50 Years Ago

By and large the effect of automization is to reduce severely the demand for unskilled and semi-skilled workers and to increase sharply the need for skilled workers … This trend is surely to be welcomed. Repetition work is an insult to the people who have to do it. It treats them as less than human. It is not surprising if it often turns them into something less than human. If you make a man spend eight hours a day in which he has nothing to … exercise his mental powers on, is it surprising that he is incapable of exercising those powers in his leisure time and must spend it watching television or wrecking a dance hall? Automation offers the prospect of giving every man and woman a job that is interesting and worth doing in itself, a job requiring initiative or creative thought. Surely that is as desirable an object as providing a higher standard of material living.
From *Nature* 22 June 1963

100 Years Ago

After expressing his admiration for the character of Wilbur Wright … the lecturer considered the resemblance and differences of the manufactured aëroplane and the living bird. The resemblance may be simply the result of copying the bird, or it may be that similar designs have been arrived at independently by birds and men … These resemblances are remarkable, but there are great differences … No flying animal uses a continuously rotating propeller to drive him forward on soaring wings, and it is perhaps scarcely too much to say that if birds only knew how, they would now copy the Wright brothers. Muscular action and the circulation of the blood, however, put supreme difficulties in the way of the development of the continuous rotation of a part of an animal.
From *Nature* 19 June 1913

from a balance of competing effects. As revealed by an ensemble representation of proteins, effector binding stabilizes both the active and inactive forms of the functional domain, which means that the effector is potentially an activator and an inhibitor. So what determines whether the effector will activate or inhibit?

The answer is the relative stability of each state in the ensemble. Under one set of conditions (Fig. 2a), the ensemble could be poised such that effector binding causes activation. But under another set (Fig. 2b), effector binding can cause inhibition. Crucially, a switch in cooperativity can arise as a result of any type of perturbation (such as the binding of another molecule, post-translational modification or protein truncation) that can redistribute the ensemble of conformations[11], even to the extent of transforming effector binding from activating to inhibiting, or vice versa.

Although Ferreon and colleagues' work does not reveal how the observed cooperativity switch occurs, it does help to clarify the following key questions that underlie a quantitative understanding of signalling in IDPs, and perhaps also in structured proteins. What states comprise the protein ensemble, and what are their probabilities? And are there ground rules that dictate whether signalling, or even activation–inhibition switching, can occur in an ensemble[10,11]? The take-home message of Ferreon and colleagues' work, and the reason that a switch is possible, is that proteins should not be thought of as multiple copies of identical structures that respond uniformly to a signal. Instead, proteins — especially IDPs — exist as ensembles of sometimes radically different structural states. This structural heterogeneity can produce ensembles that are functionally 'pluripotent', a property that endows IDPs with a unique repertoire of regulatory strategies. ■

Vincent J. Hilser *is in the Departments of Biology and Biophysics, Johns Hopkins University, Baltimore, Maryland 21218, USA.*
e-mail: hilser@jhu.edu

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VIROLOGY

The virus whose family expanded

The discovery of many new species of hepaciviruses and pegiviruses, which exhibit enormous genetic diversity, in wild rodent and bat populations might help us to understand the origins of the hepatitis C virus.

OLIVER G. PYBUS & REBECCA R. GRAY

The hepatitis C virus does not give up its secrets lightly. Despite infecting about 3 out of every 100 people worldwide, a small proportion of whom consequently develop severe liver disease, the virus eluded discovery for decades. It was eventually identified in 1989 as the cause of 'non-A, non-B hepatitis'. Researchers who have since sought the origins of hepatitis C virus (HCV), as it is now known, have been frustrated in equal measure. The virus infects chimpanzees in the laboratory, but studies of wild and captive primates uncovered no evidence of an animal population that might have transmitted HCV to humans[1], contrasting with the success of other surveys that exposed close relatives of HIV-1 and human malaria in great apes[2]. Now, however, Kapoor *et al.*[3] and Quan *et al.*[4], writing in *mBio* and *Proceedings of the National Academy of Sciences*, respectively, report a diverse and widespread array of HCV-like viruses in wild populations of rodents[3] and bats[4]. Although none of these viruses can yet be claimed as the source of HCV, their discovery may represent the beginning of the end of the search for HCV's origins.

HCV belongs to the *Hepacivirus* genus of viruses, whose closest taxonomic neighbour is the *Pegivirus* genus[5]; the newly discovered bat and rodent viruses include members of both groups. Kapoor *et al.* found five provisional virus species among more than 400 blood samples from four North American rodent species. Quan and colleagues describe 11 virus lineages

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