146. Si K, Kandel ER (2016) The role of functional Prion-Like proteins in the persistence of memory. Cold Spring Harb Perspect Biol 8(4):a021774. https://doi.org/10.1101/cshperspect.a021774
147. A yeast prion provides a mechanism for genetic variation and phenotypic diversity. Nature. https://www.nature.com/articles/35035005 . Accessed 2025-02-24
148. Eroglu M, Zocher T, McAuley J, Webster R, Xiao MZX, Yu B, Mok C, Derry WB (2024) Noncanonical inheritance of phenotypic information by protein amyloids. Nat Cell Biol 26(10):1712–1724. https://doi.org/10.1038/s41556-024-01494-9
149. Atkinson CJ, Zhang K, Munn AL, Wiegmans A, Wei MQ (2015) Prion protein scrapie and the normal cellular prion protein. Prion 10(1):63–82. https://doi.org/10.1080/19336896.2015.1110293
150. Frost B, Diamond MI (2010) Prion-like mechanisms in neurodegenerative diseases. Nat Rev Neurosci 11(3):155–159. https://doi.org/10.1038/nrn2786
151. Darling AL, Uversky VN (2018) Intrinsic disorder and posttranslational modifications: the darker side of the biological dark matter. Front Genet 9:158. https://doi.org/10.3389/fgene.2018.00158
152. Walsh CT, Garneau-Tsodikova S, Gatto GJ (2005) Protein posttranslational modifications: the chemistry of proteome diversifications. Angew Chem Int Ed Engl 44(45):7342–7372. https://doi.org/10.1002/anie.200501023
153. Deribe YL, Pawson T, Dikic I (2010) Post-Translational modifications in signal integration. Nat Struct Mol Biol 17(6):666–672. https://doi.org/10.1038/nsmb.1842
154. Witze ES, Old WM, Resing KA, Ahn NG (2007) Mapping protein Post-Translational modifications with mass spectrometry. Nat Methods 4(10):798–806. https://doi.org/10.1038/nmeth1100
155. Ramazi S, Zahiri J (2021) Posttranslational modifications in proteins: resources, tools and prediction methods. Database (Oxford) 2021(baab012). https://doi.org/10.1093/database/baab012
156. Hermann J, Schurgers L, Jankowski V (2022) Identification and characterization of Post-Translational modifications: clinical implications. Mol Aspects Med 86:101066. https://doi.org/10.1016/j.mam.2022.101066
157. Wang H, Yang L, Liu M, Luo J (2023) Protein Post-Translational modifications in the regulation of Cancer hallmarks. Cancer Gene Ther 30(4):529–547. https://doi.org/10.1038/s41417-022-00464-3
158. Mann M, Jensen ON (2003) Proteomic analysis of Post-Translational modifications. Nat Biotechnol 21(3):255–261. https://doi.org/10.1038/nbt0303-255
159. Baumann M, Meri S (2004) Techniques for studying protein heterogeneity and Post-Translational modifications. Expert Rev Proteom 1(2):207–217. https://doi.org/10.1586/14789450.1.2.207
160. Zhong Q, Xiao X, Qiu Y, Xu Z, Chen C, Chong B, Zhao X, Hai S, Li S, An Z, Dai L (2020) Protein posttranslational modifications in health and diseases: functions, regulatory mechanisms, and therapeutic implications. MedComm 2023(4 3):e261. https://doi.org/10.1002/mco2.261
161. Wang S, Osgood AO, Chatterjee A (2022) Uncovering Post-Translational Modification-Associated Protein-Protein interactions. Curr Opin Struct Biol 74:102352. https://doi.org/10.1016/j.sbi.2022.102352
162. Dunker AK, Brown CJ, Obradovic Z (2002) Identification and functions of usefully disordered proteins. Adv Protein Chem 62:25–49. https://doi.org/10.1016/s0065-3233(02)62004-2
163. Dunker AK, Brown CJ, Lawson JD, Iakoucheva LM, Obradović Z (2002) Intrinsic disorder and protein function. Biochemistry 41(21):6573–6582. https://doi.org/10.1021/bi012159+
164. Iakoucheva LM, Radivojac P, Brown CJ, O'Connor TR, Sikes JG, Obradovic Z, Dunker AK (2004) The importance of intrinsic disorder for protein phosphorylation. Nucleic Acids Res 32(3):1037–1049. https://doi.org/10.1093/nar/gkh253
165. Xie H, Vucetic S, Iakoucheva LM, Oldfield CJ, Dunker AK, Obradovic Z, Uversky VN (2007) Functional anthology of intrinsic disorder. 3. Ligands, Post-Translational modifications, and diseases associated with intrinsically disorder.d proteins. J Proteome Res 6(5):1917–1932. https://doi.org/10.1021/pr060394e
166. Radivojac P, Vacic V, Haynes C, Cocklin RR, Mohan A, Heyen JW, Goebl MG, Iakoucheva LM (2010) Identification, analysis, and prediction of protein ubiquitination sites. Proteins 78(2):365–380. https://doi.org/10.1002/prot.22555
167. Pejaver V, Hsu W-L, Xin F, Dunker AK, Uversky VN, Radivojac P (2014) The structural and functional signatures of proteins that undergo multiple events of Post-Translational modification. Protein Sci 23(8):1077–1093. https://doi.org/10.1002/pro.2494
168. Bludau I, Willems S, Zeng W-F, Strauss MT, Hansen FM, Tanzer MC, Karayel O, Schulman BA, Mann M (2022) The structural context of posttranslational modifications at a Proteome-Wide scale. PLoS Biol 20(5):e3001636. https://doi.org/10.1371/journal.pbio.3001636
