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Quantum Mechanics in Biomolecular Simulations: Benefits and Cost-Reduction Strategies for Integrated QM/MM Approaches

Mecânica Quântica em Simulações Biomoleculares: Benefícios e Estratégias de Redução de Custos para Abordagens Integradas QM/MM

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Quantum calculations play a fundamental role in understanding biological systems at the atomic level, as they allow detailed investigation of electronic interactions, enzymatic mechanisms, and molecular recognition processes. However, the direct application of these methods to large biomolecules is limited by the high computational cost involved. An efficient alternative consists of combining classical Molecular Mechanics (MM) simulations, such as molecular dynamics, with quantum mechanical (QM) methods, enabling a more comprehensive multiscale description. This hybrid approach, however, introduces another challenge: classical simulations generate a very large number of conformations, which makes it impractical to perform quantum calculations on every frame. Therefore, the efficiency of this strategy depends on selecting a reduced and representative set of structures to be analyzed in subsequent quantum stages. In this mini-review, we present three complementary methods to achieve this selection: (1) Clustering, (2) Statistical Inefficiency (SI), and (3) Optimal Wavelet Signal Compression Analysis (OWSCA). This filtering step makes it possible to explore quantum effects with high accuracy without compromising conformational representativeness, drastically reducing the computational cost and expanding the applicability of a sequential workflow of hybrid QM/MM methodologies to the study of complex biological systems.

Keywords: QM/MM calculations; computational cost; clustering methods; statistical inefficiency; OWSCA.

1. Introduction

The late 19th and early 20th centuries were marked by major scientific breakthroughs that witnessed the emergence of a theory destined to revolutionize the entire understanding of the atomic universe: Quantum Mechanics (QM). This theoretical computational method is primarily grounded in the formalism of mathematics and physics.[1]

Centered around the concept of the wave function, it stands out as a powerful tool for the investigation of chemical systems, enabling the accurate description of molecular structures, reaction mechanisms, and electronic properties at the atomic level. Its development laid the foundation for modern computational chemistry and continues to influence a wide range of scientific disciplines.[2]

With the advent of modern computers capable of performing high-level numerical calculations, quantum calculations have proven to be a powerful tool in the investigation of chemical, physical, and biological systems.[3] This technological evolution has not only enhanced the precision of theoretical predictions but also significantly reduced the need for costly and time-consuming experimental procedures. As a result, many scientists rely on Computational Chemistry to predict or assess a wide range of molecular, spectroscopic, thermodynamic, and kinetic properties of interest, facilitating the rational design of new drugs and biocatalysts with increased efficiency and reliability.[4]

Consequently, Computational Chemistry applied to the study of biological systems has evolved substantially over the years. A clear testament to this progress is the awarding of the 2024 Nobel Prize in Chemistry to scientists David Baker, Demis Hassabis, and John Jumper.[5] Their contributions were recognized for the development of computational tools capable of predicting the three-dimensional structure of proteins, as well as designing novel proteins with specific functions. These advances have not only deepened our understanding of fundamental biological mechanisms but also opened new frontiers in drug discovery, enzyme engineering, and synthetic biology.[6]

Biological systems – particularly proteins – lie at the core of molecular activity in living organisms. The three-dimensional structure of these biomolecules determines their function, ranging from enzymatic catalysis to cellular recognition and signaling. Understanding these structures from quantum principles enables the elucidation of fundamental electronic interactions, stabilization energies, and conformational changes that govern functional behavior. Such advances highlight the relevance of exploring the structural and functional aspects of biological macromolecules in greater depth.[7]

As shown, quantum calculations have become essential for investigating and understanding biological systems at the atomic level. By explicitly describing the electronic structure of biomolecules, these methods enable the elucidation of enzymatic catalysis mechanisms, the prediction of protein-ligand interactions, the characterization of electronic and vibrational spectra, and the understanding of energy and electron transfer processes that are fundamental to life.[8]

