

with interactions, known as $N = 4$ supersymmetric theories. These theories are not realistic descriptions of real-world particle physics, but they do have elementary particles such as gluons and quarks (and even Higgs bosons), and they provide a valuable testing ground for new calculational techniques.

Arkani-Hamed and colleagues² exploit a combination of twistor theory — a non-local description of space-time developed by Roger Penrose in the 1970s — and algebraic geometry to obtain a complete description of the scattering of all the elementary particles in these theories, in ascending powers of the interaction coupling. In doing so, the authors provide an excellent characterization of the scattering process when the interaction coupling is small. By contrast, Alday and colleagues¹ derive relations between non-local quantities known as Wilson loops, named after their inventor, the Nobel prizewinner Kenneth G. Wilson. The loops represent the flux of the strong nuclear-force fields through various geometrical areas. Using the powerful mathematical machinery of quantum integrability, Alday *et al.* are able to determine the behaviour of these fluxes in the limit at which the interaction coupling is large. The two sets of authors have therefore described the theory in its two opposite extreme limits — small and large coupling — and the hunt is now on for a complete description, one that is valid for any value of the interaction coupling.

Quantum field theory is the most powerful mathematical formalism known to physics, successfully predicting, for example, the magnetic moment of the electron to one part in a trillion. The recent discovery of mathematical structures that are now seen to control quantum field theory is likely to be of enormous significance, allowing us not only to calculate complex physical processes relevant to real experiments, but also to tackle fundamental questions such as the quantum structure of space-time itself. The fact that the new formulations of the theory^{1,2} jettison much of the traditional language of quantum field theory, and yet are both simpler and more effective, suggests that an improved set of founding principles may also be at hand. ■

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STRUCTURAL BIOLOGY

Finding the wet spots

The functions of proteins are critically coupled to their interplay with water, but determining the dynamics of most water molecules at protein surfaces hasn't been possible. A new spectroscopic method promises to change that.

VINCENT J. HILSER

Proteins in cells are responsible for the vast majority of biological functions. Because life evolved in water, protein molecules are uniquely adapted to use their aqueous environments to facilitate their functions¹. Yet remarkably little is known about the interactions between solvent water and protein molecules, or how those interactions affect (or are affected by) the conformational changes at the heart of protein function. In *Nature Structural and Molecular Biology*, Nucci *et al.*² now report that nuclear magnetic resonance (NMR) spectroscopy of proteins encapsulated in reverse micelles³ — cell-like compartments in which nanometre-scale pools of water are surrounded by a membrane — can provide a comprehensive picture of how water molecules bind to proteins. This picture not only challenges current dogma about protein hydration, but also promises to illuminate key aspects of the relationship between protein and water dynamics, and of how proteins use water to perform their functions.

Early studies^{4,5} of protein–water interactions — the exchange of water molecules between a protein's surface and the surrounding bulk water — were performed in bulk solution using NMR. But because of ambiguities resulting from the timescale of the exchange process, as well as the inability to distinguish between that process and another in which labile hydrogens in the protein exchange with those in water⁶, direct experimental analysis of protein–water dynamics (hydration dynamics) was restricted to only the most long-lived of interactions. Attempts to rectify this have relied mostly on X-ray crystal structures of proteins to identify the locations of resolvable water molecules in the structure, which, in spite of well-documented reservations⁷, have generally been presumed to represent the 'hydration shell' of water molecules around the protein⁸ (Fig. 1a). Nucci and colleagues' new NMR approach² overcomes the previous experimental limitations, thus providing a comprehensive picture of the whole hydration shell around a test protein, ubiquitin.

The reverse-micelle technology used by Nucci *et al.*² was previously developed³ to overcome the protein-size limitation inherent to NMR studies — large proteins can't be studied by NMR because they tumble too slowly in solution. Encapsulation of large proteins in

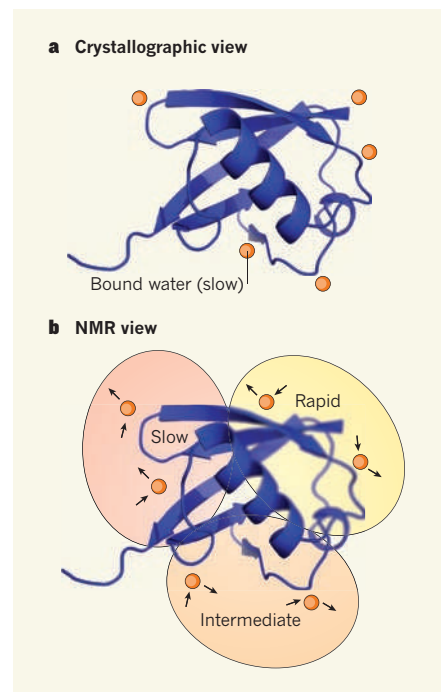


Figure 1 | Crystallographic versus NMR views of protein hydration. **a**, Certain sites at which water molecules associate with protein surfaces can be identified in X-ray crystal structures, as shown schematically here for ubiquitin. The sites are assumed to be those where water molecules reside for longest (that is, where the dynamics of water movement are slowest). **b**, This cartoon depicts the NMR view of hydration obtained by Nucci *et al.*², wherein a complete picture of the locations and dynamics of water molecules bound to ubiquitin was ascertained. They observed that water molecules cluster into regions corresponding to slow, intermediate and rapid average dynamics. Little correlation was found between the crystallographic and NMR views of hydration dynamics. Arrows indicate that the rates of water-molecule exchange between the protein's surface and the solvent are directly measured by NMR. By contrast, the X-ray picture is static, and exchange rates must be inferred or calculated. Images were created using PyMOL¹⁵.

reverse micelles dissolved in a low-viscosity fluid, however, allows them to tumble at rates similar to those of much smaller proteins. What's more, such encapsulation dramatically slows both the hydration dynamics and the hydrogen-exchange kinetics of proteins compared with the same quantities in bulk solvent. This is the cornerstone of Nucci and colleagues' advance², because it enables

the dynamics of water molecules bound to proteins to be unambiguously resolved for the first time.

