Conformational entropy in molecular recognition of intrinsically disordered proteins

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Conformational entropy in molecular recognition of intrinsically disordered proteins

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Abstract

Broad conformational ensembles make intrinsically disordered proteins or regions entropically intriguing. Although methodologically challenging and understudied, emerging studies into their changes in conformational entropy (ΔSC) upon complex formation have provided both quantitative and qualitative insight. Recent work based on thermodynamics from isothermal titration calorimetry and NMR spectroscopy uncovers an expanded repertoire of regulatory mechanisms, where ΔSC plays roles in partner selection, state behavior, functional buffering, allosteric regulation, and drug design. We highlight these mechanisms to display the large entropic reservoir of IDPs for the regulation of molecular communication. We call upon the field to make efforts to contribute to this insight as more studies are needed for forwarding mechanistic decoding of intrinsically disordered proteins and their complexes.

Introduction

Molecular communication relies on specific protein-protein interactions (PPIs), where binding is a thermodynamic compromise between changes in enthalpy (ΔH°) and entropy (ΔS°). Intrinsically disordered proteins or regions (collectively IDPs) exist in broad ensembles of conformations separated by low energy barriers allowing easy transit [1,2]. This gives IDPs a large conformational entropy, Sconf.

Many IDPs undergo coupled folding and binding [3], resulting in changes in conformational entropy, ΔSconf, and contributing unfavorably to the free energy of binding, ΔG°, as shown in Figure 1a [4]. This is anticipated to enable high specificity without high affinity [5]. Indeed, an unfavorable ΔS° is documented when comparing disordered to ordered complexes [6]; although the penalty for folding is relatively small (0.7–3.5 kcal mol⁻¹) [6,7], it is within a range to pivot biological outputs. Furthermore, intrinsic disorder (ID)-based high-affinity interactions are amply described [8–10]. So, how do IDPs meet the thermodynamic compromise?

For IDPs, the functionally relevant disorder can remain in a complex, lowering the entropic penalty for binding, as shown in Figure 1b. Also, the desolvation of protein groups with the release of water or counterions works favorably to increase the entropy through changes in solvent entropy, ΔS°, and remaining contributions, ΔS°other, resulting in four major entropy terms for binding (BOX 1) [12,13]. With the intriguing thermodynamics related to ID-based interactions, the decomposition of these entropic contributions is highly relevant for mechanistic insight. Through recent examples, we discuss how ΔS°conf is a source for advancing mechanistic understanding.

Methods for quantification of conformational entropy in ID-based interactions

Direct measurement of ΔS° is challenging. It can be obtained from the measurement of ΔH° and the equilibrium constant, Kₐ ( = K₋₁), using isothermal titration calorimetry (ITC), which enables the calculation of ΔG° and ΔS° (BOX 1) [14]. The Spolar and Record (SR) method represents an indirect approach for
quantifying $\Delta S^0_{\text{conf}}$ [12]. It relies on empirical thermodynamic relationships and determination of the heat capacity change on binding, $\Delta C_p$, which, through the determination of $\Delta S^0_{\text{conf}}$ enables quantification of the number of residues, $\mathfrak{R}_{\text{res}}$, folding upon binding (BOX 1). Recently, the SR method was adapted to ID-based interactions (SRID) [15]. In particular, changing the ratio of desolvation of non-polar and polar surfaces is important for ID-based interactions, adjusting also $\Delta S^0_{\text{conf}}$ and the average per-residue $\Delta S^0_{\text{conf}}$ for folding (BOX 1) [15]. Nuclear magnetic resonance (NMR) relaxation measurements and molecular dynamics (MD) simulations are other ways to approximate $\Delta S^0_{\text{conf}}$. From order parameters ($S^0$) [16], the changes in fast time-scale dynamics of methyl-bearing residues can be used as proxy for $\Delta S^0_{\text{conf}}$ in PPIs [13,16,17]. Using this so-called entropy meter, $\Delta S^0_{\text{conf}}$ can vary, be significant for PPIs, and also involving ID partners [16,18]. Trajectories from MD simulations sampling side-chain dynamics can be used to back-calculate $S^0$, and hence extract $\Delta S^0_{\text{conf}}$. 

