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Reconstructing kinetic pathways from single-molecule FRET experiments using Bayesian inference JAN-WILLEM VAN DE MEENT, RUBEN L. GONZALEZ, JR., CHRIS H. WIGGINS, Columbia University — Single-molecule FRET studies have enabled observation of conformational transitions in individual molecules, allowing targeted investigations into the mechanistic function of molecular machines. Like in many single-molecule platforms, sm-FRET studies yield observations of hundreds of noisy time series, which report on the same underlying conformational steps, but exhibit significant variations in photophysical properties and kinetic rates. Reconstruction of a consensus kinetic pathway from such noisy measurements is statistically challenging. Hidden Markov Models are widely used to identify states and estimate the associated kinetic rates. Existing techniques perform inference on one time series at a time, yielding variable parameter estimates that must now be 'averaged' using ad-hoc experiment specific post-processing steps. Here, we propose a technique known as Empirical Bayes estimation, which performs simultaneous analysis on a collection of trajectories in an experiment. This results in a single estimate for a consensus kinetic model, as well as a significantly reduced estimation error. By comparing models with different constraints, we show how these methods may be used to test detailed mechanistic hypotheses in a statistically principled, adaptable manner.

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