ligands and co-factors can now be studied intact using mass spectrometry[5]. As progressively more complex systems are studied, however, a crucial question remains: to what extent do these macromolecular assemblies maintain their solution-phase characteristics in the gas phase?

One approach that can address this question — and indeed one of the approaches used by Liu and colleagues[3] — is ion-mobility spectrometry. This technique monitors the progression of ions through an inert buffer gas, and provides information about the size of molecules that is complementary to that obtained using traditional mass spectrometry. Such experiments have shown that the global structure of macromolecules, including the topology of fragile multi-protein assemblies, can be preserved in a vacuum[6]. But the extent and, importantly, the timescale over which local elements of structure are maintained remain less well understood[2], particularly for hydrophobic interactions. It is, therefore, vital that less complex systems are examined in detail, such that individual interactions can be addressed at almost the atomic level.

Liu *et al.*[3] have done just this, by examining the binary complexes formed between the protein β-lactoglobulin and different fatty acids in the gas phase. These small molecules, composed of a water-repellent hydrocarbon chain and an acidic head-group, bind in a hydrophobic pocket within the protein, and the resultant complexes can be maintained intact in a vacuum. The researchers slowly heated these complexes in a mass spectrometer, causing the fatty acids to dissociate from the protein, and monitored the process with mass spectrometry. The great advantage of the authors' approach is that it allows temperature-dependent kinetic parameters for the dissociations to be obtained.

Backed up by ion-mobility measurements and molecular-dynamics simulations, Liu *et al.* found evidence for two distinct types of structure. In the first, the protein adopts a 'closed' conformation, wherein the head-group of the fatty acid forms hydrogen bonds with residues at the entrance to the pocket. It is therefore not surprising that this protein–ligand complex survives in the gas phase.

In the second, more 'open' structure, however, such stabilizing hydrogen-bonding interactions are absent, yet the complex nevertheless remains intact within the mass spectrometer. The authors observed that the energy required to dissociate fatty acids from this structure (the activation energy for dissociation) scales linearly with the length of the acid's hydrocarbon chain, and hence with the amount of nonpolar interaction between the acid and the protein. Moreover, the authors found the activation energies to be similar to the energies expected to be required to dissolve the fatty-acid chains in organic, nonpolar solvents. So, although in both kinds of structure the fatty acid is bound within the hydrophobic cavity, in the open case the lack of hydrogen bonding means that the interactions are solely nonpolar, occurring between the fatty acid's hydrocarbon chain and the hydrophobic amino-acid residues lining the protein's binding pocket.

The fact that these hydrophobic interactions can be maintained in the gas phase (albeit in a simple bimolecular interaction) on the timescale of mass-spectrometry investigations is a crucial observation. The extent to which these findings apply to other systems remains to be seen. Nevertheless, Liu and colleagues' results[3] provide a clear rationale for how the structural integrity of various non-covalently bound complexes is maintained in the gas phase — particularly for those that rely heavily on hydrophobic interactions, such as membrane–protein complexes[7], or assemblies of molecular 'chaperones' with unfolded client proteins[8]. Moreover, the authors' observations demonstrate that even those interactions that seem, intuitively, to be the most susceptible to deformation upon dehydration can be maintained in the gas phase. This provides strong validation of the idea that mass spectrometry can be used not only as a tool for identifying and quantifying the proteins in cells, but also for characterizing the complexes they form.

The emergence of mass spectrometry as a tool for structural biology comes as the field itself is undergoing dramatic changes. Although initiatives in structural genomics have been determining protein structures at a remarkable rate, the structures of many vital targets remain frustratingly elusive. Furthermore, the essential role of conformational fluctuations in protein function has become increasingly apparent, although the characterization of these protein dynamics is difficult. As such, there is a realization that new tools need to be developed to complement traditional methods in structural biology. Hybrid techniques are emerging that combine information collated using several different methods[9]; mass spectrometry, with its ubiquity, speed and ability to work with small samples, is well placed to contribute. Indeed, with Liu and colleagues' report[3], the advent of reliable structural information — everything from simple binding stoichiometries to diffraction patterns of individual macromolecules[10] — obtained from gas-phase measurements alone moves one step closer. ■

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50 YEARS AGO

Composition with an Electronic Computer. By Prof. L. A. Hiller, Jr., and Leonard M. Isaacson — So much is heard nowadays of the capabilities of the computer robot in imitating every human activity that it is not surprising to read of experiments in which the computer is made to compose music. Perhaps to say that the machine 'composes' is putting the experiments described in this book at too high a level ... Nevertheless, these experiments are amusing and the account of them is well written, so that one does not need to be a *habitué* of the computer room to understand what the authors were planning.
From *Nature* 5 December 1959.

100 YEARS AGO

My attention has just been directed to a letter which appeared in NATURE of March 11 ... It was signed by Prof. McKendrick, and dealt with the vexed question of the blind and their faculties. I am a blind man, and have mixed with blind people of all ages for the past thirty years ... Permit me to thank you for what you say about the popular notion that when a person loses his sight he is compensated by a gift of ability in one, if not all, his other faculties. The intelligent blind know how foolish this idea is, and constantly protest against it ... We are credited with marvellous powers in music, basket-making, &c., and yet when we assert our claim to live the ordinary life of the citizen these people are shocked at our audacity ... My own experience has compelled me to take heed of the varying degrees of what I shall call, for want of a better name, ear-power ... When people are speaking to me, they are never on guard to control their countenance as they would be if conversing with a sighted person ... I know when a person smiles, frowns, when the face lights up with an intelligence or when apathy and want of perception cloud the countenance.
From *Nature* 2 December 1909.

50 & 100 YEARS AGO