Responses to Reviewer Comments for:

Best Practices for Computing Transport Properties 1. Self-Diffusivity and Viscosity from Equilibrium Molecular Dynamics v1

by

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Overview

We are grateful for your comments and for the feedback we received from each reviewer. Specifically, we are encouraged that the reviewers found the manuscript well-written, of high importance, and in need of only minor revisions. We believe that the review process has strengthened this manuscript and that it is now ready to be published. We appreciate your consideration of the revised manuscript for publication in the *Living Journal of Computational Molecular Science*.

Itemized List of Changes to Manuscript (Page numbers refer to revised manuscript.)

Response to Editor, Comment 1:
Response to Editor, Comment 2: pp 12, 13, 16
Response to Editor, Comment 3: p 4
Response to Editor, Comment 4: p 8
Response to Editor, Comment 5: p 6
Response to Editor, Comment 6: pp 16-17
Response to Editor, Comment 7: p 17
Response to Editor, Comment 8: p 2
Response to Editor, Comment 9: GitHub repository
Response to Reviewer 2, Comment 1: p 6
Response to Reviewer 2, Comment 2: p 4
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Response to Reviewer 3, Comment 1: p 4

Editor

Comment #1

Some questions were raised about rationales for some recommendations by reviewers. Please make sure all recommendations have specific rationales clearly listed.

Response #1

We have gone through the manuscript again and added the following rationales:

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Comment #2

When possible, all references should have literature citations. One rationale discussed the GROMACS manual; ideally, a more direct primary citation should be used.

Response #2

We have included the following more direct primary citations:

- Page 12, caption to Figure 9, references 51 and 52 for LINCS algorithm
- Page 13, second paragraph in left column, reference 53 for Equation 9
- Page 16, top of right column, reference 57 for particle mesh Ewald
- Page 16, final paragraph before “Conclusions”, references 58 and 59 for tail modifications

Comment #3

The check lists for computing self-diffusivity/shear viscosity with the Einstein and Green-Kubo equilibrium approaches are identical, with the exception of some varying section numbers. It would almost certainly be clearer to consolidate the checklists, one per property, with alternate options for Einsten and Green-Kubo approaches.

Response #3

We agree that the checklists are clearer now that we have combined the Einstein and Green-Kubo approaches. This helps the reader distinguish the two methods while also seeing the strong similarities between the two. The checklists have now been combined on page 4 with the sections for the two approaches clearly prescribed.

Comment #4

It would be extremely helpful to put somewhat of a more quantitative requirement on what "middle" of the simulation is, and how to recognize it. Even if the subject is an open area of research, at least having quantitative measures is important for implementability.

Response #4

We agree that further explanation was needed regarding what constitutes the “middle” region. To clarify how to recognize and quantify the middle region, we have included the following paragraph in Section 5.2.3 (page 8):

> A typical log-log plot, borrowed from Ref. [35], is provided in Figure 2 where the linear regression to the ``middle'' region is included. From visual inspection, the ``ballistic'' short time interval ranges from the beginning of the simulation to approximately 100 ps. The ``middle'' region is identified by the linear regime with a slope of 1 (for a log-log plot) spanning from approximately 100 ps to 1000 ps. Note that the noisy ``long time'' simulation data (beyond 1000 ps) are not depicted in Figure 2 and are excluded from the linear fit.

We have also modified the caption of Figure 2 (page 8) to read, “The gray dashed lines are linear fits to the “middle” region of the MSD, as determined by the authors.”

Comment #5

Comments on the reviewer's need to use double precision for NVE vs. NVT (we can facilitate more information from the reviewer as necessary)

Response #5

We strongly discourage the use of single precision. The accumulation of round-off error inherent in single precision calculations will eventually cause major issues with the forces, especially on the time scales required for simulations that are long enough for "good" determination of diffusion constants. We have included the following recommendation on page 6, “When simulating in the NVE ensemble, it is imperative that the integrator conserve energy. Performing simulations with single precision is one of the main causes for poor conservation of energy due to the accumulation of round-off errors. For this reason, we recommend the use of full double precision or double/fixed precision.”

Comment #6

It would be better to make recommendations in active voice "we recommend" versus passive voice "it is recommended" in order to clarify which recommendations are coming directly from the authors of this article, rather than the existing literature.

Response #6

We have changed most instances of passive voice into active voice. The majority of these changes were in the conclusions section on pages 16-17.

Comment #7

D.M.Z. lists funding acknowledgements, but is not an author.

Response #7

This funding acknowledgment was a mistake and has been removed.

Comment #8

For the list of extra sources near the beginning, the authors and titles should be provided in the lists, not just in the references (full details can be left in the references).

Response #8

We have included the authors and titles in the lists on page 2.

Comment #9

Is it possible to include records (text + headers of emails, perhaps?) of the permission on use of figures from other publishers, and the conditions, in the GitHub repository? This could avoid later questions about what the permissions were if the article were further shared.

Response #9

Yes. The permissions to reuse figures are found in the “permissions” folder on GitHub.

Reviewer #2

Comment #1

The only difficulty I had was conserving energy in the NVE ensemble (which you cover in common pitfalls) using GROMACS 2018. I investigated the hints given in common pitfalls, but it turned out that I needed to use double precision. Rather than deal with slower double precision, I ended up using NVT, as shown to be acceptable by Basconi and Shirts, with a long time constant.

Response #1

We have addressed this issue in Response #5 to the editor. See page 6 of manuscript.

Comment #2

I think it's worth considering moving "common pitfalls" to the second major bullet point (before "Post-simulation data analysis"). It's likely you can take steps to avoid them before running production simulations of many replicates.

Response #2

We agree with the reviewer and have moved “common pitfalls” to the second major bullet point in both checklists (see page 4).

Comment #3

I think it can be improved by another thorough read-through. There are some very long sentences and a few minor typos.

Response #3

We have re-read the manuscript, reworded some long sentences, and fixed some minor typos.

Reviewer #3

Comment #1

For novice readers, there is an opportunity to make a small tweak to the checklists to improve their understanding. On page 5, experienced practitioners will understand why the checklist for calculating viscosity with the Green-Kubo equilibrium approach appears before the Einstein equilibrium approach. However, a person new to simulations might not catch the significance, and if not careful, not read the explanation in Section 6.3. It seems like a short note next to the checklists for viscosity, alerting readers to the intention behind switching the order of appearance of the methods (and directing them to the explanation in Section 6) would be helpful for novice readers.

Response #1

This is a good recommendation by the reviewer. Since the Green-Kubo and Einstein checklists have been merged for the revised manuscript (see page 4), according to Comment #3 from the editor, the confusion expressed by the reviewer should not be an issue anymore.