Qeios

Peer Review

Review of: "Machine Learning of Slow Collective Variables and Enhanced Sampling via Spatial Techniques"

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The paper, titled *"Machine Learning of Slow Collective Variables and Enhanced Sampling via Spatial Techniques"*, provides a comprehensive review of spatial techniques for identifying slow collective variables in MD simulations. The authors focus on methods that do not rely on temporal information, such as diffusion maps, anisotropic kernels, reweighted stochastic embedding (RSE), and spectral maps. While the paper covers a wide range of techniques, explains each methodology in great detail, and highlights their potential for understanding rare events in complex systems, it would benefit from including more critical analysis, comparison of methods, and potentially some case studies. Below, I provide an overview of the paper's strengths and weaknesses, followed by section-specific comments and suggestions for improvement.

General Comments:

- The paper provides a comprehensive and well-structured overview of spatial techniques for identifying slow collective variables (CVs), including recent advancements such as diffusion maps, anisotropic kernels, reweighted stochastic embedding (RSE), and spectral maps. The integration of machine learning with molecular dynamics is particularly noteworthy, as it demonstrates how advanced ML techniques can address fundamental challenges in MD simulations, such as the sampling problem and rare event detection.
- The paper primarily focuses on summarizing and explaining existing methods with limited analysis of their computational cost or comparing them to highlight their strengths and weaknesses.
- It would be beneficial to provide detailed examples of how these methods have been applied to real-world systems, which would help readers understand their practical utility, instead of simply mentioning some names.

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- While the paper introduces a lot of methods for finding CVs, it does not provide a systematic framework for validating CVs or discuss how to assess their quality in practice (e.g., committor probability, quality of the free-energy landscape).
- The authors should provide more intuitive explanations of key concepts, using analogies or examples where appropriate. They should also avoid jargon and define technical terms when they are first introduced. This would make the paper more accessible to a broader audience and increase its impact. (See comments for section background.)
- The paper acknowledges the sampling problem in MD simulations, where the system gets trapped in local energy minima and struggles to explore the full configuration space. However, the discussion is largely focused on stating the difficulty rather than providing a detailed explanation of how, if any among the proposed methods, may aim to resolve or mitigate this problem.

Section Specific Comments:

Introduction:

The introduction could provide a stronger motivation for focusing on spatial techniques. For example:

- Spatial techniques are particularly useful for systems where long-timescale transitions are rare and temporal information is scarce.
- These techniques can leverage thermodynamic information (e.g., equilibrium probabilities, free-energy landscapes) to identify slow CVs, making them well-suited for enhanced sampling simulations.

Background:

The background section, in general, provides a very mathematical overview of different concepts. However, for a broader audience who needs this section to learn certain concepts, it could provide a clearer definition of what these concepts are and why they are important to the problem of interest.

For example, in the CV section, the authors could explain:

- CVs are low-dimensional representations of high-dimensional systems that capture the slow dynamics of the system.
- They are used to simplify the description of complex processes and make it possible to estimate free-energy landscapes and kinetics.

In Enhanced Sampling Methods, the author could state more clearly:

- Enhanced sampling methods (e.g., metadynamics, umbrella sampling) use bias potentials to drive the system out of local energy minima and explore the full configuration space.
- These methods require high-quality CVs to be effective, which is why identifying slow CVs is such an important challenge.

Section 3E:

- Figures 2 are placed far from where they are explained in the text. Not sure if this is in control by the authors, but it is a bit confusing for the reader.
- The authors state that spectral maps proceed by "mapping the dynamics into z space using a neural network," but later claim that spectral maps can use a linear model instead of a deep neural network. This inconsistency is not explained, creating confusion for the reader.
- The authors state: "It was demonstrated that spectral maps can be used to construct interpretable reaction coordinates for protein folding with a linear model instead of a deep neural network, and they are slower than the fraction of native contacts or end-to-end distance." This statement is too vague and lacks sufficient detail to be meaningful. It would be necessary to include a more detailed demonstration, or it would be nice to include this as a case study. Without it, it is difficult to assess the validity or practical utility of this claim. It would be nice to include:
  - A comparison of the linear model to a deep neural network in terms of accuracy, interpretability, and computational cost.
  - A comparison of the learned reaction coordinates to traditional CVs (e.g., fraction of native contacts, end-to-end distance) in terms of capturing the slow dynamics of the system.
  - A discussion of the implications of these results for understanding protein folding and designing enhanced sampling simulations.

Section 3F:

- The authors state: "By accumulating the biasing potential in CV space, the neural network can be used to push the system out of local minima." This sentence is misleading because it implies that the neural network itself is responsible for pushing the system out of local minima. In reality, the neural network serves as a transformation rule that maps configurations x to CVs z, and the biasing potential is accumulated in CV space (z) and acts as a force that drives the system out of local minima.
- The authors state: "Consequently, applying bias to neural networks with $\nabla xf(x) \approx 0 \nabla xf(x) \approx 0$ in energy minima might be inefficient due to the large mass and lead to numerical stability issues in MD

simulations." This statement is unclear and requires further explanation. In particular:

- Why is $\nabla x f(x) \approx 0 \nabla x f(x) \approx 0$ a problem for neural network-based CVs but not for traditional force fields, which also have gradients of zero near energy minima?
- Does this numerical stability issue relate to the vanishing gradient problem of NNs?

Declarations

Potential competing interests: No potential competing interests to declare.