Moreover, quantum approaches provide insights into reaction pathways, transition states, and intermediate species that are often inaccessible through experimental techniques alone. This detailed molecular-level information supports drug design, biomarker discovery, and the rational engineering of enzymes and biomaterials, thereby bridging the gap between theoretical predictions and practical biomedical applications.[9]

However, to evaluate different chemical environments, as well as to explore conformational space and account for thermal and solvent effects, Molecular Dynamics (MD) simulations are more widely employed.[10-12] The combination of MD with subsequent quantum calculations on representative frames makes it possible to simultaneously capture the dynamic nature of biomolecules and the quantum-level details required to understand their behavior in complex biological environments. This sequential hybrid workflow – often referred to as sequential QM/MM or more generically classified as integrated quantum–classical (QM/MM) approaches – is recognized as a robust standard in studies of reactive biomolecular systems and forms the basis of recent implementations that link extensive MD sampling with accurate electronic structure calculations.[13]

In line with this, an important application employing quantum NMR (Nuclear Magnetic Resonance) calculations was carried out to evaluate the chemical shift of platinum in two distinct chemical environments: aqueous and enzymatic.[11] However, in order to investigate the behavior of the PI3K–(platinum complex) system in different environments, it was first necessary to simulate this system using Molecular Dynamics (MD) to account for thermal and solvent effects, thereby allowing energy barriers to be overcome and new conformations to be explored.[11,14]

A similar approach was adopted by Gonçalves *et al.* (2022), who combined MD and quantum chemical calculations to investigate the structural and spectroscopic properties of metal-based complexes in biological environments, reinforcing the importance of hybrid methodologies for accurate modeling of metallodrugs.[10] In this regard, the sequential workflow of quantum chemistry methods and Molecular Dynamics simulations has proven essential for the accurate investigation of complex biomolecular systems, particularly in the context of metal-based drugs and their interactions in biological environments.[12]

In this context, the importance of Molecular Dynamics – whose formalism is based on Molecular Mechanics (MM) – can be emphasized for the computational study of complex systems. These methods allow for the simulation of atomic motions of proteins, nucleic acids, and other biomolecules within a realistic virtual environment, providing detailed insights into conformational flexibility, structural stability, and molecular interactions over time, as highlighted in *"Biomolecular Dynamics in the 21st Century"*.[15]

On the other hand, MD simulations generate a significantly large number of conformations, making it impractical to subsequently perform quantum calculations on all these structures due to the associated computational cost. In this regard, it becomes essential to apply techniques that select the most representative conformations from the classical simulations, thereby reducing the computational burden of the subsequent quantum mechanical (QM) calculations.[16]

The combination of Molecular Mechanics (MM) techniques with Quantum Mechanics (QM) approaches enables, within a sequential workflow, the assessment of (1) thermal effects, (2) solvent effects, and (3) conformational space sampling. Following the appropriate selection of representative frames, it becomes possible to investigate (4) quantum properties of the selected structures. This sequential hybrid approach, involving QM/MM methodologies, constitutes a powerful strategy for multiscale modeling.[17]

As can be seen, in order to successfully apply the aforementioned hybrid approach, it is necessary that, following classical molecular dynamics simulations (MM), the most representative conformations be selected so that subsequent QM calculations can be focused on them – thereby reducing the computational cost of quantum mechanical computations.[11] In light of this, in the present mini-review, we present three principal methods (Clustering, Statistical Inefficiency and OWSCA) for selecting the most relevant conformations obtained from MD simulations.