Changes in conformational entropy in ID-based interactions may be (a) unfavorable, (b) favorable, or (c) conditional. Selected concepts influencing the conformational entropy of ID-based interactions. (a) Coupled folding and binding and touching sites incur a conformational entropy penalty. Membrane tethering leads to a redistribution of the conformational ensemble, increasing $S_{\text{conf}}$ affecting the membrane and/or ID conformations. (b) The entropy of ID-based interactions may be favorably influenced by prestructuring or heterogeneity in the bound state and disassembly of higher order structures. Druggability of IDPs using small molecules can change $S_{\text{conf}}$ of the free state as indicated by the two arrows. (c) Conditional changes are $\Delta S^0_{\text{conf}}$, for example, from $S_{\text{conf}}$ buffering, resulting in similar SLiM positioning across different linker lengths and sequences or from intra vs inter-ID interactions in dilute and dense phases. Motif contexts may influence $S_{\text{conf}}$ and affect structure and dynamics of both partners. Lines along surface or IDPs indicate dynamics, while perpendicular lines indicate focus regions. Light orange IDPs represent other conformation of the orange generic IDP, while black represents a different IDP.
using changes in dihedral angles on binding [19] may be
different source for an ID-entropy-meter to
amyloid fibrils of
plexes differ in
Parkinson’s disease, and the chaperone
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Linking thermodynamics and structure

ΔC_p constitutes an important link between thermodynamics and structure. Large ΔC_p,s are caused by coupled folding and binding leading to the exclusion of ordered water from hydrophobic areas [11,12]. Thus, ΔC_p can be used to estimate the contributions from different ΔS’s in PPIs, as exemplified by evolutionary studies of complexes of the disordered CREB-binding protein (CBP) interaction domain (CID) and nuclear coactivator-binding domain (NCBD) from transcriptional coregulators [20]. Increased affinity for modern complexes is associated with new interactions and more favorable ΔS*. Based on ΔC_p,s, the ancestral and modern complexes differ in ΔS* conf instead of ΔS* HE [20]. Recently, ΔC_p was key to understanding the interaction between amyloid fibrils of α-synuclein, which is associated with Parkinson’s disease, and the chaperone αB-crystallin. αB-crystallin binds α-synuclein fibrils with entropy-driven high affinity [21]. Since the interaction is associated with a positive ΔC_p, the entropic gain is unlikely

CONFORMATIONAL ENSEMBLE MODULATION

IDPs employ strategies to reduce ΔS* upon binding, including compaction and pre-folding in the free state and dynamics in the bound state, as shown in Figure 1b [2,22]. For Son of Sevenless (SOS), binding to its ID-region (IDR) is entropically favorable at low temperatures, but becomes less so at increasing temperatures [23]. As IDPs compact at higher temperatures [24], ΔS* HE may be less favorable and compensate less for an unfavorable ΔS* conf. Environmental changes thus affect S* conf [25], and cellular crowding can impact compaction lowering S* conf, but with elusive thermodynamics [26]. For the interaction between Grb2-associated binding protein 1 (Gab1) and the SH2 domain protein tyrosine phosphatase (SHP2), crowding-induced residual structure in the disordered SHP2-binding regions of Gab1 likely results in reduced ΔS* conf, explaining a decreased entropic penalty of binding [27], as shown in Figure 1b. Helix propensity modulation may impact binding affinity [7,28]. For the interaction between the negative

BOX 1.
The thermodynamics of binding relate the Gibbs free energy difference between the free and bound states (ΔG°) to changes in binding enthalpy (ΔH°) and entropy (ΔS°):

\[ ΔG° = ΔH° - TΔS°; ΔG° = -RTlnK_a \]

where R is the gas constant, and T is the temperature in Kelvin. ΔH° reflects the changes in bonds, whereas ΔS° depends both on the changes in protein and ligand translational and rotational entropy, ΔS° rt, solvent entropy, ΔS° HE, conformational entropy ΔS° conf, and other contributions, ΔS° other [12,13]:

\[ ΔS° = ΔS° HE + ΔS° conf + ΔS° rt + ΔS° other \]

ΔS° thus reflects the difference in the number of states of the system. This is described by configurational and conformational entropy, where the configurational entropy originates from statistical mechanics and conformational entropy, used here, from chemical thermodynamics.

