Abstract Submitted
for the 4CS20 Meeting of
The American Physical Society

Conformational change and substrate binding to the bile acid transporter $\mathbf{ASBT_{NM}}$ FIONA NAUGHTON, OLIVER BECKSTEIN, Arizona State University — The apical sodium-dependant bile acid transporter (ASBT) utilises the sodium gradient to drive the reabsorption of bile acids from the intestine, operating through an alternating-access mechanism. It is of interest as a potential target for the treatment of hypercholesterolemia as well as for drug delivery. Structures of bacterial homologues, including that from Neisseria meningitidis ($ASBT_{NM}$) in an inward-facing conformation with sodium and the bile acid taurocholate bound, are available. However, less is known about the more dynamic details, including those involving substrate binding and the nature of the conformational transition. We have used molecular dynamics simulations to investigate the behaviour of $ASBT_{NM}$ on an atomistic scale. Metadynamics was used to explore the inward-outward transition and the binding landscape of taurocholate and sodium to inward facing $ASBT_{NM}$, with refinement using bias-exchange umbrella sampling to quantify the latter, characterising both the main and alternate binding sites. Together, these results represent an important step towards understanding the complete transport cycle of ASBT.

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Date submitted: 25 Sep 2020 Electronic form version 1.4