2. Techniques to Reduce the Computational Cost in Sequential Hybrid QM/MM Methods

2.1. Clustering

This selection method uses the Geometric clustering performed to identify similar structures sampled during the MD simulation. There are several different clustering methods, one of the most often used clustering algorithms applied to MD trajectories is the one developed by Daura's

research group.[18] By applying this strategy, it becomes possible to capture the most recurrent structural patterns while minimizing redundancy, thereby improving the efficiency of downstream analyses. In addition, geometric clustering offers a clearer view of how conformational states are distributed along the simulation, supporting a more detailed interpretation of dynamic behavior and transitions between relevant structural populations.[18]

Clustering is the most suitable computational intelligence technique for dividing MD conformations into structurally homogeneous groups and for quickly understanding the resulting sets. In this approach, every MD conformation is divided into several groups by using a measure of similarity/dissimilarity. Clustering of MD conformations is especially useful for molecular docking simulations since it provides groups of similar receptor structures. In that regard, clustering of MD conformations is particularly relevant in molecular docking studies because MD simulations generate a large ensemble of receptor conformations that capture its intrinsic flexibility. By grouping similar structures according to a similarity metric (typically pairwise RMSD), clustering allows the identification of representative conformational states. These representative structures are commonly used in ensemble docking approaches, reducing the number of redundant conformations and enabling a more efficient and realistic evaluation of ligand-receptor interactions. MD conformations that are placed in the same group are, according to some criterion, similar to each other and dissimilar from the conformations of other groups. Hence, if a receptor conformation belongs to a cluster that interacts favorably with a specific ligand, one could assume that other conformations within the same cluster will behave similarly. Otherwise, the conformations belonging to this cluster are considered unpromising and consequently may be discarded in order to reduce the number of docking experiments in the model.[19]

The method is based on the mutual RMSD (root-mean-square deviation) between all conformations sampled during the MD simulation. The Root mean square deviation (RMSD) values obtained by pairwise or matrix error distances are the most traditional and popular measure of similarity used for partitioning MD trajectories, allowing the extraction of representative structures, identification of dominant conformational states, and simplification of complex dynamical data.[20]

For instance, Lyman and Zuckerman (2006) generated a set of reference structures by enforcing a cutoff radius in RMSD for cluster assignment from biomolecular simulation trajectories of metenkephalin, a pentapeptide neurotransmitter.[21] On the other hand, Shao and co-workers (2007) made use of several clustering algorithms and two validity metrics to find the best clustering partition based on the pairwise RMSD values of small samples from an MD trajectory.[20]

Thus, as can be seen, the clustering method is very effective for the selection of MD structures, used in the selection of proteins and organic molecules. The spectral clustering used is robust to anomalies introduced by structural alignment, and different intrinsically disordered protein classes can be reliably discriminated, leading to a high level of reliability. In addition, its ability to capture subtle similarities in high-dimensional conformational data makes it particularly useful for exploring heterogeneous ensembles. This ensures a more accurate representation of the underlying conformational landscape and improves the selection of representative structures for subsequent computational analyses.

2.2. Statistical Inefficiency (SI)

Another widely used and robust method for structure selection is the Statistical Inefficiency (SI)-based approach, which focuses on the temporal correlations within molecular dynamics trajectories to identify statistically uncorrelated configurations. This ensures that the selected structures are not biased by the intrinsic autocorrelation of the simulation data, providing a representative and independent subset of configurations. Canuto and Coutinho's research group have proposed and applied the sequential quantum mechanical/molecular mechanics methodology. This methodology suggests the structure selection by using Statistical Inefficiency (SI) calculations and has been previously reviewed on several different occasions.[22] The method can be efficiently applied in the treatment of MD signals. The method uses the autocorrelation energy function to calculate the correlation time (τ), which is obtained by an exponential decay following a Markovian process, equation 1. Thus, through the autocorrelation function, it is possible to calculate the correlation time (τ) and, then obtaining the statistical inefficiency (s), equation 2. The correlation time between the structures shows that they are statistically different.[22,23]

