The authors knew that if a 2D TSC could be produced, it would be located in a region of the lead film directly above a magnetic island. The growth procedure would produce seamless lateral interfaces between the 2D TSC and the surrounding lead, and Majorana modes would be expected to propagate along these interfaces.

To look for evidence of such edge modes, the authors used a scanning tunnelling microscope to obtain an energy spectrum of electrons in the lead film across the putative interfaces. The microscope had a superconducting tip to maximize the spectral resolution. However, because scanning tunnelling microscopy is a tool operating in real space, it does not directly reveal the chiral nature of Majorana edge modes, which is evident only when the energy spectrum is measured in momentum space.

In the absence of exotic excitations, the real-space energy spectrum of a superconductor contains a gap — a range of energy values that electrons cannot have. Ménard *et al.* found that gaps in the material's energy spectrum were missing at positions corresponding to magnetic-island boundaries (Fig. 1b). The authors interpreted these features as evidence of exotic edge modes. They argue that these states are topological because they are resistant to the relatively strong disorder in the lead film. Furthermore, although non-topological states could give rise to a reduced gap, they would not necessarily remove the gap entirely. The observed X-shaped gap boundaries are therefore indicative of Majorana edge modes.

Ménard and colleagues' work provides strong, albeit indirect, evidence for 2D topological superconductivity in a 2D magnetic–superconductor composite system. The evidence is indirect because it cannot rule out the possibility that non-chiral edge modes are responsible for the observed X-shaped gap boundaries. If the chiral character of the edge modes is confirmed, the authors' system might be an excellent platform for studying Majorana states, which are of interest, not only for topological quantum computation, but also in elementary-particle physics[10]. ■

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BIOPHYSICS

Tight complexes from disordered proteins

Charged groups on protein surfaces often take part in molecular interactions. Two unstructured proteins have been found to use charge complementarity to form a tight complex that has biologically useful kinetic properties. SEE ARTICLE P.61

REBECCA B. BERLOW & PETER E. WRIGHT

The axiom 'opposites attract' applies to many aspects of life, including the many positively and negatively charged biological molecules that control the intricate cellular processes that enable an organism to survive. Even in the crowded environment of a cell, proteins can seek out their binding partners by using charged regions to attract oppositely charged molecules. This is certainly the case for the extreme example described by Borgia *et al.*[1] on page 61, in which a high degree of opposing charge in two binding partners that lack a defined 3D structure enables the partners to associate rapidly to form a tight complex, without the need for specific interactions between amino-acid residues. Remarkably, the complex forms without either binding partner adopting a defined structure, thereby revealing a previously unknown interaction mechanism for biological molecules.

The authors sought to characterize the binding between two highly charged proteins: negatively charged prothymosin-α (Pro-Tα) and the positively charged linker histone H1.0 (H1). Both Pro-Tα and H1 are intrinsically disordered, meaning that they do not adopt defined structures in solution, but remain flexible and accessible for binding interactions. Previous studies[2] have shown that intrinsically disordered proteins typically lose some of their native flexibility when forming complexes, either by adopting a structure of their own, or by wrapping around a folded partner.

Surprisingly, Borgia *et al.* do not observe any gain of structure for either Pro-Tα or H1 on complex formation. Using a combination of nuclear magnetic resonance (NMR) spectroscopy, single-molecule fluorescence techniques and complementary computational approaches, the authors show that both proteins remain highly flexible in the complex.

Furthermore, Pro-Tα and H1 associate with extremely high affinity at physiological salt concentrations (the dissociation constant for the complex is of the order of picomolar), even though their complex is highly disordered. Because the formation of complexes is driven by complementary charge interactions, the binding strongly depends on the salt concentration and becomes much weaker as the concentration is increased beyond the physiological range. Moreover, the authors find that amino-acid residues throughout Pro-Tα and H1 are affected similarly by binding. This implies that complex formation does not depend on the existence of specific binding sites in each of the proteins — instead, interactions are distributed widely over regions of opposite charge.

Charged amino-acid residues on the surface of globular proteins are commonly associated with binding 'hot spots' — localized

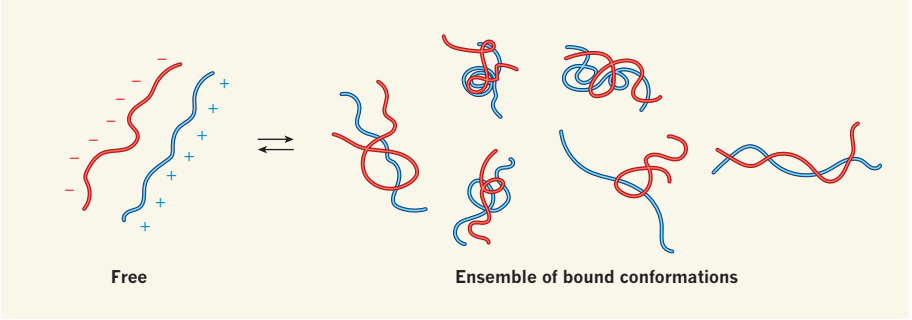

Figure 1 | Charge complementarity allows formation of tight complexes between disordered proteins. Borgia *et al.*[1] studied the formation of a complex between two proteins that, in solution, lack a defined 3D structure: prothymosin-α, which is negatively charged, and the linker histone H1.0, which is positively charged. The authors find that the complementarity of the charges on the two proteins enables them to bind reversibly and with extremely high affinity. This produces a large ensemble of bound protein conformations, many of which are adopted by only a few individual complexes and occur with approximately equal probability.

regions of the molecular surface that are involved in ligand recognition[3]. It is energetically favourable for hydrophobic amino-acid side chains in globular proteins to associate to form a hydrophobic core, a process called hydrophobic collapse. Charged amino-acid side chains are excluded from the hydrophobic core and become exposed to solvent at the surface. For disordered proteins such as Pro-Tα and H1, however, the high percentage of charged amino-acid residues precludes hydrophobic collapse, and the distribution of charges skews the conformational ensemble to a more expanded state than would be observed if the proteins were stably folded[4], leaving the charged side chains fully exposed to the solvent.