The SR approach can be used to quantify coupled folding and binding [12]. For the ID-adapted SR approach [15], this is based on the following:

\[ ΔS° conf = -1.66ΔC_p × \ln \left( \frac{T_S}{386K} \right) + 110 J \text{mol}^{-1} K^{-1} \]

where ΔC_p, the change in heat capacity at constant pressure, is determined from the temperature dependence of ΔH°, and T_S is the isentropic temperature (ΔS° = 0). Through this, Σ_s, the number of residues undergoing coupled folding and binding can be calculated from the equation:

\[ Σ_s = \frac{ΔS° conf}{-24.0 J \text{mol}^{-1} K^{-1}} \]
regulator Radical-Induced Cell Death1 (RCD1) and the transcription factor Dehydration-Responsive Element-Binding protein 2A (DREB2A), a correlation between the amount of residual helical structure and binding affinity is seen [29]. Lower affinity is associated with less favorable $\Delta H^\circ$, only partly compensated by $\Delta S^\circ$. Since the amount of helix in free and bound states of DREB2A variants correlates, the thermodynamics most likely reflects differences in interactions and structural heterogeneity, which is associated with a larger $S^\circ_{conf}$ in the complex. Thus, the degree of helicity in the free state carries information to complex structure and thermodynamics [29].

Long ID regions are abundant in transcription factors and may function by a “rigid-segment model” [30]. The model is based on studies of IDRs from HOX transcription factor sex-combs reduced (SCR) and deformed (DFD), both having short less flexible regions separated by more flexible linkers and implicated in PPIs. Fewer conformations lower $\Delta S^\circ_{conf}$, increasing affinity [30]. Short linear motif (SLiM) clusters represent a different way to lower $\Delta S^\circ_{conf}$, [2] enhancing individual weak interactions leading to allovalency, avidity, and specificity [22]. For rapid rewiring, high affinity is undesirable, as for the Phe-Gly nucleoporins (FG-Nups), with multiple SLiMs connected by disordered linkers. For nuclear transport factor 2 (NTF2) interactions, the favorable $\Delta H^\circ$ of increasing the number of SLiMs above four is counteracted by unfavorable $\Delta S^\circ$ due to linker structuring [31,32]. Thus, enthalpy–entropy ($\Delta H^\circ: \Delta S^\circ$) compensation prevents high-affinity interactions between FG-Nups and NTF2, while multiple SLiMs ensure translational selectivity [31].

SLiM context in long ID regions can negatively affect both $S^\circ_{conf}$ and $\Delta S^\circ_{conf}$. Using a proteomic screen against the EVH1 domain of ENAH, bait-peptide analyses show that binding of single and dual-SLiM peptides is driven to similar affinities by favorable $\Delta S^\circ$ and $\Delta H^\circ$, respectively [33]. $\Delta S^\circ$ of the dual-SLiM interactions are an order of magnitude less favorable, leading to the proposal of a model according to which the long, disordered dual-SLiM peptides pay a $S^\circ_{conf}$ penalty from wrapping around the target domain.

Although protein complexes have a high degree of energetic frustration [34], structural heterogeneity may contribute favorably to affinity, as shown in Figure 1b. Thus, for the CcdA:CcdB2 antitoxin-toxin complex, mutations in CcdA promote complex heterogeneity, ensuring $\Delta S^\circ_{conf}$ optimization to avoid adverse functional effects [7]. Proline-cis/trans-isomerization represents a way of introducing heterogeneity. For NCBD from CBP, proline isomerization affects interactions with partner proteins as well as the conformational ensembles to different extents, enabling differential partner binding and regulation [35,36]. According to a statistical thermodynamic model based on helix-coil theory [37], heterogeneous bound-state ensembles are constrained by IDP-target interactions through hotspots. Although the distribution of hotspot residues defines the allowed microstates, the helix propensity determines their probabilities in the diverse target-bound ensembles [37].