169. Sharma K, D'Souza RCJ, Tyanova S, Schaab C, Wiśniewski JR, Cox J, Mann M (2014) Ultradeep human phosphoproteome

reveals a distinct regulatory nature of Tyr and Ser/Thr-Based signaling. Cell Rep 8(5):1583–1594. https://doi.org/10.1016/j.celrep.2014.07.036
170. Yang X-J (2005) Multisite protein modification and intramolecular signaling. Oncogene 24(10):1653–1662. https://doi.org/10.1038/sj.onc.1208173
171. Liu R, Wu J, Guo H, Yao W, Li S, Lu Y, Jia Y, Liang X, Tang J, Zhang H (2020) Post-Translational modifications of histones: mechanisms, biological functions, and therapeutic targets. MedComm 2023(4 3):e292. https://doi.org/10.1002/mco2.292
172. Peng Z, Mizianty MJ, Xue B, Kurgan L, Uversky VN (2012) More than just tails: intrinsic disorder in histone proteins. Mol Biosyst 8(7):1886–1901. https://doi.org/10.1039/c2mb25102g
173. Mersfelder EL, Parthun MR (2006) The Tale beyond the tail: histone core domain modifications and the regulation of chromatin structure. Nucleic Acids Res 34(9):2653–2662. https://doi.org/10.1093/nar/gkl338
174. Venne AS, Kollipara L, Zahedi RP (2014) The next level of complexity: crosstalk of posttranslational modifications. Proteomics 14(4–5):513–524. https://doi.org/10.1002/pmic.201300344
175. Lim WA, Pawson T (2010) Phosphotyrosine signaling: evolving a new cellular communication system. Cell 142(5):661–667. https://doi.org/10.1016/j.cell.2010.08.023
176. Leutert M, Entwisle SW, Villén J (2021) Decoding Post-Translational modification crosstalk with proteomics. Mol Cell Proteom 20:100129. https://doi.org/10.1016/j.mcpro.2021.100129
177. Hunter T (2007) The age of crosstalk: phosphorylation, ubiquitination, and beyond. Mol Cell 28(5):730–738. https://doi.org/10.1016/j.molcel.2007.11.019
178. Cuijpers SAG, Vertegaal ACO (2018) Guiding mitotic progression by crosstalk between Post-Translational modifications. Trends Biochem Sci 43(4):251–268. https://doi.org/10.1016/j.tibs.2018.02.004
179. Meparishvili M, Chitadze L, Lagani V, McCabe B, Solomonia R (2021) Src and memory: A study of filial imprinting and predispositions in the domestic chick. Front Physiol 12:736999. https://doi.org/10.3389/fphys.2021.736999
180. Gupta MN, Uversky VN (2023) Moonlighting enzymes: when cellular context defines specificity. Cell Mol Life Sci 80(5):130. https://doi.org/10.1007/s00018-023-04781-0
181. Jeffery CJ (1999) Moonlighting proteins. Trends Biochem Sci 24(1):8–11. https://doi.org/10.1016/s0968-0004(98)01335-8
182. Jeffery CJ (2003) Moonlighting proteins: old proteins learning new tricks. Trends Genet 19(8):415–417. https://doi.org/10.1016/S0168-9525(03)00167-7
183. Tompa P, Szász C, Buday L (2005) Structural disorder throws new light on moonlighting. Trends Biochem Sci 30(9):484–489. https://doi.org/10.1016/j.tibs.2005.07.008
184. Jeffery CJ (2018) Protein moonlighting: what is it, and why is it important?? Philos Trans R Soc Lond B Biol Sci 373(1738):20160523. https://doi.org/10.1098/rstb.2016.0523
185. Jeffery CJ (2004) Molecular mechanisms for multitasking: recent crystal structures of moonlighting proteins. Curr Opin Struct Biol 14(6):663–668. https://doi.org/10.1016/j.sbi.2004.10.001
186. Cheng X-Y, Huang W-J, Hu S-C, Zhang H-L, Wang H, Zhang J-X, Lin H-H, Chen Y-Z, Zou Q, Ji Z-L (2012) A global characterization and identification of multifunctional enzymes. PLoS ONE 7(6):e38979. https://doi.org/10.1371/journal.pone.0038979
187. Bertolini E, Babbi G, Savojardo C, Martelli PL, Casadio R, MultifacetedProtDB (2024) A database of human proteins with multiple functions. Nucleic Acids Res 52(D1):D494–D501. https://doi.org/10.1093/nar/gkad783
188. Wistow GJ, Mulders JW, de Jong WW (1987) The enzyme lactate dehydrogenase as a structural protein in avian and crocodilian lenses. Nature 326(6113):622–624. https://doi.org/10.1038/326622a0
189. Gunawardena ND, Schrott V, Richardson C, Cole TN, Corey CG, Wang Y, Shiva SS, Bullock GC (2016) Aconitase: an Iron sensing regulator of mitochondrial oxidative metabolism and erythropoiesis. Blood 128(22):74. https://doi.org/10.1182/blood.V128.22.74.74
190. Philpott CC, Klausner RD, Rouault TA (1994) The bifunctional iron-responsive element binding Protein/Cytosolic Aconitase: the role of active-site residues in ligand binding and regulation. Proc Natl Acad Sci USA 91(15):7321–7325. https://doi.org/10.1073/pnas.91.15.7321
191. Banerjee S, Nandyala AK, Raviprasad P, Ahmed N, Hasnain SE (2007) Iron-Dependent RNA-Binding activity of Mycobacterium Tuberculosis aconitase. J Bacteriol 189(11):4046–4052. https://doi.org/10.1128/JB.00026-07
192. Kennedy MC, Mende-Mueller L, Blondin GA, Beinert H (1992) Purification and characterization of cytosolic aconitase from beef liver and its relationship to the Iron-Responsive element binding protein. Proc Natl Acad Sci USA 89(24):11730–11734. https://doi.org/10.1073/pnas.89.24.11730
