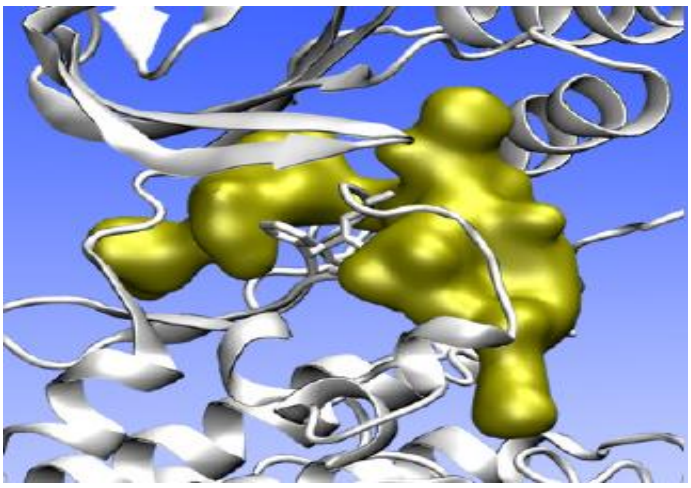
Case Study: University of Manchester and Johnson & Johnson

Protein Conformational Change using Molecular Simulations



Testimonial

"The simulations were aimed at understanding protein kinase conformational changes and were conducted together with the team from the University of Manchester. The expertise and flexibility of the team from the University of Manchester, as well as the computational resources from N8 HPC were key in defining new opportunities for drug design."

- Dr Berthold Wroblowski, Johnson & Johnson

Project

Polaris, the N8 HPC facility, is being used to reveal hidden pockets in protein structures. Protein structures solved by X-ray crystallography provide a static picture of protein topology. Computational approaches have the potential to reveal concavities in the protein's topology. However, the energetic barriers between protein conformations can be large, which hinders the use of conventional computational approaches such as molecular dynamics simulations. We have developed an approach which improves the conformational sampling of molecular dynamics simulation by using a swarm of coupled replicate simulations. In this method, which we call swarm-enhanced sampling molecular dynamics (sesMD), the replicas sense each other's presence via a particle-like potential. We are applying this method to study conformational changes in protein kinase structure.

Partners

Dr Richard Bryce – University of Manchester

Dr Berthold Wroblowski – Johnson and Johnson Research and Development, Belgium

Professor Pascal Bonnet – University of Orleans, France

Impact

Accurate prediction of protein plasticity has the potential to reveal druggable pockets on the surface of protein structures that may not have been apparent from experimental structure determination methods. Targeting these pockets with structure-based design can provide new directions in the design of therapeutics, for example, in the generation of small molecule inhibitors of protein function which have a novel chemical scaffold, novel mode of action and improved selectivity.

Success

The sesMD method involves multiple interacting simulation systems and therefore is inherently a parallel algorithm, requiring good interconnect linking multiple fast cores. N8 HPC was able to provide this capability and also the capacity to run multiple simulations to allow the exploration of different initial structures and simulation conditions. We applied the sesMD approach to predict the plasticity of p38a mitogen-activated protein kinase, an anti-cancer enzyme target linked to key cellular processes such as proliferation, apoptosis and differentiation. From a single structure a p38a mitogen-activated protein kinase, we were able to generate a range of different conformations involving particularly the DFG loop region of the active site. While some of these conformations had been observed in other crystal structures, some conformations were novel and have formed the basis of further investigation of their druggability at Johnson and Johnson.

Johnson & Johnson

N8 HIGH PERFORMANCE COMPUTING