Denver

CHEMISTRY

Fall 2021

Seminar Series

12pm-1pm

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Zoom

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"From molecular dynamics to kinetic network analysis: How kinetic selection can drive biomolecular processes"

It is increasingly apparent from single molecule experiments that proteins often use multiple mechanistic pathways (sequences of transitions between intermediates). An outstanding challenge in biophysics is thus discerning how these competing pathways contribute to the overall mechanism. *How is the flux of a reactive process distributed between pathways? How does it change under different reaction conditions? And when does this sub-ensemble distribution really matter?* Herein, I will describe multiscale kinetic modeling, a framework aimed at addressing these questions, and its application to coupled Cl^-/H^+ exchange in chloride channel antiporters. By combining bottom-up quantification of transition rates from multiscale simulations with top-down refinement based on experimental data, ion-exchange networks are constructed and the flux through those networks is analyzed. The kinetic solutions reveal the molecular origin of the unusual 2.2:1 Cl^-/H^+ stoichiometry and influence of protein orientation. The dominance of different pathways will be shown to shift as a function of pH, highlighting the importance of the lower H^+ binding site in maintaining the ion exchange ratio over a range of pH values. The flux will also be shown to shift in response to transmembrane electrical gradient distinctly from that due to a chemical gradient of the same magnitude, pointing to a more nuanced influence of electrochemical potentials than commonly assumed by the Nernst relationship. These findings will be placed in the context of other biomolecular processes in which kinetics determines the dominance of different pathways and thereby defines unique mechanistic outcomes.