193. Jeffery CJ, Bahnson BJ, Chien W, Ringe D, Petsko GA (2000) Crystal structure of rabbit phosphoglucose isomerase, a glycolytic enzyme that moonlights as neuroleukin, autocrine motility factor, and differentiation mediator. Biochemistry 39(5):955–964. https://doi.org/10.1021/bi991604m
194. Yang D, Han Z, Oppenheim JJ (2017) Alarmins and immunity. Immunol Rev 280(1):41–56. https://doi.org/10.1111/imr.12577
195. Kapurniotu A, Gokce O, Bernhagen J (2019) The multitasking potential of alarmins and atypical chemokines. Front Med (Lausanne) 6:3. https://doi.org/10.3389/fmed.2019.00003
196. Uversky VN (2017) Looking at the recent advances in understanding α-Synuclein and its aggregation through the proteoform prism. F1000Res 6:525. https://doi.org/10.12688/f1000research.10536.1
197. Stolzenberg E, Berry D, Yang D, Lee EY, Kroemer A, Kaufman S, Wong GCL, Oppenheim JJ, Sen S, Fishbein T, Bax A, Harris B, Barbut D, Zasloff MA (2017) A role for neuronal Alpha-Synuclein in Gastrointestinal immunity. J Innate Immun 9(5):456–463. https://doi.org/10.1159/000477990
198. Porter LL, Looger LL (2018) Extant fold-switching proteins are widespread. Proc Natl Acad Sci USA 115(23):5968–5973. https://doi.org/10.1073/pnas.1800168115
199. Madhurima K, Nandi B, Sekhar A (2021) Metamorphic proteins: the Janus proteins of structural biology. Open Biol 11(4):210012. https://doi.org/10.1098/rsob.210012
200. Volkman BF, Liu TY, Peterson FC (2009) Chapter 3. Lymphotactin structural dynamics. Methods Enzymol 461:51–70. https://doi.org/10.1016/S0076-6879(09)05403-2
201. Alberti S (2017) The wisdom of crowds: regulating cell function through condensed States of living matter. J Cell Sci 130(17):2789–2796. https://doi.org/10.1242/jcs.200295
202. Sasidharan S, Nag N, Tripathi T, Saudagar P (2023) Chapter 12 - interactions and interplay of MLOs with classical membrane-bound Organelles. In: Uversky VN (ed) Droplets of Life. Academic Press, pp 375–395. https://doi.org/10.1016/B978-0-12-823967-4.00024-5
203. Subedi S, Uversky VN, Tripathi T (2025) Chapter 11 - liquid–liquid phase separation, biomolecular condensates, and membraneless organelles: a novel blueprint of intracellular organization. In: Tripathi T, Uversky VN (eds) The three functional states of proteins. Academic, pp 177–195. https://doi.org/10.1016/B978-0-443-21809-5.00010-7
204. Antifeeva IA, Fonin AV, Fefilova AS, Stepanenko OV, Povarova OI, Silonov SA, Kuznetsova IM, Uversky VN, Turoverov KK (2022) Liquid-Liquid phase separation as an organizing principle of intracellular space: overview of the evolution of the cell

compartmentalization concept. Cell Mol Life Sci 79(5):251. https://doi.org/10.1007/s00018-022-04276-4
205. Brangwynne CP, Eckmann CR, Courson DS, Rybarska A, Hoege C, Gharakhani J, Jülicher F, Hyman AA (2009) Germline P granules are liquid droplets that localize by controlled dissolution/condensation. Science 324(5935):1729–1732. https://doi.org/10.1126/science.1172046
206. Li P, Banjade S, Cheng H-C, Kim S, Chen B, Guo L, Llaguno M, Hollingsworth JV, King DS, Banani SF, Russo PS, Jiang Q-X, Nixon BT, Rosen MK (2012) Phase transitions in the assembly of multivalent signalling proteins. Nature 483(7389):336–340. https://doi.org/10.1038/nature10879
207. Hyman AA, Weber CA, Jülicher F (2014) Liquid-Liquid phase separation in biology. Annu Rev Cell Dev Biol 30:39–58. https://doi.org/10.1146/annurev-cellbio-100913-013325
208. Bergeron-Sandoval L-P, Safaee N, Michnick SW (2016) Mechanisms and consequences of macromolecular phase separation. Cell 165(5):1067–1079. https://doi.org/10.1016/j.cell.2016.05.026
209. Banani SF, Lee HO, Hyman AA, Rosen MK (2017) Biomolecular condensates: organizers of cellular biochemistry. Nat Rev Mol Cell Biol 18(5):285–298. https://doi.org/10.1038/nrm.2017.7
210. Boeynaems S, Alberti S, Fawzi NL, Mittag T, Polymenidou M, Rousseau F, Schymkowitz J, Shorter J, Wolozin B, Van Den Bosch L, Tompa P, Fuxreiter M (2018) Protein phase separation: A new phase in cell biology. Trends Cell Biol 28(6):420–435. https://doi.org/10.1016/j.tcb.2018.02.004
211. Nesterov SV, Ilyinsky NS, Uversky VN (2021) Liquid-Liquid phase separation as a common organizing principle of intracellular space and biomembranes providing dynamic adaptive responses. Biochim Biophys Acta Mol Cell Res 1868(11):119102. https://doi.org/10.1016/j.bbamcr.2021.119102
212. Nesterov SV, Ilyinsky NS, Fonin AV, Uversky VN (2025) Signal transduction by phase Separation-Unnoticed revolution in molecular biology. J Mol Recognit 38(2):e70003. https://doi.org/10.1002/jmr.70003