Pro-Tα and H1 become more compact when they bind to each other, probably because charge complementarity in disordered proteins can mediate the compaction of protein chains through electrostatic attractive forces, in addition to driving intermolecular interactions[5]. The authors find that the high degree of charge complementarity between Pro-Tα and H1 also provides a substantial electrostatic contribution to the binding energy of the system, making complex formation extremely favourable — as reflected by the high binding affinity of Pro-Tα for H1. The distribution of charges throughout the amino-acid sequences of both Pro-Tα and H1 allows the formation of a wide range of stable complexes that lack defined binding sites.

Many disordered proteins form 'fuzzy' complexes[6], which have a high degree of structural heterogeneity. Pro-Tα and H1 form an archetypal fuzzy complex that involves a large ensemble of possible bound protein conformations, many of which are adopted by only a small number of individual complexes and occur with approximately equal probability. The rate of association of Pro-Tα and H1 is limited by the diffusion of the molecules, a hallmark of electrostatic attraction[7]. The rapid association, slow dissociation and broad distribution of charge throughout the Pro-Tα and H1 sequences are responsible for the formation of the heterogeneous ensemble of complexes, in which the proteins entwine in many different configurations (Fig. 1).

The interaction mechanism of Pro-Tα and H1 probably aids their biological function. Pro-Tα assists with the assembly and disassembly of chromatin, the material in which DNA is packaged with histone proteins (such as H1) in cells[8]. To perform its function, Pro-Tα must recognize its histone substrates rapidly and with sufficient affinity to compete with the high affinity of histone–DNA interactions. The high binding affinity of Pro-Tα for H1 and the association rate of the two proteins imply that the dissociation of Pro-Tα–H1 complexes is slow enough to allow functional outcomes, but fast enough not to slow down biological turnover.

Many mechanistic questions remain. Can Pro-Tα form complexes with chromatin-bound H1, to promote the dissociation of H1 from DNA and to usher it to a new binding site, without having to wait for spontaneous dissociation? Similarly, can Pro-Tα remain bound to H1 once it has been deposited at a new DNA site? The flexibility in the Pro-Tα–H1 complexes would facilitate such processes: the positively charged regions of H1 would be exposed even when in complex with Pro-Tα, and thus be available for simultaneous binding to chromatin.

It is evident that the amino-acid sequences of Pro-Tα and H1 have a crucial role in dictating the proteins' molecular function. The amino-acid sequences of disordered regions in proteins evolve rapidly, yet recent studies have shown that the net charge is conserved despite a high degree of sequence diversity (see ref. 9, for example). Highly charged proteins such as Pro-Tα and H1 might therefore be more tolerant to mutation than their less-charged counterparts. As noted by Borgia and colleagues, many disordered proteins have levels of net charge similar to those of Pro-Tα and H1, suggesting that the formation of dynamic complexes between disordered proteins of opposite charge might be common.

Charge complementarity between disordered proteins and their molecular partners is of great importance to signalling pathways that rely on post-translational modifications (protein modifications that occur after protein biosynthesis), and to phase-separation processes that result in the formation of concentrated droplets of proteins and nucleic acids[10]. Although it has long been evident that electrostatic interactions have a central role in the formation of biological complexes, Borgia and colleagues' work highlights how crucial these attractive forces can be for the assembly of very strong, yet highly dynamic, molecular complexes in the cell. ■

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COSMOLOGY

A surprising chill before the cosmic dawn

An experiment to estimate when stars began to form in the Universe suggests that gas temperatures just before stars appeared had fallen well below predicted limits, and that dark matter is not as shadowy as was thought. SEE LETTER P.67

LINCOLN GREENHILL

The first stars to form generated copious fluxes of ultraviolet radiation that suffused the early Universe — a phenomenon referred to as the cosmic dawn. Many calculations have been performed to estimate when this occurred[1], but no data-driven constraints on the timing have been available. On page 67, Bowman *et al.*[2] report what might be the first detection of the thermal footprints of these stars, tracking back to 180 million years after the Big Bang.

Less than one million years after the Big Bang, the Universe consisted of atomic gas (chiefly hydrogen) and a form of matter that outweighs regular matter by more than five times[3] but has yet to be seen directly. Measurements over decades have indicated that, oddly enough, this 'dark' matter interacts with itself and with regular matter only through the action of gravity. It was mainly the gravity of dark matter that amplified small, localized density perturbations in the Universe shortly after the Big Bang to generate the first large-scale structures. But it was the hydrogen within these perturbations that collapsed piecemeal to form stars, bringing about the cosmic dawn.

The observable thermal footprints of early stars derive from small variations in the ratio of the number of interstellar hydrogen atoms found in two particular energy states;