*This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.*

nature portfolio

# Peer Review File

# Deciphering the complexities of crystalline state(s) with molecular simulations

Corresponding Author: Professor Jerome Delhommelle

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
I have had the opportunity to review Caroline Desgranges and Jerome Delhommelle's paper "Deciphering the Complexities of the Crystalline State(s): The Next Frontiers for Molecular Simulation."
My overall assessment of this comprehensive review article is positive. The authors present a well-argued case for the pivotal role of molecular simulations, particularly when augmented by Machine Learning (ML), in addressing the long-standing challenge of predicting crystallization outcomes in solid-state chemistry.

The paper thoroughly elucidates the intricate interplay between thermodynamics and kinetics that governs crystal formation, systematically exploring inherent complexities such as polymorphs, competing pathways, liquid metastability, and preordering. It effectively highlights recent advancements in computational methods, including the development of resilient force fields like partitioned quantum-based force fields and adaptive machine-learned potentials, which are crucial for high-accuracy free energy calculations and reliable ranking of structures. The review also details progress in understanding order formation through advanced order parameters, enhanced sampling simulations, and their application in crystal structure prediction. Furthermore, the authors thoughtfully outline future research directions, such as far-from-equilibrium crystallization and the development of self-adaptive crystals.

This comprehensive synthesis provides valuable insights into how these methods bridge the gap between microscopic molecular properties and macroscopic crystal behavior, significantly advancing the understanding of crystallization processes.

Regarding specific sections, I believe that Section 4.3, "Recent Advances in Crystal Structure Predictions," could be further strengthened.
I recommend that the authors consider incorporating references to novel methodologies for the finite-temperature refinement of Crystal Structure Prediction (CSP) results, such as the work by Francia et al. (Crystal Growth & Design, 20(10), 6847-6862 2020, CrystEngComm, 23(33), 5575-5584 2021.) and Butler and Graeme Day (Proceedings of the National Academy of Sciences, 120(23), e2300516120, 2023).

Additionally, I suggest adding information on the development, application, and refinement of foundational Machine-Learned Force Fields (MLFFs), including works such as Csanyi et al. (MACE-OFF, JACS 2025), Price et al. (Crystal Growth & Design 25, no. 9 (2025): 3186-3209, 2025), and Della Pia (Chem Sci 2025). These additions would enhance the comprehensiveness of the discussion on advanced CSP techniques and MLFFs.

Reviewer #2

(Remarks to the Author)
The review "Deciphering the Complexities of the Crystalline State(s): the Next Frontiers for Molecular Simulation" by Desgranges and Delhommelle discusses recent progress in molecular simulation applied to crystallization. The manuscript covers the most important current topics in this field, including complex crystallization pathways, machine learning potentials, machine learning collective variables for enhanced sampling, and crystal structure prediction. The review ends with a discussion of future directions that can be explored by leveraging recent advances in modeling.

In my opinion, the review covers the most important current research topics and discusses research carried out by numerous groups. It is thus representative of the status of the field. The manuscript is well organized and well written, and the authors have extensive experience on these topics. I think this review will be of interest to researchers in this large and active field, and a good resource to learn the state of the art and current trends.

I am happy to recommend this review for publication and I have some minor suggestions for improvement noted below.

1) On page 2, line 68, "... high and negative ends of the phase diagram". I think this refers to pressure, but I suggest clarifying the sentence.
2) On Page 8 and 9, line 253 and line 269, big O notation is used to describe the number of atoms in the simulations, but I believe this notation is not appropriate in this context. Please double check.
3) On page 14, two future research directions are described, but the summary on page 2 states that three future research directions will be described.
4) On page 2, line 47, I do not understand the phrase "... on-the-fly determination of collective variables". As far as I know, all methods to machine learn collective variables are not carried out on the fly, but require previous simulations, for instance of the metastable basins. Also, note that the term on-the-fly is not used again in the manuscript, so the sentence is not properly justified afterwards.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
The authors have reviewed their manuscript, addressing all the points raised by reviewers. I am happy to recommend this manuscript for publication in its current form.

**Response to the reviewers and changes made to the manuscript**

# Deciphering the Complexities of the Crystalline State(s): the Next Frontiers for Molecular Simulation.

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## 1 Reviewer #1

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Author reply: We thank the reviewer for their positive comments.

