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Connecting sequence to conformational properties of intrinsically disordered proteins

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Recent work has shown that intrinsically disordered proteins (IDPs) can be classified as coils or globules based on their net charge per residue (NCPR). Naïve annotation of a predictive phase diagram suggests that a majority of IDPs are likely to form disordered globules. Globule formers (as opposed to rigid, folded globules) are likely to have poor solubility profiles and it seems unlikely that the IDP proteome is enriched in globule formers. This raises the possibility that NCPR is an incomplete descriptor of IDP phase behavior. To address this issue, we carried out systematic computational studies on a set of synthetic and naturally occurring IDPs where NCPR is likely to yield questionable designations of IDP phase behavior. Our results show that the polyampholytic nature of IDPs provides a clear descriptor of sequence-ensemble relationships. Our results highlight the connection between linear patterning of oppositely charged residues in polyampholytic sequences and the phase behavior of IDPs / IDRs in sequences where more than 30% of the residues are charged. Analysis of sequence databases shows that ∼70% IDPs/IDRs are sequence-patterned polyampholytes that are likely to form heterogeneous expanded ensembles. This has important implications for the accessibility of short linear interaction motifs that directly influence IDP function.