Research team untangles more secrets of intrinsically disordered regions of proteins

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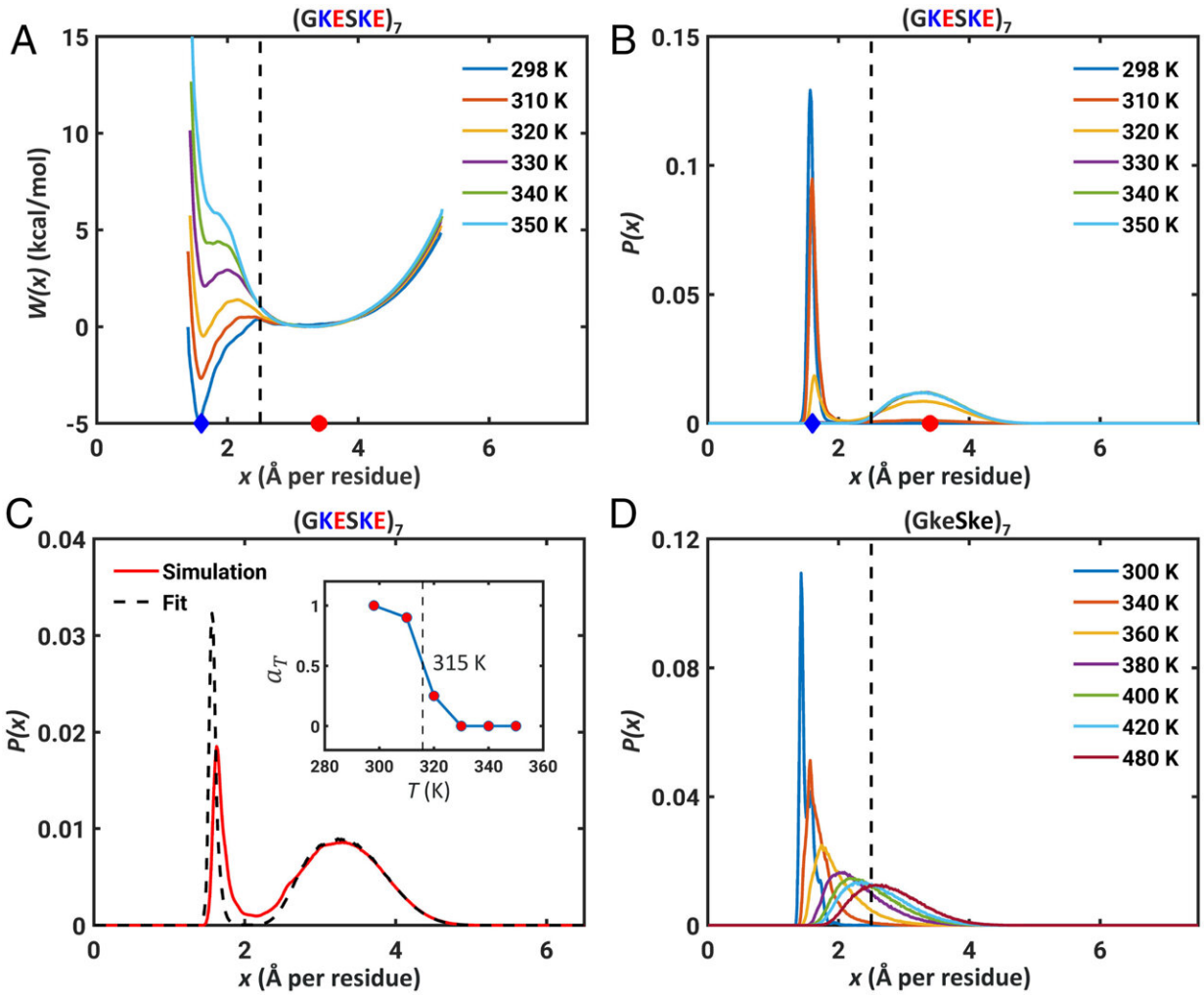

Neutral polyampholytic IDPs show two-state behavior. (A) The free energy profile W(x) for $(GKESKE)_7$ calculated for different simulation temperatures. (B) Probability distribution functions P(x) obtained from the free energy profiles show the presence of two distinct peaks corresponding to the distinct minima in

A. The dashed line in A and B indicates the reference length scale of x_{FRC} = 2.5 Å per residue. In each of the panels, the blue diamonds and red circles mark positions of $x_{globule}$ and x_{SAW}, respectively. (C) The bimodal distribution P(x) can be fit to a two-state model. The fit is shown here for an intermediate simulation temperature of 320 K. (Inset) a_T as a function of temperature and the dashed vertical line corresponds to T = 315 K, where $a_T \approx 0.5$. (D) The distributions P(x) for the neutral polymer lacking charged residues change continuously as temperature increases. Note the existence of temperatures where distributions can be peaked around x_{FRC}, which is not the case for the parent sequence $(GKESKE)_7$ that has charged residues. Credit: *Proceedings of the National Academy of Sciences* (2022). DOI: 10.1073/pnas.2200559119

Intrinsically disordered regions (IDRs) of proteins, when tethered to folded domains, function either as flexible tails or as linkers between domains. Most IDRs are composed of a mixture of oppositely charged residues. Recent measurements of tethered polyampholytes have shown that arginine- and lysine-rich sequences tend to behave very differently from one another.

In a paper published May 5 in the *Proceedings of the National Academy of Sciences*, Rohit Pappu, the Gene K. Beare Distinguished Professor in the Department of Biomedical Engineering at the McKelvey School of Engineering at Washington University in St. Louis, presented research based on computer simulations that showed the differences are determined by differences in free energies of hydration, steric volumes and other considerations.

Further, the interplay between electrostatic attractions and favorable free energies of hydration creates distinct stable states for polyampholytic IDRs. These findings have implications for switch-like transitions and the regulation of effective concentrations of interaction motifs by IDRs.

More information: Xiangze Zeng et al, Competing interactions give rise to two-state behavior and switch-like transitions in charge-rich intrinsically disordered proteins, *Proceedings of the National Academy of Sciences* (2022). DOI: 10.1073/pnas.2200559119

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