



DEPARTMENT OF CHEMISTRY

November 18, 2016

Dear Dr. Hamm,

We are resubmitting the following report, entitled “Identification of simple reaction coordinates from complex dynamics,” for publication in the *Journal of Chemical Physics*. This report was originally submitted on February 26, 2016 (Manuscript No. A16.02.0269), and was recommended for revision on March 31, 2016. The resubmitted report is a heavily revised version of the original, with an additional contributing author, in which we have incorporated or addressed suggestions from the original review.

The subject of this manuscript is the inference of reaction coordinates from molecular dynamics (MD) simulations. We first introduce a general definition of the reaction coordinate suitable for condensed phase and biomolecular systems, which we show is equivalent to a leading eigenfunction of an integral operator governing a system's ensemble dynamics. Subsequently, we develop a practical new estimator designed to find sparse, interpretable approximations to these reaction coordinates from MD simulations using a small number of structural order parameters. This work bridges recent developments in the fields of machine learning and optimization, such as sparsity-inducing regularizers and the alternating direction method of multipliers, with contemporary needs in biological and chemical physics arising out of the analysis of large-scale simulation data sets.

We are grateful to the two referees for their informative and constructive comments and present a detailed response to each of their suggestions (which we have reproduced) on the following pages. We believe that this report, especially in its revised form, will be of interest to the broad readership of *JCP*.

Sincerely,

Vijay Pande

Camille and Henry Dreyfus Distinguished Chair in Chemistry and (by courtesy)
Professor of Structural Biology and of Computer Science
Director, Program in Biophysics
Director, Folding@home Distributed Computing Project

Detailed responses to referee comments:

Referee 1:

1. **(Contribution of the manuscript) “...the discussion about the optimal choice of reaction coordinate in sections II and III does not provide new insights. Saying that ψ_2 is an optimal choice of reaction coordinate is not new. ... Furthermore, the interpretation of transfer operator eigenfunctions as choices for reaction coordinates has at least been explicitly suggested in Ref. 19, but probably also in earlier publications.”**

We agree with the referee that the reaction coordinate discussed in this work is not new. However, the adaptation of a reaction coordinate as discussed in this work (and previous works) has not been widespread. Furthermore, the natural reaction coordinate described here is intentionally designed to be a sparse approximator so that it is easily interpretable. We agree that the main novel contribution is this sparse solver, but maintain that the discussion synthesizes our argument in a compelling way and will be interesting and helpful to a broad readership.

2. **(Introduction) “it should be pointed out that at least in the sensible situation that the system has metastable states and the end-states are chosen to be in the cores of these metastable states, the eigenfunctions are excellently approximated by a basis spanned by the committor functions between these cores.”**

We thank the referee for pointing this out and have clarified in our discussion of the committor function (Section II D) that the reaction coordinate produced by a committor function should correspond to the natural reaction coordinate described in this work when the system of interest contains two metastable states. We retain our note that extending the natural reaction coordinate framework described in this work to multiple metastable states is more straightforward than extending the committor function framework. These changes can be found in the manuscript on pg. 9, line 210ff.

3. **(Examples) “A more detailed analysis of the BPTI example is needed. I suggest to show a similar graphical representation as in Fig. 5. Please show the coefficients and pseudoeigenvalues for various choices of \mathbf{q} . Moreover, please show in more detail how the ARG 42 dihedral angle is identified as uniquely representative of the slow transition. Surely, there are other coordinates that also flip if the slow structural transition occurs. Please show that the ARG 42 angle is really outstanding from this group of coordinates. Moreover, it would also be interesting (for both examples) to see how the normalization of the approximate eigenfunction changes with \mathbf{q} . How strongly does $\mathbf{x}^T \Sigma \mathbf{x}$ deviate from one for the sparse solutions?”**

In the resubmitted manuscript, we have chosen to broaden the examples section and modify related sections of the main text in order to demonstrate that the dominant reaction coordinate is not always the one of interest (see responses to Referee 2, below). We have therefore pursued a broader overview of the utility of the natural reaction coordinate introduced in this work and have chosen not to focus on the specifics of examples. Instead, we present the different ways that the natural reaction coordinate can be utilized in the context of the specific modeling case. We have therefore not addressed this change in the text because of the new direction of the examples presented in the manuscript.

4. **(Approximation method) “In order to avoid confusion, it should at least be pointed out that here, TICA is understood in this general sense, which is more commonly called the variational approach to conformation dynamics (VAC) in the literature.”**

This has now been pointed out when tICA is introduced. The change can be found on pg. 2, lines 42-43.

5. **(II.C + III.B) “Eq. (1) needs to be motivated more clearly.”**

We thank the referee for his or her discussion of Eqn. (1) and agree with the conclusions presented in the review. We have therefore changed the format of the equation so its various components are more clearly motivated. These changes can be found on pg. 7, lines 156-157, in Eqn. (1), and lines 161-162.