213. Fonin AV, Antifeeva IA, Kuznetsova IM, Turoverov KK, Zaslavsky BY, Kulkarni P, Uversky V (2022) N. Biological soft matter: intrinsically disordered proteins in Liquid-Liquid phase separation and biomolecular condensates. Essays Biochem 66(7):831–847. https://doi.org/10.1042/EBC20220052
214. Uversky VN, Kuznetsova IM, Turoverov KK, Zaslavsky B (2015) Intrinsically disordered proteins as crucial constituents of cellular aqueous two phase systems and coacervates. FEBS Lett 589(1):15–22. https://doi.org/10.1016/j.febslet.2014.11.028
215. Uversky VN (2017) Protein intrinsic Disorder-Based Liquid-Liquid phase transitions in biological systems: complex coacervates and Membrane-Less organelles. Adv Colloid Interface Sci 239:97–114. https://doi.org/10.1016/j.cis.2016.05.012
216. Darling AL, Liu Y, Oldfield CJ, Uversky VN (2018) Intrinsically disordered proteome of human Membrane-Less organelles. Proteomics 18(5–6):e1700193. https://doi.org/10.1002/pmic.201700193
217. Uversky VN, Finkelstein AV (2019) Life in phases: Intra- and Inter- molecular phase transitions in protein solutions. Biomolecules 9(12):842. https://doi.org/10.3390/biom9120842
218. Uversky VN (2021) Recent developments in the field of intrinsically disordered proteins: intrinsic Disorder-Based emergence in cellular biology in light of the physiological and pathological Liquid-Liquid phase transitions. Annu Rev Biophys 50:135–156. https://doi.org/10.1146/annurev-biophys-062920-063704
219. Turoverov KK, Kuznetsova IM, Fonin AV, Darling AL, Zaslavsky BY, Uversky VN (2019) Stochasticity of biological soft matter: emerging concepts in intrinsically disordered proteins and biological phase separation. Trends Biochem Sci 44(8):716–728. https://doi.org/10.1016/j.tibs.2019.03.005
220. Darling AL, Zaslavsky BY, Uversky VN (2019) Intrinsic Disorder-Based emergence in cellular biology: physiological and pathological Liquid-Liquid phase transitions in cells. Polym (Basel) 11(6):990. https://doi.org/10.3390/polym11060990
221. Ovádi J, Srere PA (2000) Macromolecular compartmentation and channeling. Int Rev Cytol 192:255–280. https://doi.org/10.1016/s0074-7696(08)60529-x
222. Srere PA (1987) Complexes of sequential metabolic enzymes. Annu Rev Biochem 56:89–124. https://doi.org/10.1146/annurev.bi.56.070187.000513
223. Martin W (2010) Evolutionary origins of metabolic compartmentalization in eukaryotes. Philos Trans R Soc Lond B Biol Sci 365(1541):847–855. https://doi.org/10.1098/rstb.2009.0252
224. Sweetlove L, Fernie A (2013) The Spatial organization of metabolism within the plant cell. Annu Rev Plant Biol 64. https://doi.org/10.1146/annurev-arplant-050312-120233
225. Zecchin A, Stapor PC, Goveia J, Carmeliet P (2015) Metabolic pathway compartmentalization: an underappreciated opportunity?? Curr Opin Biotechnol 34:73–81. https://doi.org/10.1016/j.copbio.2014.11.022
226. Azaldegui CA, Vecchiarelli AG, Biteen JS (2021) The emergence of phase separation as an organizing principle in Bacteria. Biophys J 120(7):1123–1138. https://doi.org/10.1016/j.bpj.2020.09.023
227. Al-Husini N, Tomares DT, Bitar O, Childers WS, Schrader JM (2018) α-Proteobacterial RNA degradosomes assemble Liquid-Liquid Phase-Separated RNP bodies. Mol Cell 71(6):1027–1039e14. https://doi.org/10.1016/j.molcel.2018.08.003
228. Al-Husini N, Tomares DT, Pfaffenberger ZJ, Muthunayake NS, Samad MA, Zuo T, Bitar O, Aretakis JR, Bharmal M-HM, Gega A, Biteen JS, Childers WS, Schrader JM (2020) BR-Bodies provide selectively permeable condensates that stimulate mRNA decay and prevent release of decay intermediates. Mol Cell 78(4):670–682e8. https://doi.org/10.1016/j.molcel.2020.04.001
229. Cabrera JE, Jin DJ (2003) The distribution of RNA polymerase in Escherichia Coli is dynamic and sensitive to environmental cues. Mol Microbiol 50(5):1493–1505. https://doi.org/10.1046/j.1365-2958.2003.03805.x
230. Weng X, Bohrer CH, Bettridge K, Lagda AC, Cagliero C, Jin DJ, Xiao J (2019) Spatial organization of RNA polymerase and its relationship with transcription in Escherichia Coli. Proc Natl Acad Sci U S A 116(40):20115–20123. https://doi.org/10.1073/pnas.1903968116
231. Perez AM, Mann TH, Lasker K, Ahrens DG, Eckart MR, Shapiro L (2017) A localized complex of two protein oligomers controls the orientation of cell Polarity. mBio 8(1):e02238–e02216. https://doi.org/10.1128/mBio.02238-16
232. Holmes JA, Follett SE, Wang H, Meadows CP, Varga K, Bowman GR (2016) Caulobacter PopZ forms an intrinsically disordered hub in organizing bacterial cell Poles. Proc Natl Acad Sci U S A 113(44):12490–12495. https://doi.org/10.1073/pnas.1602380113
233. Ebersbach G, Briegel A, Jensen GJ, Jacobs-Wagner CA (2008) Self-Associating protein critical for chromosome attachment, division, and Polar organization in Caulobacter. Cell 134(6):956–968. https://doi.org/10.1016/j.cell.2008.07.016
