The benefits of disorder

From being initially a puzzling oddity, intrinsically disordered proteins have emerged as a central class of important biomolecules. A large fraction of proteins are thought to have disordered domains, including many with roles vital to the health of cells and the development of organisms, such as transcription factors that control gene activity.

This realization undermines the cosy assumption that proteins work by exquisitely sculpted molecular recognition. Instead, such proteins look more akin to other polymers, in the sense that their conformation in solution will be related to the classic, highly mobile random coil. One of the biggest puzzles for this view is that such proteins must be very sensitive to solvent effects. Co-solutes such as ions — present at fluctuating concentrations in cells — would be expected to alter their conformation landscape and thus their binding affinity for ligands. How could life survive such mutability?

That question is addressed by Vancraenenbroeck et al. using experiments, simulations and theory that all draw from experience in polymer science¹. They find that disordered proteins can sustain their function despite highly solvent-sensitive pliability if they operate in networks, among which the competition for a shared ligand is barely altered even though the states of the individual proteins might be significantly changed by shifts in ionic strength of the solvent.

The researchers consider a network of five interacting proteins that plays

an important part in regulating the cell cycle and controlling metabolism. These proteins are all disordered individually, but may form pairs with folded structures. Changes to the solvent, such as ionic strength, will alter the affinities with which the proteins form these dimers. Primarily these shifts are caused by charge screening, whereby counterions in solution shield and reduce the strength of the electrostatic interactions between polar groups on the polypeptide chains.

To monitor dimerization in vitro, Vancraenenbroeck et al. label one protein with a fluorescent donor and acceptor, which are held far apart, reducing the energy transfer between them, when dimerization happens. The energy transfer is also reduced if the monomer chains become expanded — which happens as the salt concentration is increased. At very high (rather unphysiological) salt levels, however, the chains become compact again, apparently because of classical ‘salting out’ collapse driven by hydrophobic interactions.

What is the effect of such changes on binding affinities? These increase among the five proteins for increasing salt concentration (except at the very high extreme), but they do so in synchrony — so that the various dimer concentrations remain much the same in the network. The network’s ‘output’ is thus largely insensitive to fluctuations in co-solutes. In calculations, the researchers find that this noise suppression is even greater if the networks have more nodes, so

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long as binding affinities change synchronously. In other words, here the disorder in protein conformation seems to serve a homeostatic function.

The implication is that disordered proteins may be insensitive to fluctuations in their solvent “not despite but because of their structural disorder”. Vancraenenbroeck et al. suggest that the effect should be seen for other influences on solvation, such as pH or molecular crowding. What’s more, the solvent sensitivity that would come from having anti-synchronous changes in binding in a network — a noise amplification — might also be useful, for example, to initiate rapid sensing of environmental changes. Either way, the disorder might then be seen as a clever ruse for the cell to harness the principles of polymer chemistry to good effect. □

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References

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