HIV

See a pocket, block it

John P. Moore and Tatjana Dragic

Although drugs such as protease and reverse-transcriptase inhibitors have had a huge effect on treating AIDS in the developed world, they are not without their problems: they do not eradicate HIV-1 from infected people[1]; long-term side effects have been observed[2]; and drug-resistant variants of HIV-1 are emerging[3]. There is a pressing need to identify new classes of anti-HIV-1 drugs, and, reporting in *Cell*, Eckert *et al.*[4] signal a way forward. They have discovered that a cavity formed in the HIV-1 gp41 transmembrane glycoprotein can accommodate small, circular D-peptides — peptides that could prevent HIV-1 from fusing with, and entering, human cells.

Central to the immunodeficiencies of AIDS is a block to production of T cells bearing the cell-surface protein called CD4. When drugs reduce viral replication, the immune system gains time to repair this block[5]. The gp41 trimer mediates the initial fusion of HIV-1, and its potential as a drug target was revealed when large peptides derived from gp41 were found[6,7] to inhibit HIV-1 infection *in vitro*. These peptides insert a metaphorical spanner into the works — they inhibit conformational changes within gp41, substituting for one or more components of the trimer and preventing the necessary intermolecular interactions that drive membrane fusion[8,9].

One version of these peptides, known as T-20, has been shown in clinical trials to reduce viral load, an important proof of concept for HIV-1 fusion inhibitors[10]. But large peptides make imperfect drugs because they cannot be administered orally and they are rapidly metabolized. Indeed, most successful drugs have a relative molecular mass of less than 1,000. So do any inhibitors of gp41-mediated fusion not have the drawbacks of conventional peptides? Eckert and colleagues' results[4] indicate that some, to a certain extent at least, do.

The same group previously described[11,12] a cavity in gp41 that seemed to be of a suitable size and location to act as the binding site for a fusion inhibitor. This cavity is not identical to the binding site for T-20 and related peptides, but it is a part of it. Eckert *et al.* have now engineered a simplified version of the cavity, designated IQN17, by fusing a soluble, trimeric helical peptide (GCN4–pIQI) to 17 residues of the relevant gp41 region. This, in effect, produces a stable gp41 intermediate[4]. The authors then used IQN17 as a bait in a sophisticated screening procedure, based on phage-display library technology, to fish out the D-peptides that bind from a random pool. They showed that these peptides bind within the pocket of authentic gp41, successfully inhibiting membrane fusion (Fig. 1).

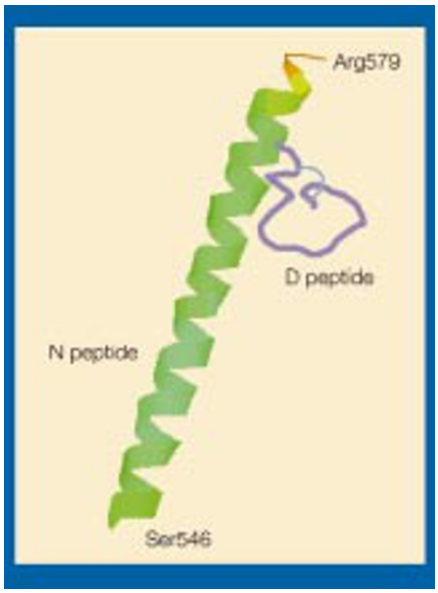

Figure 1 **Plugging the gp41 pocket. Ribbon representation of a circular D-peptide inhibitor (purple) bound to an α-helical stretch of gp41 (green). Of the 16 residues in the peptide, only six interact directly with the gp41 pocket.**

Why did the authors choose D-peptides? These peptides contain D-amino acids, whereas all natural peptides contain the mirror-image L-form. But, because D-amino acids are unnatural, the peptide bonds between them resist digestion by cellular enzymes, increasing the stability of the peptide *in vivo*. Indeed, Eckert *et al.* note that cyclosporine A, a widely used drug that can be given orally to counter transplant rejection, contains D-amino acids and is not much smaller than the best of their inhibitory D-peptides.

