and reefs of that age is difficult. Deep-sea $\delta^{18}\text{O}$ records (including some new data presented at the symposium) show isotopic depletions during MIS 11 that are consistent with a sea-level high, but in the isotope records the effects of warmer temperatures cannot be easily untangled from the effects of decreased ice volume.

To produce such a high sea level would require the collapse of at least one major ice sheet (candidates include the West Antarctic and Greenland Ice Sheets). The stability of these ice sheets in the face of high-latitude warming is one of the main questions in climate-change research.

These extremes in the ocean's thermal and geochemical state all lower its ability to hold CO_2 , leaving more in the atmosphere. First, CO_2 is less soluble in a warmer ocean. Second, as sea level and surface temperature rise, a greater proportion of biological production is in the form of calcium carbonate. This increased production and burial of calcium carbonate lowers the ocean's alkalinity, again reducing its ability to hold on to CO_2 . Third, decreased biological production of soft tissue reduces the export of carbon from the surface (in contact with the atmosphere) to the deep ocean⁵. These changes in the ocean's carbonate-carbon cycle during MIS 11 point to what might be an important set of interactions between temperature, ecology and CO_2 . Model simulations of oceanic CO_2 uptake have recently begun to take such feedbacks into account⁶.

Was the stage-11 warming driven by increased atmospheric CO_2 concentrations? The Vostok ice core now provides a palaeoclimate record extending to about 425,000 years ago⁷. Preliminary measurements suggest that atmospheric CO_2 levels during stage 11 are comparable to those of later interglacials, which would mean that the link between warming mechanisms and the carbon cycle may not be so simple. However, ice disturbance at the stage-11 level may have altered the CO_2 record (D. Raynaud, LGGE, Grenoble).

The symposium addressed only some of the evidence from and implications of the stage-11 warm interval. Was the climate stable, or punctuated by high-frequency 'flickers'? What was the global distribution of sea-surface temperature? Stage 11 has not been studied in detail, in part because few climate records have reached it. But new cores, extracted by Ocean Drilling Program technology and long gravity-driven piston cores in high-accumulation-rate drift deposits, are beginning to provide more evidence.

Stage 11 may provide some important perspectives on future climate change. Are we adding greenhouse gases to a climate that, left to its own devices, should be on the way into another glaciation, as in the short-lived stage 5; or one that would stay warm, or get

warmer, for another 40,000 years, as in stage 11? Are we setting in motion a chain of biogeochemical feedbacks that will add an oceanic contribution to the anthropogenic greenhouse-gas enrichment? □

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Protein engineering

Reading, writing and redesigning

Michael Groß and Kevin W. Plaxco

Nature doesn't have a protein-folding problem — but we do. Although we know that the line-up of the amino-acid building-blocks in a protein encodes the architecture of its correctly folded (native) form, we still cannot properly read or write this code. That is, we find it difficult to predict structures from sequences, or to design sequences that fold into a desired structure. In 1994, this dilemma prompted George Rose and Trevor Creamer¹ to offer a cash prize for the solution to a specific protein-design problem. And in this month's issue of *Nature Structural Biology*, Lynne Regan and co-workers report² that they have redesigned a protein into an entirely different fold by exchanging only 50% of its amino acids. This remarkable achievement has earned them the prize, less than four years after it was announced.

Engineering prizes have, arguably, driven technological advances in the past — from the first human-powered flight across the English Channel (Kremer prize), to the first steps in nanotechnology (Feynman prize). The protein-design equivalent of the first cross-Channel flight is the 'Paracelsus chal-

lenge', named after the sixteenth-century Swiss physician, philosopher and alchemist. In an editorial in *Proteins*, Rose and Creamer proposed the challenge, pledging \$1,000 for the first person to show a pair of proteins which have distinctly different topologies, but which retain no less than 50% sequence identity. Such pairs are not found in nature — databases show that pairs of proteins sharing 25% of their amino-acid residues usually have very similar structures³.

An identity score of 50% between two natural protein sequences would convince any biochemist that the proteins must be nearly identical in structure. On the other hand, because the structural identity of a protein is determined by roughly a quarter of its building blocks, the task — which is a bit like turning this article into a report about a tennis match by exchanging only half of the words — is a realistic one. In the language of proteins, most of the words seem to be space fillers that do not convey a specific meaning, so the challenge is to find the important words and rewrite them. Regan and co-workers have met the challenge with style. Rather than simply converting a given pro-

Figure 1 The two faces of protein folding. Dalal *et al.*² have risen to meet the 'Paracelsus challenge', by designing a pair of proteins that have completely different folds yet have no less than 50% sequence identity. a, The starting material was the B1 domain of the streptococcal IgG-binding protein G, which is mainly β -sheet. b, By modifying just 28 of the 56 amino acids in this region, they created a new protein which they called Janus. Janus has 50% sequence identity with the B1 domain, yet its mainly helical structure resembles that of the RNA-binding protein Rop. c, Rop, a homodimeric four-helix bundle protein. Blue boxes, residues from B1; red boxes, residues from Rop; black boxes, residues that are identical in B1 and Rop; white boxes, residues from neither B1 nor Rop.

tein into whatever different structure was the most easily attainable, they specifically set out to convert the B1 domain of protein G, which consists of a four-stranded β -sheet packed against a single helix⁴, into a new protein with the folded structure of another protein, Rop (repressor of primer). Rop is an RNA-binding protein that folds as two helices associating to form a four-helix bundle⁵. Their strategy was to identify the key residues of the B1 domain that encode its mostly β -sheet structure, and to replace those residues with the corresponding, structurally critical amino acids of Rop.