6. **(II.C + III.B) “Second, an optimization problem for a reaction coordinate is formulated, where q is defined as minimizing the error functional $E[q]$. The error functional is defined by the maximal $L^2_{\mu^{-1}}$ -error between the correct density p_t and the projected density \tilde{p}_t over all possible initial densities p_0 . My concern is that the maximum in Eq. (3) could be infinite.”**

We thank the referee for pointing out this concern. While we agree that certain systems with limited degrees of freedom can produce pathological cases, our use-case (namely, protein dynamics) will not produce infinite maxima of Eqn. (3). We have therefore chosen not to address this in the manuscript.

7. **(IV) “Typo in Eq. (27): this must be $E[\chi_i(X_t)\chi_j(X_0)]$.”**

This typo has been addressed and the change can be found on pg. 17 in what is now Eqn. (23).

8. **(V) “Eq. (29): p should be m (number of basis functions as previously introduced). In Eq. (30), n should also be replaced by m .”**

The relevant indexes have been changed to m . These changes can be found on pg. 19 in what are now Eqns. (25) and (26).

9. (V) “Algorithm 1: Please define S^n , S_{++}^n , λ_{\min} , and also $D(w^l)$.”

These symbols are now defined in Algorithm 1 and the description is clearer. These changes can be found on pg. 20 in Algorithm 1.

10. (VI) “Eq. (36): $z^{(k)}$ should be z .”

This typo has been corrected. This change can be found on pg. 21 in what is now Eqn. (32).

11. (VI) “Can you provide a short derivation of the closed-form solution Eq. (39)?”

We thank the reviewer for this suggestion but believe that the derivation is too tangential to the story of the paper to include it here. Instead, we have cited the appropriate reference in the body of the text for the reader who is seeking background. This change can be found on pg. 22 near the top of the page.

12. (VII) “Typo, third paragraph, in the sentence beginning “The pseudoeigenvalue, $\hat{\lambda}$, ...: The timescale is given by $\tau = -1/\ln \hat{\lambda}$.”

This typo has been corrected. The change can be found on pg. 25, line 454.

Referee 2:

“1) While it would be nice to be able to obtain reaction coordinates without human input, the solution suggest by the authors is not general. For example, it shall fail in the analysis of sufficiently long realistic atomistic simulations of protein folding. There, the timescales of trans-cis transitions are usually longer than that of the folding. A dominant eigenfunction would describe a trans-cis transition rather then folding process. In other words, a dominant eigenvector does not always correspond to the eigenvector of interest. This point was discussed in a recent work by Banushkina and Krivov JCP 2015, 143, 184108.”

We thank the referee for the suggested reference, and we have added the recommended citation as well as an additional citation and have incorporated a discussion of those findings. This change can be found on pg. 15, line 296ff.

Furthermore, throughout the revised version of the manuscript, we have added emphasis that the method presented naturally produces *multiple* reaction coordinates and have explicitly addressed that the dominant reaction coordinate may not correspond to the process of interest (see, e.g., pg. 3, lines 73-75 and pg. 18, lines 355-356).

To expand upon this result, we have incorporated into the manuscript the analysis of a third example system (MD simulations of the folding of three-helix bundle a3D), in which the reaction coordinate that corresponds to protein folding is not the dominant

reaction coordinate. This new example comprises Sec. VII C of the new manuscript which begins on pg. 28, line 501.

“2) While the definition of optimality as maximally predicting, is intuitively appealing, it is not clear how it is related to other conventional requirements on reaction coordinates, in particular, the committor, e.g., that it provides an accurate description of the reaction dynamics, that it can be used to obtain accurate estimates of the reaction flux (ref 39), or reaction free energy barrier, etc.”

Again, we thank the referee for this suggestion. Section II D extensively discusses the committor function formulation. The main difference between the two formulations is that the spectral approach doesn't require prior identification of metastable states. In situations where metastable states are known *a priori*, the committor function is an appealing way to generate a reaction coordinate. We have augmented this section in the manuscript on pg. 9, line 210ff.

“3) Can the authors describe how the proposed framework is different from the framework of diffusion maps (Ref .61). For example, Eq.2 in the current work seems to be identical with Eq. 9 in Ref. 61; the same can be said about Eqs. 13 in both works. Both works claim that dominant eigenvectors are optimal in "diffusion distance" metric. Can the authors explicitly state which results are new.”

We thank the referee for this final suggestion and have incorporated a discussion of the diffusion maps framework at the end of Section II D. The most crucial distinction between the natural reaction coordinate as defined in this work and the dominant eigenvector in the diffusion maps framework is that the former yields a straightforward mathematical relationship between a dynamical process's eigenvector and the timescale with which it is associated, whereas diffusion maps do not provide timescale information in a straightforward way. This addition can be found on pg. 10, line 223ff.