234. Bowman GR, Comolli LR, Zhu J, Eckart M, Koenig M, Downing KH, Moerner WE, Earnest T, Shapiro L (2008) A polymeric protein anchors the chromosomal origin/parb complex at a bacterial cell pole. Cell 134(6):945–955. https://doi.org/10.1016/j.cell.2008.07.015
235. Mahone CR, Goley ED (2020) Bacterial cell division at a glance. J Cell Sci 133(7):jcs237057. https://doi.org/10.1242/jcs.237057
236. Monterroso B, Zorrilla S, Sobrinos-Sanguino M, Keating CD, Rivas G (2016) Microenvironments created by Liquid-Liquid phase transition control the dynamic distribution of bacterial

division FtsZ protein. Sci Rep 6:35140. https://doi.org/10.1038/srep35140
237. Rabouille C, Alberti S (2017) Cell adaptation upon stress: the emerging role of Membrane-Less compartments. Curr Opin Cell Biol 47:34–42. https://doi.org/10.1016/j.ceb.2017.02.006
238. Patel A, Lee HO, Jawerth L, Maharana S, Jahnel M, Hein MY, Stoynov S, Mahamid J, Saha S, Franzmann TM, Pozniakovski A, Poser I, Maghelli N, Royer LA, Weigert M, Myers EW, Grill S, Drechsel D, Hyman AA, Alberti S (2015) A Liquid-to-Solid phase transition of the ALS protein FUS accelerated by disease mutation. Cell 162(5):1066–1077. https://doi.org/10.1016/j.cell.2015.07.047
239. Anderson P, Kedersha N (2009) Stress Granules. Curr Biol 19(10):R397-398. https://doi.org/10.1016/j.cub.2009.03.013
240. Buchan JR, Parker R (2009) Eukaryotic stress granules: the Ins and outs of translation. Mol Cell 36(6):932–941. https://doi.org/10.1016/j.molcel.2009.11.020
241. Kroschwald S, Maharana S, Mateju D, Malinovska L, Nüske E, Poser I, Richter D, Alberti S (2015) Promiscuous interactions and protein disaggregases determine the material state of Stress-Inducible RNP granules. eLife 4:e06807. https://doi.org/10.7554/eLife.06807
242. Molliex A, Temirov J, Lee J, Coughlin M, Kanagaraj AP, Kim HJ, Mittag T, Taylor JP (2015) Phase separation by low complexity domains promotes stress granule assembly and drives pathological fibrillization. Cell 163(1):123–133. https://doi.org/10.1016/j.cell.2015.09.015
243. Glauninger H, Wong Hickernell CJ, Bard JAM, Drummond DA (2022) Stressful steps: progress and challenges in Understanding stress-Induced mRNA condensation and accumulation in stress granules. Mol Cell 82(14):2544–2556. https://doi.org/10.1016/j.molcel.2022.05.014
244. Campos-Melo D, Hawley ZCE, Droppelmann CA, Strong MJ (2021) The integral role of RNA in stress granule formation and function. Front Cell Dev Biol 9:621779. https://doi.org/10.3389/fcell.2021.621779
245. Marcelo A, Koppenol R, de Almeida LP, Matos CA, Nóbrega C (2021) Stress granules, RNA-Binding proteins and polyglutamine diseases: too much aggregation?? Cell Death Dis 12(6):592. https://doi.org/10.1038/s41419-021-03873-8
246. Zaslavsky BY, Ferreira LA, Darling AL, Uversky VN (2018) The solvent side of proteinaceous Membrane-Less organelles in light of aqueous Two-Phase systems. Int J Biol Macromol 117:1224–1251. https://doi.org/10.1016/j.ijbiomac.2018.06.030
247. Choi H-J, Lee JY, Kim K (2023) Glutathionylation on RNA-Binding proteins: A regulator of Liquid–liquid phase separation in the pathogenesis of amyotrophic lateral sclerosis. Exp Mol Med 55(4):735–744. https://doi.org/10.1038/s12276-023-00978-2
248. Aguilera-Gomez A, van Oorschot MM, Veenendaal T, Rabouille C (2016) In vivo vizualisation of Mono-ADP-Ribosylation by dPARP16 upon amino-acid starvation. eLife 5:e21475. https://doi.org/10.7554/eLife.21475
249. Zacharogianni M, Aguilera-Gomez A, Veenendaal T, Smout J, Rabouille C (2014) A stress assembly that confers cell viability by preserving ERES components during Amino-Acid starvation. eLife 3:e04132. https://doi.org/10.7554/eLife.04132
250. McInerney GM, Kedersha NL, Kaufman RJ, Anderson P, Liljeström P (2005) Importance of eIF2α phosphorylation and stress granule assembly in alphavirus translation regulation. MBoC 16(8):3753–3763. https://doi.org/10.1091/mbc.e05-02-0124
251. Wippich F, Bodenmiller B, Trajkovska MG, Wanka S, Aebersold R, Pelkmans L (2013) Dual specificity kinase DYRK3 couples stress granule condensation/dissolution to mTORC1 signaling. Cell 152(4):791–805. https://doi.org/10.1016/j.cell.2013.01.033
252. Nott TJ, Petsalaki E, Farber P, Jervis D, Fussner E, Plochowietz A, Craggs TD, Bazett-Jones DP, Pawson T, Forman-Kay JD, Baldwin AJ (2015) Phase transition of a disordered Nuage protein generates environmentally responsive membraneless organelles. Mol Cell 57(5):936–947. https://doi.org/10.1016/j.molcel.2015.01.013
253. Hofweber M, Dormann D (2019) Friend or Foe-Post-Translational modifications as regulators of phase separation and RNP granule dynamics. J Biol Chem 294(18):7137–7150. https://doi.org/10.1074/jbc.TM118.001189