The current D-peptide inhibitors are not very potent, with IC_{50} values (the concentration of inhibitor that is needed to block gp41-mediated fusion by half) in the 10–100-μM range. However, the skilled hands of medicinal chemists can work wonders with starting compounds. Furthermore, Eckert and colleagues outline a plausible strategy in which IQN17 and the currently available D-peptides could be used in high-throughput screening assays to identify small-molecule inhibitors from conventional chemical libraries. There are many steps along the path from the bench to the pharmacy, but the first is often the most difficult. Together with inhibitors aimed at other components of the HIV-1 fusion process[13], derivatives of the newly identified D-peptides may eventually be valuable weapons with which to fight HIV-1 infection. ■

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Computational neuroscience

Think positive to find parts

Bartlett W. Mel

How do you tell a shovel from an acorn? A bicycle from a mango? A young face from an old one? They look different, of course, but what exactly are the 'features'or 'parts' that our brains use to tell one thing from another? On page 788 of this issue, Lee and Seung[1] present a new algorithm for learning object parts. Known as non-negative matrix factorization (NMF), their algorithm follows from the simple prescription that parts are collections of input elements that tend to come and go together, and which can be added together in different combinations to give objects of interest.

In the visual realm, the authors' view of parts is similar to the idea behind identikits — the collections of mix-and-match face parts used to reconstruct the identities of wanted fugitives or lost children. Parts that are too much like whole objects are rejected, because this would require an impracticably large inventory. Lee and Seung's approach also shuns parts which, although few in number, must be combined in counter-

intuitive mixtures to reconstruct objects of interest.

Learning techniques (the core of 'neural-network' theory) have been used in various ways to find components of objects or images[2,3]. Lee and Seung take a so-called unsupervised approach, the goal of which is to find structures — or 'basis functions' — that help to 'explain' a training set, in the sense that training examples can be faithfully reconstructed using appropriate combinations of the discovered basis functions. What distinguishes Lee and Seung's approach from other structure-finding algorithms is the way in which the basis functions must be combined to build target objects — these authors say that the combinations should be exclusively additive. Their approach reflects the idea that objects are most naturally described by the inventory of the parts they contain. Or, to look at things the opposite way, parts are precisely those entities that allow objects to be reassembled using purely additive combinations.

When Lee and Seung asked their NMF algorithm to decompose a set of faces, they found that the resulting basis functions were visibly different — and more part-like — than those found by conventional structure-finding algorithms such as principal components analysis (PCA) or vector quantization (VQ), although see ref. 4. Unlike NMF, PCA decomposes images into conceptually opaque additive and subtractive combinations of basis functions. The VQ technique represents objects using a set of whole-object prototypes, similar to the way in which suitcases are identified at an airline's lost-baggage counter. In other words, PCA finds parts that are not very intuitive and VQ ignores part structure altogether.

What is the importance of Lee and Seung's contribution? Most compelling is the argument that NMF's non-negativity constraint is well matched to our intuitive ideas about decomposition into parts. Second is the fact that the resulting basis functions differ in an interesting way from those generated without the non-negativity constraint. And third is the elegance and simplicity of the algorithm.

But there are caveats too. The authors rely on subjective appraisal — the look and feel — of their results to support the claim that NMF is better at finding the underlying component-based structure of complex objects than, say, PCA. And although Lee and Seung find that the NMF basis functions learned from faces seem to consist of "several versions of mouths, noses and other facial parts", another observer might describe many of these same basis functions as partial renderings of several face parts in unintuitive combinations (see Fig. 1 on page 789). Moreover, a simple threshold applied to PCA or VQ basis functions could considerably reduce the differences between these more 'global' basis functions and the more 'local' NMF ones.