Understanding mechanisms from quantitative analyses of entropy

The relevance of $\Delta H^\circ: \Delta S^\circ$ compensation in PPIs has been much debated [38]. However, several studies in addition to the FG-Nup:NTF2 interactions [31] support this biochemical concept. Bona-fide $\Delta H^\circ: \Delta S^\circ$ compensation was shown for the IDR of the mitogen-activated protein kinase MKK4 [39]. Using the same SLiM, MKK4 forms different conformations in complexes with the kinases JNK1 and p38 with unfavorable and favorable $\Delta S^\circ$, respectively. In this case, $\Delta H^\circ: \Delta S^\circ$ compensation plays an important role in providing similar kinase-binding affinities of MKK4 [39]. The association of an IDR of munc-18 interacting protein 3 (Mint3) with factor inhibiting hypoxia-inducible factor-1 (FIH-1) showed large changes in $\Delta H^\circ$ and $\Delta S^\circ$ [40]. Combined with NMR and CD analyses, this suggests that the IDR, in addition to primary binding sites, has touching sites, silent to affinity, but affecting the thermodynamic profiles [40] and thus likely affecting $\Delta S^\circ_{conf}$ unfavorably, as shown in Figure 1a. The relative contributions of $\Delta H^\circ$ and $\Delta S^\circ$ to ID-based binding were addressed for transcriptional networks of the $\alpha\alpha$-hub RST domain from different regulators and transcription factors [41]. RCD1–RST binds its biological ligands with high affinity driven by enthalpy and with considerable structuring, whereas entropy drives the binding of RCD1-RST-specific ligands to the TAF4-RST domain, but with lower affinity and less structuring. This shows how balancing $\Delta H^\circ$ and $\Delta S^\circ$ fine-tunes affinity, and, importantly, specificity. Entropically responsive partners of IDPs also play significant roles in binding energetics [8], allowing ligand-dependent $\Delta S^\circ_{conf}$ (or $S^2$) responses, as reported for ligand selection by CBP-TAZ1 [42,43], calmodulin using the entropy meter [44], and ID-binding PDZ domains, as shown in Figure 1c [45]. Contrasting compensatory $\Delta H^\circ: \Delta S^\circ$, MD simulations suggest $\Delta H^\circ: \Delta S^\circ$ reinforcement for the oppositely charged H1 and ProTz [46], which form a high-affinity disordered complex governed by electrostatic mean-field type interactions [9]. Changing the polyelectrolytic properties and charge-patterning changes affinity, with contributions from $\Delta H^\circ$ and $\Delta S^\circ_{conf}$. The favorable $\Delta S^\circ_{conf}$ is suggested to be due to lower $S^\circ_{conf}$ of the unbound state resulting from intrachain repulsion [46]. Together, this demonstrates how $\Delta S^\circ_{conf}$ can be fine-tuned in ID-based interactions [47], leading to adaptation and selectivity in binding.
Quantifying folding in ID-based interactions using $\Delta S_{\text{conf}}$ to reach models

In the SR method, $\Delta S_{\text{conf}}$ is a tool for quantification of coupled folding and binding [12]. For the cell cycle-regulating p27:cyclin-dependent kinase (Cdk)2 interaction [48,49], SR pushes structural analysis showing that p27 tyrosine phosphorylation leads to the displacement of the p27-inhibitory domain from Cdk2 [49]. In the interactions between CID and NCBD, the extant human interaction is suggested to involve increased structuring compared to the earlier CID:NCBD complexes [20], supported by SRID analysis [15]. For the RCD1-RST:DREB2A interaction, the inclusion of ID context of the DREB2A RST-binding SLiM induces further structuring in both the SLiM and the RCD1-RST domain, resulting in major $\Delta H^\circ:\Delta S^\circ$ compensation, as shown in Figure 1c. In this case, SRID analysis was essential for revealing the entropy-based allosteric effect of the SLiM context [15]. SRID analysis was also used to address the effect of the long linker between the two essential SLiMs of E1A, jointly essential for high-affinity binding to the host protein Rb [50]. The $\text{R}_{\text{ID}}$ value did not increase for a SLiM-linker fragment compared to a SLiM-only fragment, suggesting linker residues not to be involved in coupled folding and binding. This supports a model where the linker functions in motif tethering by providing conformational, and thus $S_{\text{conf}}$, buffering needed for competitive hijacking of host Rb by viral E1A, as shown in Figure 1c. These examples illustrate how SR analysis can identify new features of ID-based interactions and propose models of IDD-based interactions.