*Regarding specific sections, I believe that Section 4.3, "Recent Advances in Crystal Structure Predictions," could be further strengthened. I recommend that the authors consider incorporating references to novel methodologies for the finite-temperature refinement of Crystal Structure Prediction (CSP) results, such as the work by Francia et al. (Crystal Growth & Design, 20(10), 6847-6862 2020, CrystEngComm, 23(33), 5575-5584 2021.) and Butler and Graeme Day (Proceedings of the National Academy of Sciences, 120(23), e2300516120, 2023).*

*Author reply: We thank the reviewer for drawing our attention to the finite-temperature refinment of CSP results. We now include a discussion of these studies in a revised Section 4.3. Here is the added paragraph:*

*Metadynamics simulations can also be instrumental in reducing the common overprediction of the number of plausible structures by clustering subsets of structures that can easily interconvert at finite temperature and pressure [123]. This approach was recently applied to post-process a CSP dataset of 555 crystal structures for ibuprofen, identify 65% of these structures were labile, and obtain a final reduced dataset that contained all experimentally known structures [124]. Recent work has also highlighted how a threshold algorithm could cluster potential energy minima into basins for a series of organic molecules, including*

*benzene, acrylic acid, and resorcinol, thereby providing an efficient method to address overprediction in computational CSPs [125].*

*Additionally, I suggest adding information on the development, application, and refinement of foundational Machine-Learned Force Fields (MLFFs), including works such as Csanyi et al. (MACE-OFF, JACS 2025), Price et al. (Crystal Growth & Design 25, no. 9 (2025): 3186-3209, 2025), and Della Pia (Chem Sci 2025). These additions would enhance the comprehensiveness of the discussion on advanced CSP techniques and MLFFs.*

*Author reply: Thank you for bringing up these papers. We fully agree and discuss the findings in revised Section 4.3. Here is the corresponding paragraph:*

*Furthermore, ML potentials have recently emerged as extremely efficient and accurate tools in CSP studies. Very interestingly, the MACE-OFF ML force fields leverage an equivariant message-passing architecture and exhibit transferability, generalizing well in the chemical and configuration space [131]. MACE-OFF force fields were recently tested on a dataset of experimental and hypothetical polymorphs for 20 organic molecules [132] and provided reasonable lattice energies and crystal structures across the dataset, despite being only trained on a large database of organic molecules and dimers. This bodes well for the success of condensed-phase and molecule-specific versions of these ML force fields in CSP studies, as evidenced by recent results obtained with fine-tuned MACE force fields for the sublimation enthalpies of crystals of paracetamol and aspirin [133].*

## 2 Reviewer #2

*The review "Deciphering the Complexities of the Crystalline State(s): the Next Frontiers for Molecular Simulation" by Desgranges and Delhommelle discusses recent progress in molecular simulation applied to crystallization. The manuscript covers the most important current topics in this field, including complex crystallization pathways, machine learning potentials, machine learning collective variables for enhanced sampling, and crystal structure prediction. The review ends with a discussion of future directions that can be explored by leveraging recent advances in modeling.*

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*Author reply: We thank the reviewer for their positive comments,*

*1) On page 2, line 68, "... high and negative ends of the phase diagram". I think this refers to pressure, but I suggest clarifying the sentence.*

*Author reply: We agree with the reviewer and have changed the end of the sentence into*

*high pressures and temperatures, but also at negative pressures*

*2) On Page 8 and 9, line 253 and line 269, big O notation is used to describe the number of atoms in the simulations, but I believe this notation is not appropriate in this context. Please double check.*

*Author reply: We have replaced this notation with the number of atoms used in the studies referenced in the text. Specifically, we have changed this notation into typically of the order of* $10^2$ *on page 8, and into systems of* $\sim 3 \times 10^4$ *on page 9.*

*3) On Page 14, two future research directions are described, but the summary on page 2 states that three future research directions will be described.*

*Author reply: Thank you for pointing out this. We have changed the last sentence of the introduction accordingly.*

*In the last Section, we present two future directions, which include the study of far-from-equilibrium crystallization processes that give rise to unusual crystallization patterns and structures, and the formation of self-adaptive crystals that can crystallize reversibly in response to environmental cues.*

*4) On page 2, line 47, I do not understand the phrase "... on-the-fly determination of collective variables". As far as I know, all methods to machine learn collective variables are not carried out on the fly, but require previous simulations, for instance of the metastable basins. Also, note that the term on-the-fly is not used again in the manuscript, so the sentence is not properly justified afterwards.*

*Author reply: We have removed "on-the-fly" on page 2 and line 47.*