The authors' key finding is that water molecules that have similar hydration dynamics form clusters across the protein surface (Fig. 1b). That is, the residence time of water on the surface is often similar at proximal regions of the protein. To understand the importance of this result, one should note that liquid water makes and breaks hydrogen bonds with other water molecules in a dynamic network⁷. The rapid molecular motions of liquid water result from cooperative rearrangements of this network — the water molecules can rearrange without going through transition states wherein one or several hydrogen bonds must break^{7,9}.

The presence of a protein can alter this network, however, changing not just the probabilities of the different structural rearrangements of solvent, but also the ease with which water molecules can interconvert between them (by altering the transition states of low-energy water arrangements). In principle, geometrical features on the protein surface can affect the residence times of individual water molecules^{10,11}: if one or many hydrogen bonds must be broken to facilitate the movement of a molecule constrained by a particular feature, the probability of such an event will be decreased, and the water molecule will tend to stay where it is. One might therefore expect the residence times of individual water molecules at the protein surface to be determined by the precise structural features of the neighbourhood of each molecule, and to be independent of the residence times at other sites.

But this isn't what Nucci and colleagues' observed for ubiquitin². Remarkably, they found that the protein confers regional effects on the solvent, so that rates of water-rearrangement processes vary by a factor of more than 10^{10} from one region of the protein's surface to another. In other words, the geometric constraints imposed by ubiquitin on the surrounding water molecules effectively create (to a first approximation) independent solvent networks around each region.

The water molecules in these regional networks seem to act cooperatively, but in a way that is blind to the behaviour of bulk solvent or of the other regions. Networks that require many hydrogen bonds to be broken in order to rearrange solvent molecules will reside longer at the surface than those that don't. Qualitatively, this observation is not altogether unexpected, as it is clear that several water molecules must be involved in any water rearrangement. It is the level at which these differences are manifested, however, that has broad implications for understanding protein function and evolution. Proteins function by recognizing and binding to ligand molecules such as cofactors, binding partners or enzymatic substrates¹². Insight into the structural and energetic factors that make a

good binding site is central to an understanding of protein function, and to the development of *de novo* protein design¹³. The fact that hydration dynamics are regionally segregated across ubiquitin suggests that some protein surfaces are more conducive to rapid solvent rearrangement than others.

Are surface-hydration properties an evolutionarily selectable trait for proteins? Certainly it is easy to imagine why enzymes, which are optimized to accelerate catalytic processes, would benefit from the evolutionary selection of rapid hydration dynamics. But are regional patterns of hydration dynamics hard-wired into the folds of particular proteins, or are they tunable through mutation? Whatever the answer, Nucci and colleagues' study² forces us to think again about the ways proteins can manipulate not just their own structure and dynamics, but also the dynamics of their solvent environment¹⁴.

It remains to be seen whether the regional patterns of hydration dynamics observed in ubiquitin also occur in other proteins. Currently, the main obstacle to applying Nucci and colleagues' analytical method² to other proteins is that preparing protein samples in reverse micelles is a non-trivial task. Nevertheless, the potential of this method to fundamentally alter our view of how proteins interact with their

solvent environment — and so also of how they function — makes the effort worthwhile. ■

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CONDENSED-MATTER PHYSICS

The conducting face of an insulator

Stacking two oxide insulators together is known to yield a conducting system at the interface between the oxides. But the discovery that simply cleaving such an insulator yields the same outcome is unexpected. [SEE LETTER P.189](#)

ELBIO DAGOTTO

On page 189 of this issue, Santander-Syro *et al.*¹ report the discovery of a conducting two-dimensional electron system on the surface of an insulator, strontium–titanium oxide (SrTiO₃; or STO for short). The finding is unexpected, because STO has been much studied in the past and was believed to be fully understood; and it may have implications for all areas of research that routinely use STO, such as the rapidly growing fields of oxide superlattices and oxide electronics^{2,3}.

With its frequent discovery of new materials, condensed-matter physics is a dynamic field of research, full of surprises that regularly challenge our understanding of how electrons and atoms behave in solids. Well-known examples are high-temperature superconductors,

and transition-metal oxides (TMO) that have large magnetoresistance⁴ — a material's ability to change its electrical resistance when placed in a magnetic field. In TMO, and in bulk materials in general, the total energy of the system is minimized as a result of the atomic ions and electrons adopting a specific crystal arrangement, for example the perovskite structure, and by modifications to low-temperature properties such as their magnetic states. But it is hard to predict how a certain property will change without first preparing a sample of the compound and investigating it. And if a particular property is needed for a specific application, it is difficult to anticipate which chemical composition will produce the desired outcome. Thus, the crystal structure of bulk TMO, and its associated properties, cannot be easily controlled.

For this reason, the artificial preparation