

**Achieving Long Time-Scale Sampling of Biomolecules: Hidden  
Free Energy Barriers and Orthogonal Space Sampling**  
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The “slow configuration response” problem has been the bottleneck problem in the field of biomolecular dynamics sampling. This issue has been significantly limiting the actual sampling capability of the entire enhanced sampling scheme. To systematically tackle this challenge, the orthogonal space theory and methods were developed and have been continuously enriched in the past years. With the maturing of this algorithmic framework, unprecedented sampling accelerations can be readily gained and encouraging results indicate that the dream of achieving biologically significant timescales is within reach.