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Title: Adaptive Markov State Model estimation using short reseeding trajectories

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Dear Professor Voelz,

I have received the review of your manuscript from the referee to whom it was sent. The comments are below.

I apologize for the time taken in review and the fact that there is only one report. Another was promised but ultimately never delivered.

Please revise your manuscript accordingly, and return it within 4 weeks, along with a letter responding to each of the referee's points and describing in detail the revisions you have made.

With best regards,

John Straub,

Associate Editor

The Journal of Chemical Physics

Boston University

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P.S. You may submit a revised version (double spaced and in preprint format) at:

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In order to expedite the consideration of your manuscript and provide clarity to the reviewers, for each comment from each reviewer we ask that you respond in three ways: 1) reproduce the comment, 2) respond to the comment (even if you are not making any changes in the manuscript) and 3) indicate what changes (if any) you have made and where (specifically by page) in the manuscript these changes appear. In addition, it would be desirable to show all revisions made to the manuscript in color.

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Reviewer #2 Evaluations:

Recommendation: Major revision

New Potential Energy Surface: No

Reviewer #2 (Comments to the Author):

Wan and Voelz perform an empirical study of adaptive reseeding strategies for accelerating estimates of kinetic rates and reaction pathways. The work explores an important current topic in modeling-fitting for chemical reaction networks. The authors do a good job of summarizing the relevant literature, motivating the present work, and explaining the driving issues. The basic questions to be explored are well posed and potentially of broad value to users of model estimation methods. The study explores a few systems, both real and contrived, to gain insight into the effectiveness of a few classes of estimation method in this domain. The experimental protocols appear sound, with some caveats discussed below. The results lead to useful insights into the relative merits of various methods for integrating many reseeding trajectories and a suggestion for a good generally effective strategy. Overall, it appears to be a useful addition to the literature on the topic, although the work could be improved in some important respects.

**Reviewer concerns**

1. **Analytical models of convergence**

Probably the biggest weakness of the study is the strictly empirical focus on questions that would seem in principle to be at least partially amenable to analytical approaches. Perhaps complicated energy landscapes can only be understood empirically, but it would seem that questions about bias and convergence rates of the main estimators considered ought to be analytically solvable for at least some simple energy functions (e.g., a completely flat energy landscape or a single Gaussian potential well). The paper might be enhanced quite a bit by considering a few such trivial models, deriving analytical theory for how they perform, and comparing that to the empirical results on real systems. Even if one starts with the purely empirical study, rationalizing results in the same way --- via analytical derivations on toy versions of the empirical systems --- would seem a helpful step in explaining why the methods perform as they do.

We thank the reviewer or these suggestions. Simple diffusive motion\

We have

1. **More thorough modeling besides two-well and Anton data?**

Even within the purely empirical framework, the paper could benefit from some more thorough modeling. The use of the Anton data for real proteins is very nice and I think does a good job of showing that the conclusions are relevant to non-trivial real systems. Nonetheless, I believe considering more than just a single simple 1D model among the artificial data would be useful. For example, it would be helpful to know if the conclusions are greatly different for a system with many vs. one or two potential wells, with relatively smother vs. bumpier energy landscapes, deeper vs. shallower wells, many vs. few parameters, etc. While one obviously cannot try everything, I think it would be quite helpful to know if the main conclusions of the paper are robust across landscape types or vary with one or two important characteristics.

The paper might also do a bit more to compare results on the relatively simple estimators considered here to those one would get with more complex state-of-the-art methods. The paper mentions TRAM and DHAMed, for example. Head-to-head comparisons on the same model systems would be useful when possible, or at least a discussion of how one would expect a few of the more popular recent methods to perform in these same tests and why.

The paper itself is well written and easy to follow, with excellent use of informative figures, and I noted only a couple of minor errors:

Fig 5 caption: ``costuct the MSMs' --> ``construct the MSMs'

p. 8: ``greater that might' --> ``greater than might'

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