254. Bock AS, Murthy AC, Tang WS, Jovic N, Shewmaker F, Mittal J, Fawzi NL (2021) N-Terminal acetylation modestly enhances phase separation and reduces aggregation of the Low-Complexity domain of RNA-Binding protein fused in sarcoma. Protein Sci 30(7):1337–1349. https://doi.org/10.1002/pro.4029
255. Luo Y-Y, Wu J-J, Li Y-M (2021) Regulation of Liquid-Liquid phase separation with focus on Post-Translational modifications. Chem Commun (Camb) 57(98):13275–13287. https://doi.org/10.1039/d1cc05266g
256. Li J, Zhang M, Ma W, Yang B, Lu H, Zhou F, Zhang L (2022) Post-Translational modifications in Liquid-Liquid phase separation: A comprehensive review. Mol Biomed 3(1):13. https://doi.org/10.1186/s43556-022-00075-2
257. Jeon S, Jeon Y, Lim J-Y, Kim Y, Cha B, Kim W (2025) Emerging regulatory mechanisms and functions of biomolecular condensates: implications for therapeutic targets. Signal Transduct Target Ther 10(1):4. https://doi.org/10.1038/s41392-024-02070-1
258. Monahan Z, Ryan VH, Janke AM, Burke KA, Rhoads SN, Zerze GH, O'Meally R, Dignon GL, Conicella AE, Zheng W, Best RB, Cole RN, Mittal J, Shewmaker F, Fawzi NL (2017) Phosphorylation of the FUS Low-Complexity domain disrupts phase separation, aggregation, and toxicity. EMBO J 36(20):2951–2967. https://doi.org/10.15252/embj.201696394
259. Wang A, Conicella AE, Schmidt HB, Martin EW, Rhoads SN, Reeb AN, Nourse A, Ramirez Montero D, Ryan VH, Rohatgi R, Shewmaker F, Naik MT, Mittag T, Ayala YM, Fawzi NL (2018) A single N-Terminal phosphomimic disrupts TDP-43 polymerization, phase separation, and RNA splicing. EMBO J 37(5):e97452. https://doi.org/10.15252/embj.201797452
260. Boyko S, Surewicz WK (2023) Domain-Specific modulatory effects of phosphomimetic substitutions on Liquid-Liquid phase separation of Tau protein. J Biol Chem 299(6):104722. https://doi.org/10.1016/j.jbc.2023.104722
261. Ambadipudi S, Biernat J, Riedel D, Mandelkow E, Zweckstetter M (2017) Liquid-Liquid phase separation of the Microtubule-Binding repeats of the Alzheimer-Related protein Tau. Nat Commun 8(1):275. https://doi.org/10.1038/s41467-017-00480-0
262. Ferreon JC, Jain A, Choi K-J, Tsoi PS, MacKenzie KR, Jung SY, Ferreon AC (2018) Acetylation disfavors Tau phase separation. Int J Mol Sci 19(5):1360. https://doi.org/10.3390/ijms19051360
263. Parolini F, Tira R, Barracchia CG, Munari F, Capaldi S, D'Onofrio M, Assfalg M (2022) Ubiquitination of Alzheimer's-Related Tau protein affects Liquid-Liquid phase separation in a Site- and Cofactor-Dependent manner. Int J Biol Macromol 201:173–181. https://doi.org/10.1016/j.ijbiomac.2021.12.191
264. Hernández-Muñoz I, Lund AH, van der Stoop P, Boutsma E, Muijrers I, Verhoeven E, Nusinow DA, Panning B, Marahrens Y, van Lohuizen M (2005) Stable X chromosome inactivation involves the PRC1 polycomb complex and requires histone MACROH2A1 and the CULLIN3/SPOP ubiquitin E3 ligase. Proc Natl Acad Sci U S A 102(21):7635–7640. https://doi.org/10.1073/pnas.0408918102
265. Bouchard JJ, Otero JH, Scott DC, Szulc E, Martin EW, Sabri N, Granata D, Marzahn MR, Lindorff-Larsen K, Salvatella X, Schulman BA, Mittag T (2018) Cancer mutations of the tumor suppressor SPOP disrupt the formation of active, Phase-Separated

compartments. Mol Cell 72(1):19–36e8. https://doi.org/10.1016/j.molcel.2018.08.027
266. Kwon JE, La M, Oh KH, Oh YM, Kim GR, Seol JH, Baek SH, Chiba T, Tanaka K, Bang OS, Joe CO, Chung CH (2006) BTB Domain-Containing Speckle-Type POZ protein (SPOP) serves as an adaptor of Daxx for ubiquitination by Cul3-Based ubiquitin ligase. J Biol Chem 281(18):12664–12672. https://doi.org/10.1074/jbc.M600204200
267. Vidiella B, Guillamon A, Sardanyés J, Maull V, Pla J, Conde N, Solé R (2021) Engineering Self-Organized criticality in living cells. Nat Commun 12:4415. https://doi.org/10.1038/s41467-021-24695-4
268. Zhang Y, Stec B, Godzik A (2007) Between order and disorder in protein Structures – Analysis of dual personality. Fragments Proteins Structure 15(9):1141–1147. https://doi.org/10.1016/j.str.2007.07.012
269. Nonkhwao S, Leaokittikul D, Patramanon R, Jangpromma N, Daduang J, Daduang S (2024) Revealing the pH-Dependent conformational changes in Sol g 2.1 protein and potential ligands binding. Sci Rep 14(1):21179. https://doi.org/10.1038/s41598-024-72014-w
270. Lee J, Chang I (2019) Structural insight into conformational change in prion protein by breakage of electrostatic network around H187 due to its protonation. Sci Rep 9(1):19305. https://doi.org/10.1038/s41598-019-55808-1
271. Lewis SL (2006) Tropical forests and the changing Earth system. Philos Trans R Soc Lond B Biol Sci 361(1465):195–210. https://doi.org/10.1098/rstb.2005.1711