Another question is how NMF basis functions relate to 'parts' as conventionally defined[5]. Given that the basis functions depend only on coactivation of input elements, a blob in a basis function extracted from a set of facial images could arise from the collusion of nose pixels in one image, upper-lip pixels in another and shadow pixels in a third. That is, unrelated entities, or 'causes', could be lumped within the same so-called NMF 'part'. But this display of poor parts-manship is less a commentary on NMF than it is a consequence of the input format (raw pixel values) and simplified representational scheme (weighted sums). Together these variables make it difficult for NMF, or any comparable scheme, to discover the deeper semantic structure that is normally associated with a parts-based representation.

Lee and Seung draw part of the inspiration for their non-negativity constraint from biology — that is, they point out that the firing rates of neurons are never negative, and that synaptic strengths do not change sign. But is this germane? Receptive fields in the brain often come in opponent pairs, where the positive and negative ranges of a variable are represented by the positive firing rates of two separate neurons (for example, 'on'- and 'off'-centre cells). Moreover, individual neurons, which are presumed to be the feature detectors in our own visual systems, typically show one or more kinds of opponency within their receptive fields. So a stimulus that is excitatory in one part of a receptive field may be inhibitory in another. In short, positive and negative quantities seem to be intermixed throughout our perceptual systems.

Despite the caveats, Lee and Seung's work is clear and thought-provoking, bearing on a scientific question of great importance — how to extract meaningful patterns from a complex world. To boot, their NMF procedure will be a practical tool for structure-finding that will probably have a significant effect on future work in the area. ■

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erratum Due to an editorial oversight, the picture accompanying the article "Neurobiology: Cognition by a mini brain" (*Nature* **400,** 718–719; 1999), did not carry the correct attribution. It should have been credited to Karlheinz Rein of the Lehrstuhl für Genetik, Biozentrum, Würzburg.

Daedalus

Setting and upsetting

Last week Daedalus presented his 'Wet Cement', a hygroscopic concrete which set but never dried out. A building made from it could creep rather than crack while settling into the soil. He is now taking the idea to extremes. His new, even more advanced cement does not merely creep under load; impact liquefies it completely. The result is the first thixotropic, re-usable concrete.

Anyone who has wiggled a foot in damp beach sand, stirring it into a mobile porridge, will understand the principle. A pile of sand can resist steady compression; but no such pile is fully compact. A few grains take all the load, leaving the rest essentially free and unloaded. Under sudden shock or stirring, the grains shift into a denser packing which occupies a smaller volume. The water around them, however, cannot shrink. The grains find themselves suspended in excess water under strong agitation. They slump into a strengthless fluidized mass.

So DREADCO's Thixocrete contains sand to carry the load, hygroscopic compounds and water-absorbing polymers to keep it wet, and a highly impure, mixed calciferous setting cement. As in ordinary cement, its crystals precipitate from the water to hold the sand grains in place. But the crystals, loaded with impurities and dislocations, are extremely brittle. They shatter to fragments under sudden shock or vibration, freeing the sand grains to fluidize in the water. Now small crystals preferentially dissolve in water whereas bigger ones crystallize from it (this is the 'ripening' action of a chemical precipitate). So when agitation ceases, new crystals slowly precipitate, and knit into a restraining matrix round the sand grains. The Thixocrete slowly sets again.

Thixocrete will transform the building trade. The new product will be made and transported not in slowly rotating mixers but in vigorously stirred tanks. Pumped into moulds or extruded along lines of bricks, it will set in minutes. Any mistake or design error will be easily rectified by a powerful vibrator or wrecker's ball, shocking the structure back to re-usable fluid Thixocrete. By the same token, a Thixocrete structure will be easily demolished. And an earthquake or bomb attack will not shatter it disastrously. Instead it will flow and slump. Falling pieces will be soft and plastic; escapers will wade to safety through them. And the deformed building will not be a hazardous, unstable ruin. It will slowly regain its strength.

David Jones