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Ion permeation through neuronal nAChR ion channel

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Alzheimer's dementia is related to loss of inter-neuron communication by nicotinic acetylcholine receptors (nAChR) at post synaptic neurons, and successful therapy approaches rely e.g. on modulations of response signals initiated by ion flux through the receptor integrated ion channel.

We have evaluated Umbrella Sampling (US) and Steered Molecular Dynamics (SMD) pulling for calculation of the potential of mean force (PMF) of ion permeation through neuronal alpha7 nAChR, a cation selective channel, in order to understand the changes in electrical potentials connected to channel gating. SMD enables the discrimination between ion in- and efflux and allows detailed insight into permeation pathways (Figure 1).

Both methods show the same performance characteristics but require a different number of simulations with different simulation length. For construction of one PMF 300 separate 300 ps simulations are performed for US, but only one 2100 ps run for SMD pulling. Reasonable error estimates require three repetitions of US but two times twelve repetitions for SMD, which sum up to 9360 CPU hours in case of US and 6490 for SMD. SMD, therefore, needs 30% less time on low latency HPC clusters, but US gains advantage through distributed computing.

The potential energy barriers are calculated for Na^+ and Cl^- based on US and SMD pulling, enabling differentiation between ion types and their in- and efflux through the channel.

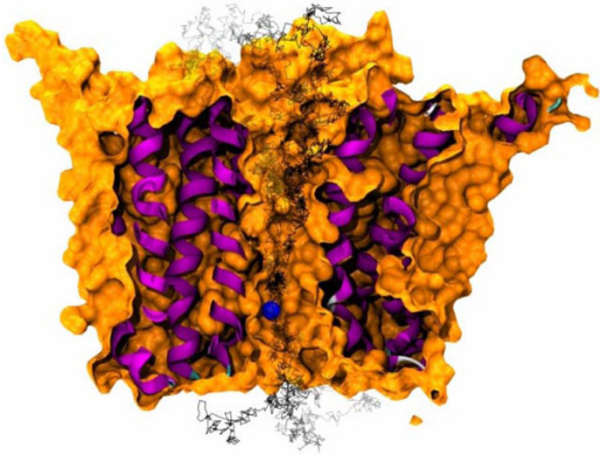

Figure 1 Cut through the transmembrane part of the nAChR. The thin gray lines correspond to individual permeation pathways.

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