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Abstract: 114O

Utilising Enhanced Sampling to Resolve a Conducting Conformation of the CFTR Ion Channel

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The dynamics of proteins is critical to the function of cells. Unfortunately, the majority of their conformational changes occur on time scales which are much longer than we can simulate with molecular dynamics (MD). This means atomistic studies of proteins are inherently limited by the availability of protein structures released by structural biologists. These limitations are slowly being addressed by a set of computational techniques known as enhanced sampling.

Here we have demonstrated how the integration of machine learning techniques into enhanced sampling can teach us more about a complex protein system, the Cystic Fibrosis Transmembrane conductance Regulator (CFTR). The dysfunction of this chloride and bicarbonate channel causes the most common fatal genetic disease in Caucasians, Cystic Fibrosis (CF).

All available structures of the CFTR ion channel exhibit a constriction which is smaller than chloride ions, leaving unresolved questions behind its conduction mechanism. However, in the presented study, the innovative application of simulation methodologies has allowed us to move beyond this limitation imposed by structural biology.

By analysing unbiased MD simulations of CFTR with dimensionality reduction techniques, we discovered motions which dilated the outer pore of the channel. The energetics of these motions were then investigated with OPES-Metadynamics, to search for stable conformations. This combination of machine learning with modern enhanced sampling techniques allowed us to discover a stable, open conformation of CFTR. Further, with simple umbrella sampling, we were able to demonstrate that this conformation is capable of conducting both chloride and bicarbonate.

In combination with other evidence from the literature, our proposed open conformation appears to be in close agreement with the *in vitro* biophysical characterisation of the open channel. The elucidation of this fully open conformation has important implications for ongoing drug discovery efforts to treat CF.

The success of our enhanced sampling methodology indicates that computational models are now of sufficient accuracy and power to be used as tools to investigate complex cellular mechanisms.