What are the essential features of a protein that we have to specify to define its fold? There are four important goals, all of which aspiring protein designers must achieve⁶. The first is to initiate and terminate elements of secondary structure (the helices and β -sheets that are shown as ribbons in structure cartoons; Fig. 1). The second is to create a hydrophobic core — a congregation of water-avoiding amino-acid side chains whose reluctance to be exposed to the solvent will stabilize the correctly folded structure. The third goal is to supply sequences that encode loops and hairpin turns in the protein backbone, to connect sequential, secondary-structural elements. Finally, specific tertiary links need to be created; that is, energetically favourable interactions between amino acids that are distant in the sequence.

Following this logic, to swap the protein identities Regan and co-workers first had to replace residues that had an empirically observed tendency to form sheets, with other residues that prefer to be in a helix. Then they constructed the appropriate core structure based on their previous characterization of simplified core variants of Rop^{7,8}. They also pinched from the Rop sequence a salt bridge (a pair of oppositely charged amino acids) and a single tyrosine residue as a spectroscopic probe of the folded state.

These modifications account for 28 amino acids — exactly 50% of the original B1 sequence. As well as the 56 residues that form the helices (and were the design target in this study), Rop has an unstructured 'tail' of seven residues. This was found to be essential for the good water solubility of Rop, although not for its structure, and it was also included in the design.

The new protein was fittingly called Janus (Fig. 1), as it looks like the B1 domain on the sequence level but was expected to show the face of Rop on the structural level. Regan's group cloned Janus into bacteria so they had enough material for structural investigations and could address the crucial question — does Janus really look both ways? As they had predicted, Janus showed the circular dichroism and nuclear magnetic resonance signatures, isotope-exchange properties and highly cooperative unfolding that would be expected of a folded protein with the structure of Rop.

Based on these results, it was agreed that Janus had met the criteria of the challenge, and Regan was awarded the Paracelsus prize in a small ceremony last month.

Although this achievement is an impressive demonstration of just how far our knowledge of the determinants of protein structure has come, a few questions remain. For example, can the limit of sequence identity be pushed higher than 50%, and can the transformation be done in the opposite direction? Regan's group is now addressing the limits of the sequence identity by reverting the changes made from B1 to Janus, one by one. But it might be more difficult to do the transformation in the opposite direction, as the formation of β -sheet structures depends on interactions between sites that may be far apart in the sequence. Still, the demonstration that

protein designers now know which half of the text they have to rewrite to change a protein fold means that, one day, we will be able to read and write the code of protein folding. □

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Sociology of science

Irregular scientific conjugations

The perception of behaviour varies with the distance of the observer from the subject. This variation generally extends along a continuum but, in the special case of the behaviour of scientists, three primary clusters of distance seem particularly important. These can be defined as identity (I), unrelatedness (U) and separated/heterologous (S/he). Results in ten areas of behavioural perception within science can thus be summarized as irregularly conjugating verbs.

I construct precise and logical sentences

You write in a standard scientific style
She produces incomprehensible papers riddled with jargon

I am frequently asked to appear in TV science documentaries

You are a typical eccentric media-friendly boffin
He is a self-promoting pseudoscientific media whore

I am a polymath

You are a jack of all trades
She has views on subjects she knows nothing about

I publish every finding for the wider scientific community

You have a refined strategy for building an impressive publications list
They are salami slicing

I am a confident speaker in panel discussions

You are charmed by the sound of your own voice
He shouts down the views of other participants

I have a reputation that enables me to attract bright young scientific talent

You have a reputation maintained by a highly able team of collaborators
He has a reputation for exploiting poorly paid postdocs

I ensure that a company's scientific approach is up to date

You reassure investors by your presence on the Scientific Advisory Board
He receives a fat retainer simply because he has a Nobel prize

I undertake peer-review carefully and thoroughly

You delay returning your comments on the paper
She conducts additional experiments for her own paper while the manuscript languishes in her pending tray

I do not publish preliminary data

You conduct follow-up experiments in order to maintain a scientific lead over competitors
He hoards data until his industrial collaborators have filed patents

I actively solicit and review high-quality papers

You provide useful comments on the occasional manuscript
They are only on the editorial board to preserve the façade of geographical balance

John Hodgson

John Hodgson is a senior editor of *Nature Biotechnology*.