272. Thorogood R, Mustonen V, Aleixo A, Aphalo PJ, Asiegbu FO, Cabeza M, Cairns J, Candolin U, Cardoso P, Eronen JT, Hällfors M, Hovatta I, Juslén A, Kovalchuk A, Kulmuni J, Kuula L, Mäkipää R, Ovaskainen O, Pesonen A-K, Primmer CR, Saastamoinen M, Schulman AH, Schulman L, Strona G, Vanhatalo J (2023) Understanding and applying biological resilience, from genes to ecosystems. Npj Biodivers 2(1):1–13. https://doi.org/10.1038/s44185-023-00022-6
273. Wolf IR, Simões RP, Valente GT (2021) Three topological features of regulatory networks control Life-Essential and specialized subsystems. Sci Rep 11(1):24209. https://doi.org/10.1038/s41598-021-03625-w
274. Halley JD, Burden FR, Winkler DA (2009) Stem cell decision making and Critical-like exploratory networks. Stem Cell Res 2(3):165–177. https://doi.org/10.1016/j.scr.2009.03.001
275. Tatti R, Haley MS, Swanson O, Tselha T, Maffei A (2017) Neurophysiology and regulation of the balance between excitation and Inhibition in neocortical circuits. Biol Psychiatry 81(10):821–831. https://doi.org/10.1016/j.biopsych.2016.09.017
276. Qiu Y, Wei G-W (2023) Artificial Intelligence-Aided Protein Engineering: From Topological Data Analysis to Deep Protein Language Models. Brief Bioinform 24(5):bbad289. https://doi.org/10.1093/bib/bbad289
277. Chen J, Vishweshwaraiah YL, Dokholyan NV (2022) Design and engineering of allosteric communications in proteins. Curr Opin Struct Biol 73:102334. https://doi.org/10.1016/j.sbi.2022.102334
278. Salo-Ahen OMH, Alanko I, Bhadane R, Bonvin AMJJ, Honorato RV, Hossain S, Juffer AH, Kabedev A, Lahtela-Kakkonen M, Larsen AS, Lescrinier E, Marimuthu P, Mirza MU, Mustafa G, Nunes-Alves A, Pantsar T, Saadabadi A, Singaravelu K, Vanmeert M (2021) Molecular dynamics simulations in drug discovery and pharmaceutical development. Processes 9(1):71. https://doi.org/10.3390/pr9010071
279. Vora LK, Gholap AD, Jetha K, Thakur RRS, Solanki HK, Chavda VP (2023) Artificial intelligence in pharmaceutical technology and drug delivery design. Pharmaceutics 15(7):1916. https://doi.org/10.3390/pharmaceutics15071916
280. Liu B, Zhou H, Tan L, Siu KTH, Guan X-Y (2024) Exploring treatment options in cancer: tumor treatment strategies. Sig Transduct Target Ther 9(1):1–44. https://doi.org/10.1038/s41392-024-01856-7
281. Fournier L, Guarnera E, Kolmar H, Becker S (2024) Allosteric antibodies: A novel paradigm in drug discovery. Trends Pharmacol Sci. https://doi.org/10.1016/j.tips.2024.10.007
282. Li J, Gong C, Zhou H, Liu J, Xia X, Ha W, Jiang Y, Liu Q, Xiong H (2024) Kinase inhibitors and Kinase-Targeted Cancer therapies: recent advances and future perspectives. Int J Mol Sci 25(10):5489. https://doi.org/10.3390/ijms25105489
283. Wong T-S, Li G, Li S, Gao W, Chen G, Gan S, Zhang M, Li H, Wu S, Du YG (2023) Protein-Coupled receptors in neurodegenerative diseases and psychiatric disorders. Sig Transduct Target Ther 8(1):1–57. https://doi.org/10.1038/s41392-023-01427-2
284. Wang RC, Wang ZP, Medicine (2023) Disease subtyping and tailored treatment. Cancers (Basel) 15(15):3837. https://doi.org/10.3390/cancers15153837
285. Olson KM, Traynor JR, Alt A (2021) Allosteric Modulator leads hiding in plain site: developing peptide and peptidomimetics as GPCR Allosteric modulators. Front Chem 9. https://doi.org/10.3389/fchem.2021.671483
286. Wu N, Strömich L, Yaliraki SN (2021) Prediction of allosteric sites and signaling: insights from benchmarking datasets. Patterns (N Y) 3(1):100408. https://doi.org/10.1016/j.patter.2021.100408
287. Dixon TA, Williams TC, Pretorius IS (2021) Sensing the future of Bio-Informational engineering. Nat Commun 12(1):388. https://doi.org/10.1038/s41467-020-20764-2
288. Chen Z, Elowitz MB (2021) Programmable protein circuit design. Cell 184(9):2284–2301. https://doi.org/10.1016/j.cell.2021.03.007
289. Zhang X, Zhang T, Wei X, Xiao Z, Zhang W (2024) Reducing potential Dual-Use risks in synthetic biology laboratory research: A dynamic model of analysis. Humanit Soc Sci Commun 11(1):1–14. https://doi.org/10.1057/s41599-024-03976-5
290. Joshi SH-N, Jenkins C, Ulaeto D, Gorochowski TE (2024) Accelerating genetic sensor development, Scale-up, and deployment using synthetic biology. BioDesign Res 6:0037. https://doi.org/10.34133/bdr.0037
291. Einfluss der Configuration auf die Wirkung der Enzyme - Fischer – 1894 - Berichte der deutschen chemischen Gesellschaft - Wiley Online Library. https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cber.18940270364. Accessed 2025-03-11
292. von Hippel PH (1969) Conformational aspects of the nucleic Acid-Protein recognition problem. J Cell Physiol 74(2):235–238. https://doi.org/10.1002/jcp.1040740426
293. Chothia C, Janin J (1975) Principles of Protein-Protein recognition. Nature 256(5520):705–708. https://doi.org/10.1038/256705a0
294. Koshland DE (1958) Application of a theory of enzyme specificity to protein synthesis*. Proc Natl Acad Sci USA 44(2):98–104
