

1. New code/analysis
 - (3.13b) Modify manuscript and code to initialize based on highest log likelihood from multiple random restarts.
 - (1) Analysis of apomyoglobin system (+new figures)
 - (3.2, 3.8, 3.13a) Add synthetic test to compare method with thresholding (two-state system with highly overlapping states), more nuanced discussion of our method vs. thresholding, discussion of using the threshold as the “first approximation” to our algorithm
 - (3.3) Comparison of model with HMM bootstrapping (perhaps with synthetic test above?)
 - (1) Analysis of two fibers of p5ab like RNA in table to show results agree within error bars (+new figures)
2. New/modified figures
 - (1.3) Add additional panel to supplementary figure 3 showing hopping in kinetic trace, plot exponential relaxation fits, amend caption
 - (1.6) New supplementary figure showing trace filtered at different bandwidths
 - (3.16) Supplementary figure with zoomed in regions of figures 2 and 3.
 - (3.17) Supplementary figure 3 on both normal and log scale.
3. Wording changes
 - (1.1, 3.4) Discussion of drift in manuscript, cite papers on instrument discussing drift (Jeff Moffitt’s PNAS paper on dual trap with analysis of S:N ratio, patent, Block papers on dual traps); In supplementary info, section illustrating behavior of 2-state system as function of drift (Is this necessary?)
 - (1.4) Clarify state exchange issue and move up discussion (reshuffling time series vs. state label exchange)
 - (3.1) Reference in letter on continuous vs. discrete input data and effects of binning (I assume this is just in the letter and not in the paper)