Conformational entropy as a regulatory source

Biomolecular phase transitions, where proteins form membrane-less non-stochiometric higher-order assemblies, are interesting entropic systems. Studies of the cancer-related speckle-type pox virus and zinc-finger protein (SPOP), which forms higher-order rod-like structures, revealed an entropically driven gel state at substoichiometric ratios with the IDR of death-associated protein (DAXX) 6 [51]. According to the proposed model, the favorable $\Delta S_{\text{conf}}$ originates from distributing DAXX along the SPOP rod. Only at high concentrations of DAXX will $\Delta S_{\text{conf}}$ exceed the loss in $\Delta S_{\text{rt}}$ paid for gel formation, transiting to the condensed liquid state [51]. According to fluorescence anisotropy experiments, a fragment, K18, of tau1 implicated in Alzheimer’s disease, exhibits increased backbone dynamics in the condensed state, and is proposed to be an entropic driving force in condensation, as shown in Figure 1c [52]. Such neatly balanced entropic systems are likely applicable to other IDPs undergoing phase separation. Also, in phase separation, the effect of sequence on backbone $S_{\text{conf}}$ was analyzed using MD simulations on model peptides, and the results indicate that the loss of $S_{\text{conf}}$ accompanying phase transitions is amply compensated by $\Delta H^\circ$ [53]. This is also the case, although with opposite signs, for phase separation of cyclic peptides, which lose less $S_{\text{conf}}$ in the process [54]. Thus, phase separation involving IDPs appears entropically diverse, likely reflecting the material properties of the different states.

The ensemble volume of an IDP likely relates to $S_{\text{conf}}$, and changes can be functionally exploitable. Indeed, favorable $\Delta S_{\text{conf}}$ through the release of histone IDRs from DNA is suggested to drive nucleosome unwinding [55]. Oppositely, tethering an IDP will reduce $S_{\text{conf}}$ [56]. To counteract this, an entropic force is generated, and the more compact the ensemble, the larger the entropic force [56]. Such change in $S_{\text{conf}}$ may tune binding. The ID tail of the UDP-β-d-glucose-6-dehydrogenase (UGDH) shifts the conformational ensemble of the linked folded domain toward a high-affinity state for an inhibitor with a force that is solely dependent on tail length [57]. Similarly, entropic brushes generated from long ID tails with large $S_{\text{conf}}$ drive membrane bending, as shown in Figure 1a, as for the endocytic adaptor proteins, Episin1 and AP180 [58]. Recent studies of chimeras show that sequence-dependent chain repulsion or attraction can determine the direction of the bend [59].

Entropic regulation is seen for ActA translocation through the bacterial cell wall. Due to confinement in the cross-linked cell wall, a loss of $S_{\text{conf}}$ provides an entropic barrier. However, beyond a critical length, the entropic cost can be overcome from access to the unconstrained exterior, driving length-dependent translocation of ActA-like polymers [60]. Large $S_{\text{conf}}$ can also act as entropic safety catch as in the ID-tail of E2, suppressing the activity of the E1 and E2 fusion proteins of hepatitis C virus [61]. Mutations that reduce $S_{\text{conf}}$ in the E2 tail turn off the safety catch and generate hyper-reactive virus with enhanced entry [61]. These examples demonstrate entropic allosteric effects. Similarly, statistical thermodynamics highlights that changing $S_{\text{conf}}$ of an IDR allosterically affects a connected IDR or folded domain through energetic coupling [62]. This was addressed experimentally for the glucocorticoid receptor (GR), where coregulator binding to the GR-IDR leads to IDR folding, improved DNA binding by the DNA-binding domain, and enhanced transcriptional activity of GR in vivo [63].

