COMPUTATIONAL CHEMISTRY

Getting focused

As any management guide will tell you, when faced with a large and complex problem, it can often help to step back and look at the big picture before focusing on the key points. Writing in the *Journal of the American Chemical Society*, Graham Richards and colleagues describe how such a strategy could be just as applicable when trying to locate ligand-binding sites in protein structures — a problem that is becoming increasingly important for drug discovery in the post-genomic era.

If you have a three-dimensional protein structure, potential binding sites for a ligand could in theory be identified computationally by calculating the energy of interaction between the ligand and the protein in all possible ligand configurations around the protein. But, in reality, the number of calculations that are needed for such a strategy means it is impractical in terms of computational time for all but the most simple ligands.

So, could the number of calculations be reduced without sacrificing predictive ability? Richards and colleagues devised an elegant approach to this problem. Initially, a very simple model of the ligand — just a single feature point — is generated using an algorithm and used in evaluations of the energy of interaction with the protein. After removal of any ligand configurations with a low score in terms of potential for binding, a new round of calculations are carried out using a ligand model generated to have two feature points. Repeating this evaluation–removal process, while increasing the complexity of the ligand model at each step, allows computational time to be efficiently distributed, as only the most relevant configurations are considered in any detail.

To validate the strategy, the authors took seven known ligand–protein structures — including structures as diverse as HIV reverse transcriptase with a non-nucleoside inhibitor and heparin with basic fibroblast growth factor — removed the ligand, and then attempted to locate the binding site using stepwise algorithmic models of the ligand.

In all cases, the binding site was correctly identified, and furthermore, so was the orientation of the ligand. So, it seems that this approach could become a valuable tool for analysing the wealth of data that is emerging from structural genomics projects.

Peter Kirkpatrick

References and links

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VASCULAR DISEASE

Getting the measure of stroke

When attempting to treat stroke, it pays to know the nature of the beast. Acute stroke consists of an evolving infarction — an area of brain tissue that is damaged beyond repair — surrounded by an 'ischaemic penumbra', which, although threatened, can potentially be rescued by restoring blood flow to the affected area. But brain 'reperfusion' with thrombolytic agents carries with it the risk of haemorraghic complications, and is effective only in those cases in which there is a penumbra to save. So, how to tell when to use it? A study published in the *Annals of Neurology* now shows how a new version of X-ray computed tomography (CT) can be used in acute stroke patients to decide whether reperfusion will be effective, and also to predict the final infarct size and expected clinical progression.

Stroke diagnosis has relied on the use of CT for more than 30 years, but this study uses a modern variant, perfusion CT, that can generate brain images at a much faster rate. Perfusion CT can be used to monitor the passage of injected CT dye through the brain, and therefore to create maps of cerebral blood volume and cerebral blood flow — measures that correlate with the size of the infarct and the affected penumbra.

The technique was applied to 22 adult stroke patients at the time of emergency-room admission, and was found to be highly predictive of the cerebral infarct size measured three days later by magnetic resonance (MR) imaging, which is the accepted best method at present for detecting the area of long-term damage. Furthermore, the initial size of the combined cerebral infarct and penumbra defined by the admission perfusion CT correlated better with various standard assessments of clinical status than did the delayed MR measurements. Interestingly, perfusion CT also seems to allow the identification of tissue within the penumbra that can be salvaged by reperfusion, and so can be used to guide the choice of therapy.

The main hurdle for the development of drugs for stroke is the difficulty of organizing large-scale clinical trials. Importantly, these new findings might pave the way for the use of perfusion CT in monitoring the effects of neuroprotective drugs in individual patients, therefore allowing small Phase II efficacy trials.

Adam Smith

References and links

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