January 2, 2017

Dear Dr. Hamm,

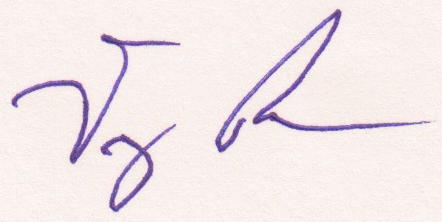
Please find our revised manuscript (No. A16.11.0215), which has been edited by the authors to address reviewer feedback received on December 30. We thank the two referees for their comments.

Since Reviewer #1 suggested the manuscript be published as is, we thank the reviewer for his or her positive feedback.

We also thank Reviewer #2 for his or her positive feedback and address the referee’s comment below:

**A minor issue is that Eq. (3) and (18) are still not equivalent since in (3) you maximize over probability densities and in (18) over the function u\_0 with ||u\_0||\_\pi = 1. Those are not the same problems, and this should at least be mentioned between the equations.**

We have incorporated this qualification after the presentation of Eq. (18) which can be found on line 260 of the revised manuscript.

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