Exploiting conformational entropy in drug targeting

With over 20% of human disease mutations occurring in IDRs, they are obvious therapeutic targets [64]. However, flexibility and $\Delta H^\circ:\Delta S^\circ$ compensation are a
challenge. Penalty in coupled folding and binding was considered in targeting the interaction between nuclear receptor peroxisome-proliferator-activated receptor γ (PPARY) and its cognate coactivators [65]. Helical peptides from the SLiM regions of the coactivators have been used as antidiabetic PPARγ antagonists through the competitive disruption of the PPARγ-coactivator interaction. However, when excised from context, the peptides do not form helical structures, resulting in an entropic binding penalty. Stabilizing the helical conformation by hydrocarbon stapling restricts $\Delta S_{\text{conf}}^e$ of the peptides in the free state and ensures a more favorable $\Delta S_{\text{conf}}^e$ [65].

Strategies for the exploitation of IDP conformational heterogeneity have been suggested for drug design. One approach is to identify small molecules, which promote entropic expansion — an increased $\Delta S_{\text{conf}}^e$ — with population of more conformations, as proposed for the IDR of the transcription factor c-Myc, as shown in Figure 1b [66,67]. Similarly, binding of the small-molecule inhibitor 10,074-G5 to amyloid-β peptide (Aβ) increases $\Delta S_{\text{conf}}^e$ of monomeric Aβ and decreases its hydrophobic surface area, delaying disease-associated aggregation [68]. For Huntingtin exon1, binding of the drug ispinesib to wild-type and pathogenic proteins leads to entropic expansion and collapse, respectively, showing an alternative targeting approach [69]. Another strategy involves ID sequestration [70,71]. Small molecules, which target -specific aromatic residues in p27 and promote the formation of soluble p27-oligomers, were identified [70,71]. This was possible because p27 dynamically fluctuates between multiple conformations of the entropy reservoirs allowing small molecules to cross-link multiple chains. Still, with few examples, general principles remain elusive.

Conclusions

From the emphasized examples, it is apparent that $\Delta H^o$: $\Delta S^o$ compensation and reinforcement play important functional roles in ID-based interactions and that quantifying $\Delta S_{\text{conf}}^e$ can uncover new mechanistic insight, interaction sites, entropic allosteric regulation, and entropy-driven molecular regulation. Examples show compensatory changes among $\Delta S_{\text{conf}}^e$, $\Delta S_{\text{rt}}^e$, and $\Delta S_{\text{HE}}^e$ and reveal entropic barriers of functional relevance. Although quantitative measures are emerging, it is still not evident how different thermodynamic strategies are employed by IDPs in translating entropy to function, and it will be long before we have enough data for generalization. Indeed, in many of the presented examples, we have extracted the entropic effects from studies with a different main focus. Thus, there is a strong need for directed studies focused on the role of conformational entropy in molecular recognition of IDPs. MD simulations and statistical thermodynamics represent promising approaches and one current strong method combination is that combining ITC and NMR. Probing the degree of structuring using the SRID approach and dissecting the results on a residue level combined with dynamic measurements by NMR can make $\Delta S_{\text{conf}}^e$ a key parameter in understanding ID-based interactions.

Declaration of competing interest

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.

Data availability

All data described in the review have all be published elsewhere, no new data is included

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References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest

** of outstanding interest

Conformational entropy and IDP interactions  Skriver et al.


Theisen et al. adapt the SR-approach for quantification of coupled folding and binding based on \( \Delta S_{\text{conf}} \) estimated from \( \Delta C_{P} \) by integrating PPIs involving IDPs. Especially, \( \Delta S_{\text{conf}} \) and the average per-residue \( \Delta S_{\text{conf}} \) for folding were adjusted. Using the SR-approach to the RCD1-DREB2A interaction revealed an unfavourable effect on \( \Delta S_{\text{conf}} \) of the DREB2A RST-binding motif context. Together with NMR-analysis, this revealed that the context allosterically induced structuring of the binding motif and major enthalpy–entropy compensation.