295. Goedert M (2020) Tau proteinopathies and the prion concept. Prog Mol Biol Transl Sci 175:239–259. https://doi.org/10.1016/bs.pmbts.2020.08.003
296. Dobson CM (1999) Protein misfolding, evolution and disease. Trends Biochem Sci 24(9):329–332. https://doi.org/10.1016/s0968-0004(99)01445-0
297. Paulson HL (1999) Protein fate in neurodegenerative proteinopathies: polyglutamine diseases join the (Mis)Fold. Am J Hum Genet 64(2):339–345. https://doi.org/10.1086/302269
298. Dobson CM (2001) The structural basis of protein folding and its links with human disease. Philos Trans R Soc Lond B Biol Sci 356(1406):133–145. https://doi.org/10.1098/rstb.2000.0758
299. Jellinger KA (2003) Neuropathological spectrum of synucleinopathies. Mov Disord 18(Suppl 6):2-12

300. Dobson CM (2004) Principles of protein folding, misfolding and aggregation. Semin Cell Dev Biol 15(1):3–16. https://doi.org/10.1016/j.semcdb.2003.12.008
301. Kwong LK, Uryu K, Trojanowski JQ, Lee VM-Y (2008) TDP-43 proteinopathies: neurodegenerative protein misfolding diseases without amyloidosis. Neurosignals 16(1):41–51. https://doi.org/10.1159/000109758
302. Ciryam P, Antalek M, Cid F, Tartaglia GG, Dobson CM, Guettsches A-K, Eggers B, Vorgerd M, Marcus K, Kley RA, Morimoto RI, Vendruscolo M, Weihl CC (2019) A metastable subproteome underlies inclusion formation in muscle proteinopathies. Acta Neuropathol Commun 7(1):197. https://doi.org/10.1186/s40478-019-0853-9
303. Olzscha H (2019) Posttranslational modifications and proteinopathies: how guardians of the proteome are defeated. Biol Chem 400(7):895–915. https://doi.org/10.1515/hsz-2018-0458
304. Jayaraj GG, Hipp MS, Hartl FU (2020) Functional modules of the proteostasis network. Cold Spring Harb Perspect Biol 12(1):a033951. https://doi.org/10.1101/cshperspect.a033951
305. Macario AJ, de Conway E (2000) Stress and molecular chaperones in disease. Int J Clin Lab Res 30(2):49–66. https://doi.org/10.1007/s005990070016
306. Menzies FM, Ravikumar B, Rubinsztein DC (2006) Protective roles for induction of autophagy in multiple proteinopathies. Autophagy 2(3):224–225. https://doi.org/10.4161/auto.2696
307. Balch WE, Morimoto RI, Dillin A, Kelly JW (2008) Adapting proteostasis for disease intervention. Science 319(5865):916–919. https://doi.org/10.1126/science.1141448
308. Sajjad MU, Samson B, Wyttenbach A (2010) Heat shock proteins: therapeutic drug targets for chronic neurodegeneration?? Curr Pharm Biotechnol 11(2):198–215. https://doi.org/10.2174/138920110790909641
309. Hacisuleyman A, Yuret D, Erman B (2025) Dynamic coupling and entropy changes in KRAS G12D mutation: insights into molecular flexibility, allostery and function. J Mol Biol 169075. https://doi.org/10.1016/j.jmb.2025.169075
310. Demirtaş K, Erman B, Haliloğlu T (2024) Dynamic correlations: exact and approximate methods for mutual information. Bioinformatics 40(2):btae076. https://doi.org/10.1093/bioinformatics/btae076
311. Berahmand K, Nasiri E, Pir mohammadiani R, Li Y (2021) Spectral clustering on Protein-Protein interaction networks via constructing affinity matrix using attributed graph embedding. Comput Biol Med 138:104933. https://doi.org/10.1016/j.compbiomed.2021.104933
312. Skinner DJ, Dunkel J (2021) Improved bounds on entropy production in living systems. Proc Natl Acad Sci U S A 118(18):e2024300118. https://doi.org/10.1073/pnas.2024300118
313. Stanley HE, Scaling (1999) Universality, and renormalization: three pillars of modern critical phenomena. Rev Mod Phys 71(2):S358–S366. https://doi.org/10.1103/RevModPhys.71.S358
314. Mikulecky DC (2001) Network thermodynamics and complexity: A transition to relational systems theory. Comput Chem 25(4):369–391. https://doi.org/10.1016/s0097-8485(01)00072-9
315. Gorban AN, Smirnova EV, Tyukina TA, Correlations (2010) Risk and crisis: from physiology to finance. Physica A 389(16):3193–3217. https://doi.org/10.1016/j.physa.2010.03.035
316. Laughlin RB, Pines D, Schmalian J, Stojković BP, Wolynes P (2000) The middle way. Proc Natl Acad Sci 97(1):32–37. https://doi.org/10.1073/pnas.97.1.32
317. Csermely P, Kunsic N, Mendik P, Kerestély M, Faragó T, Veres DV, Tompa P (2020) Learning of signaling networks: molecular mechanisms. Trends Biochem Sci 45(4):284–294. https://doi.org/10.1016/j.tibs.2019.12.005
318. Veres T, Kerestély M, Kovács BM, Keresztes D, Schulc K, Seitz E, Vassy Z, Veres DV, Csermely P (2024) Cellular forgetting, desensitisation, stress and ageing in signalling networks. When do cells refuse to learn more?? Cell Mol Life Sci 81(1):97. https://doi.org/10.1007/s00018-024-05112-7
319. Skriver K, Theisen FF, Kragelund BB (2023) Conformational entropy in molecular recognition of intrinsically disordered proteins. Curr Opin Struct Biol 83:102697. https://doi.org/10.1016/j.sbi.2023.102697