Using Monte Carlo Microstates to Follow Proton Transport in Complex I

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The aerobic electron transfer chain in mitochondria and bacteria builds a proton gradient by proton coupled electron transfer reactions through multiple proteins. Complex I is the first enzyme in this chain. The energy liberated by the transfer of two electrons from NADH to quinone is coupled to movement of four protons from the N- (negative, higher pH) to the P- (positive) side.

Complex I use linear and complex pathways to transport protons. Three antiporter pathways are linear and use a few amino acids and waters to provide a route for protons. In contrast, the E-channel pathway is a complex of competing pathways. We will show how to analyze a complex pathway, asking: which proton transfer paths are favored; which residues bind and release protons through the transport cycle, forming a proton loading site (PLS); and what structural changes cause the PLS to load and unload the proton.

The program MCCE is used to analyze MD snapshots from trajectories with apo Complex I or with quinone or quinol bound. MCCE uses Monte Carlo (MC) sampling. All accepted MC microstates are saved and analyzed. The protonation microstates identify the protonation of all residues in the E-channel. At a pH 7 the five E-channel subunits (Nq04, Nq07, Nq08, Nq010, and Nq011) have >25,000 accepted protonation microstates. The changes in protonation microstates between different snapshots show a possible mechanism for proton transfer. Specific protonation microstates aid formation and disruption of hydrogen bonds necessary for network formation. The correlation between residue protonation states in the E-channel and how they are affected by structural changes induced within molecular dynamics trajectories are found. Multiple sequence alignment shows the conservation of residues that are key to the identified PLS. This work is supported by NSF MCB- 2141824