Published Recommendation

Accurate Structure Prediction of CDR H3 Loops Enabled by a Novel Structure-Based C-Terminal Constraint.

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3D modelling of antibodies is an important problem; in general, it is possible to produce very high quality models of antibodies except in the CDR-H3 loop, which does not follow the rules that the other CDRs adopt. Many modelling methods, including Rosetta Antibody, developed by the authors, involve two steps: (1.) generating a range of conformations (sampling) and (2.) screening those conformations to find the best model (ranking). A question addressed in this paper for CDR-H3 is which of these steps needs most improvement and they find that high quality conformations are not being generated. In particular, 'kinked' conformations, identified by Shirai as long ago as 1996 and present in >80% of known structures, were not being generated. The authors have added constraints into the conformation generation to encourage the generation of more kinked conformations and this improves the CDR-H3 conformation by 0.1-1.3A for 49 antibodies but makes it worse for five antibodies (by 0.2-0.6A). The method, of course, does not help the ~20% of antibodies that do not have kinked CDR-H3s. The paper shows an improvement in performance for Rosetta Antibody and suggests useful techniques that could be incorporated into other antibody modelling methods.

Disclosures
None declared