Weighted Ensemble Simulation of Alternating Access in Sodium Symporter vSGLT

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Many transport proteins use the energy in sodium gradients to drive the uptake of small molecules. These proteins clear neurotransmitters from the synaptic cleft and remove sugar from the gut. It is thought they operate via an alternating access mechanism in which substrate is bound in an outward-facing conformation followed by a transition to an inward state that delivers the cargo to the cell. X-ray structures of both states exist, but the long time required to see such slow events makes studying this transition using traditional molecular simulations prohibitive. We employed the weighted ensemble method, which focuses computational efforts on rare events, to study changes in the sugar symporter vSGLT. With this method we have observed hundreds of transitions. Analysis of these trajectories reveals insights into the mechanism of alternating access, which we believe will impact our understanding of the operation of these proteins and their roles in human disease.