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Path Similarity Analysis: a Method for Quantifying Macromolecular Transition Pathways SEAN SEYLER, AVISHEK KUMAR, MICHAEL THORPE, OLIVER BECKSTEIN, Arizona State University — We develop a *Path Similarity Analysis* (PSA) approach to quantify the (dis)similarity of macromolecular transition paths, which are curves in a high-dimensional space. Quantitatively comparing these paths is necessary to, for instance, assess the performance of the varied enhanced path-sampling algorithms. Our approach can access the full information in $3N$-dimensional trajectories in configuration space and overcomes the limitations of low-dimensional projections and heuristic collective variables. We employ the Hausdorff or Fréchet metrics from computational geometry to measure a distance between piecewise-linear curves. Using the closed-to-open transition of the enzyme adenylate kinase (AdK) in its substrate-free form as a testbed, we compare a range of path-sampling algorithms, including the molecular dynamics (MD) approaches dynamic importance sampling (DIMS-MD) and targeted MD (TMD), geometrical targeting (FRODA), and elastic network-based methods. The new concept of a Hausdorff-pair map enabled us to extract the molecular structural determinants responsible for geometric differences in AdK transition paths, namely a set of conserved salt bridges whose charge-charge interactions are fully modeled in DIMS-MD but not in FRODA.

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