O-17.2 Invited speaker

Multiscale modelling combining atomistic and coarse-grained molecular simulations with low-resolution SAXS data: a route to the rational engineering of antibody structure and function

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Small-angle X-ray scattering (SAXS) is a powerful, low resolution, approach to exploring the structure of biological molecules in solution. In contrast to X-ray crystallography, the full solution-phase ensemble is responsible for the X-ray scattering. However, extracting structural detail at the atomistic level from SAXS data is not possible. Here we combine experimental SAXS data with coarse-grain protein modelling using the Carbonara software, to generate starting structures from which atomistic molecular dynamics (MD) simulations are initiated. Through this workflow, reweighting of the simulation trajectories is then used to generate ensembles of atomistic protein models which are consistent with the low-resolution SAXS data.

We have used this combined multiscale simulation/experiment approach to rationally optimise immunostimulatory antibodies. These antibodies have potential as anti-tumour agents. By introducing disulfide bonds to the hIgG2 hinge region of the clinically-relevant anti-hCD40 mAb ChiLob7/4, we show that the least conformationally flexible antibodies are the most biologically active. The X-ray crystal structure is then used to rationally engineer additional disulfide bonds which rigidify the antibody in solution, eliciting a strong immune response. This strategy allows for the rational design of more powerful antibody therapeutics.