By applying a microfluidic platform, Scheidt et al. quantified the thermodynamics and kinetics of the interaction between the small heat-shock chaperone β-crystallin and Σ-synuclein fibrils, associated with Parkinson’s disease. Entropy had a favorable effect on the interaction, which was associated with a positive \( \Delta C_{P} \), making a gain in \( \Delta S_{\text{HE}} \) unlikely. Instead, disassembly of β-crystallin oligomers was hypothesized to function as an entropic buffer.


Elkjær et al. dissected the functional significance of residual structure in an IDR for the interaction between DREB2A and the αx-hub RCDC1-RST. Mutations were evolutionary rationalized, and kinetics, thermodynamic and NMR analyses revealed a correlation between the amount of residual helical structure and binding affinity and in free and bound DREB2A variants. The thermodynamics of the variants reflected differences in binding optimization (\( \Delta H \)) and structural heterogeneity (\( \Delta S_{\text{conf}} \)). Thus, the study revealed how evolution can balance residual structure to regulate ID-based interactions.


Hadzi et al. addressed the principles of complexes with structurally heterogeneous IDPs using a statistical thermodynamics model based on hypothesis that for IDP-IDP interactions the heterogeneous bound-state ensemble is constrained by IDP-target interactions through hotspots. The distribution of hotspot-residues defines the allowed microstates, whereas the helix propensity determines their probabilities. Together, they determine the conformational freedom and formation of favorable interactions.


43. Berlow RB, Martinez-Yamout MA, Dyson HJ, Wright PE: Role of backbone dynamics in modulating the interactions of disordered ligands with the TAZ1 domain of the CREB-binding protein. Biochemistry 2019, 58:1354–1362.


Using coarse-grained simulations, Hazra and Levy quantify the forces driving the high-affinity disordered complex between ProTox and H1, by investigating different charge variants. The formation of H1–ProTox complex is also supported by an increase in conformational entropy. Complexes involving variants with greater absolute net charges are more stable, both enthalpically and entropically, indicating that entropy and energy have a mutually reinforcing effect, rather than compensating each other.


In this work González-Foutel et al. use thermodynamics, NMR spectroscopy, and computation to study a large set of variants of the E1A family to show that compensatory changes in amino acid sequence composition and linker length lead to conservation of optimal tethering length of two binding SLIMs. The results provide a model for how sequence features enable buffer of the conformational ensemble to maintain similar SLIM distances.


In an all-atom computational simulation study, Yu and Sukenik analyze how structural preference in a large set of IDRs contribute to the entropic force generated by a disordered ensemble. They address how the redistribution of a conformational ensemble of an IDP caused by tethering can produce an entropic force. The effect was dependent on the sequences of the IDR, where sequence promoting compact ensemble resulting in a stronger entropic force than those sequences promoting more expanded ensembles.


Halladin and coworkers built a physical model, which predicts that the entropic constraints imposed by a thin periplasm is sufficient to drive the translocation of the virulence factor AcaA from Listeria Monocytogenes across a porous barrier like the peptidoglycan cell wall. They validate their model experimentally using different microscopy studies and find that the transport process is dependent on the length of the IDR, suggesting that entropic forces are sufficient to drive the transport process.


The flexibility of IDPs challenge their potential as drug targets as illustrated in the study by Zhang et al., which aims at targeting the interaction between the nuclear receptor PPARγ and its cognate coactivators. Coactivator SLIMs functioned as anti-diabetic PPARγ antagonists by competitive displacement of the PPARγ-coactivator interaction. However, since the isolated peptides did not fold into helical structure, binding resulted in an unfavorable ∆S. Therefore, the helical conformation was stabilized by hydrocarbon stapling restricting ∆S_endf of the peptides in the free state resulting in a more favorable ∆S_cont.


