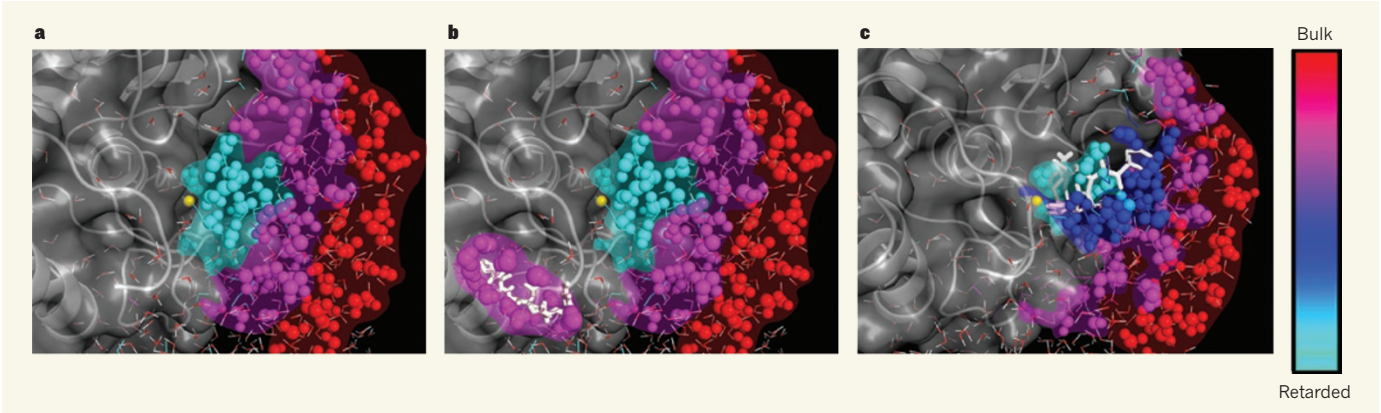

Figure 1 | Water motion in enzyme–substrate binding. Grossman *et al.*[3] report that the movements of water molecules associated with the binding site of a zinc metalloprotease enzyme change substantially during binding of a substrate to the enzyme. **a**, In this computer simulation of the free enzyme, the enzyme surface is grey and the zinc ion in the active site is yellow. Water molecules are shown as spheres, the colours of which indicate the mobility of the molecules, based on the timescale at which the hydrogen-bonded network of molecules rearranges: red indicates relatively free motion, as found in bulk water; cyan indicates strongly retarded motion; and colours in between represent intermediate levels of motion. A steep gradient of water motion is observed from outside to inside the active site. **b**, In the early stage of binding, a substrate (white) is bound nonspecifically to the surface of the enzyme. The substrate has its own cohort of hydrating water molecules. **c**, Once the substrate is specifically bound to the zinc ion, the gradient of water motion around the site is far less steep than in **a**. The motion of the water molecules solvating the substrate is also slowed down compared with **b**. Grossman *et al.* propose that the change in water dynamics assists the binding of the substrate to the active site. (Taken from Fig. 5b of the paper[3].)

of Sciences, Snyder *et al.*[2] show that the whole discourse of the hydrophobic effect, at least in ligand binding, has too long been dominated by the notion that there is a single explanation involving the expulsion of water from the binding cleft. As with any process, the free-energy change associated with ligand binding contains an entropic and an enthalpic contribution (enthalpy is a measure of the total energy of the system). During binding, water molecules constrained inside a cleft might be released, thereby boosting the free energy of binding by increasing entropy. But the enthalpic contribution to that change is by no means obvious, and could potentially counteract any entropic gain.

Snyder and colleagues' results show that it is probably unwise to make any generalizations about these thermodynamic contributions. They have characterized the binding between a rigid enzyme and a series of structurally related substrates. Some of these ligands contained groups that increase their hydrophobic contact area with the binding cavity, which has a hydrophobic and a hydrophilic side. The authors strikingly conclude that the alleged hydrophobic effect is rather insensitive to this contact area. Instead, it seems to arise primarily from structural changes in the network of water molecules between the ligand and the hydrophilic side of the cavity. Thus, although at a broad level the hydrophobic effect does involve differences in the structure of water close to solute surfaces relative to the structure of bulk water, the detailed balance of entropy and enthalpy is likely to vary on a case-by-case basis, and can be understood only by this kind of detailed analysis. Moreover, Snyder *et al.*[2] point out that "the shape of the water in the binding cavity may be as important as the shape of the cavity".

Although all this makes for a far more complicated picture of biomolecular binding than the classic geometrical 'lock and key' model, it is still predicated on a static or quasi-equilibrium picture. But that, too, is incomplete, according to Grossman and colleagues' report in *Nature Structural and Molecular Biology*[3]. They have used a combination of spectroscopy techniques, coupled to molecular-dynamics simulations, to follow changes in water and protein dynamics as a zinc metalloprotease enzyme binds its substrate. The results offer perhaps the most astonishing picture of how finely biomolecules manipulate their associated water molecules to perform their function.

The authors[3] find that, as enzyme–substrate binding develops, but before a full complex is formed, the movement of water near the protein is retarded (Fig. 1). Crudely put, it is as if the water 'thickens' towards a more glassy form, which in turn calms the fluctuations of the substrate so that it can become locked securely in place. It is not yet clear what causes this solvent slowdown as a precursor to binding; indeed, the whole question of cause and effect is complicated by the close coupling of protein and water motion and will be tricky to disentangle. In any event, molecular recognition here is much more than a case of complementarity between receptor and substrate — it also crucially involves the solvent. This suggests that changes in protein and solvent dynamics are not mere epiphenomena, but have a vital role in substrate binding and recognition: they are more cause than consequence.

As well as offering a fresh view of biomolecular shape and function, these findings[1–3] pose a daunting yet stirring challenge. Given that most drugs are ligands that bind to biological targets, will it be possible to make the fine-tuning of water structure and dynamics an element of drug design? Indeed, can we hope to compete systematically with natural recognition processes at drug targets unless that mastery is attained? ■

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CORRECTION

In the News & Views article 'Chemical biology: Many faces of a cancer-supporting protein' by John F. Darby and Paul Workman (*Nature* **478,** 334–335; 2011), the authors' declaration of competing financial interests was inadvertently omitted. Details can be found in the online article at go.nature.com/x7hedv