$$C(n) = \sum_{i=1}^{N} c_i e^{-n/\tau i} \quad (1)$$

$$\tau = \int_0^{\infty} C(t)dt \quad (2)$$

Following this line, the statistical inefficiency (s) occurs when the configurations are separated by 2τ ($s = 2\tau$) or larger intervals, i.e., in this interval, there is no correlation among the configurations. Thus, the SI method was used to obtain the uncorrelated MD configurations. In this sense, it is observed that the uncorrelated structures are able to present statistically the same results of all the structures obtained by the MD simulation.[24] For example, in the selection of MD structures by the statistical inefficiency method of compound δ-FeOOH, a correlation time of 0.42 fs was obtained for this simulation, resulting in 7801 conformations. With this treatment, 208 uncorrelated structures were obtained, a very significant reduction from the total number of initial structures. Figure 1 shows the

graph of the autocorrelation function as a function of time, in picoseconds, for δ-FeOOH.[25]

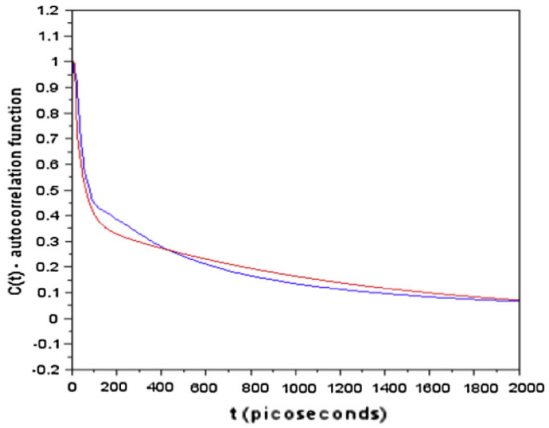

Figure 1. Graph of the auto-correlation function for the time in picoseconds of δ-FeOOH. The blue curve is the correction and the red curve the adjustment done

As already observed in Figure 1, the decay of the time autocorrelation function is used to estimate the correlation time (τ) of the δ-FeOOH MD trajectory. As shown, the curve rapidly converges toward zero, indicating that configurations separated by intervals greater than 2τ are effectively uncorrelated. The blue line represents the calculated autocorrelation values, while the red line corresponds to the fitted curve used to determine τ. This behavior corroborates the use of the statistical inefficiency method by visually demonstrating the point at which correlations vanish, reinforcing the selection of statistically independent configurations. Altogether, this analysis strengthens the rationale behind the structural selection approach adopted in this study.

2.3. Optimal Wavelet Signal Compression Algorithm (OWSCA)

Another method of selecting MD structures that is also being widely used is the so-called Optimal Wavelet Signal Compression Algorithm (OWSCA), which is based on the wavelet transform. Wavelets are functions used as tools for processing or manipulating data to analyze them at different resolution scales, and aiming, mainly, to detect transients, remove noise, and compress data. This method enables the identification of the most relevant conformational changes by decomposing the MD signal into distinct frequency components, allowing a more accurate and compact representation of the system's dynamics. As a result, it selects a reduced number of structures that still capture the essential features of the trajectory, making it particularly efficient for subsequent quantum mechanical calculations or detailed analyses.[26,27]

Wavelet transformations can be interpreted as mechanisms for data decomposition into their constituent parts, allowing them to be analyzed in different ranges of frequencies and space. The discrete wavelet transform can be defined by equation 3.

$$d_{n,m} = \int_{-\infty}^{\infty} f(t)\Psi_{n,m}\,dt \tag{3}$$

Where $d_{n,m}$ is the discrete wavelet transform of $f(t)$, which results in a vector of coefficients d. It is possible to calculate the value of the wavelet from the shrinkage (or expansion) and translation of a simple wavelet-mother function (Ψ). When changing the index m, the location of the wavelet in the domain changes; when changing the index n, the scale of the wavelet changes (shrinking or stretching function).

In the selection of MD structures, the Haar wavelet (simplest of the wavelet transforms) is used, which was proposed in 1909 by the Hungarian mathematician Alfred Haar.[28] The Haar transform is a particular case of the discrete wavelet transform. The Haar function is a square pulse that uses an orthonormal basis defined over the interval [0,1],[29] as described below in equation 4. Figure 2 shows the treatment of the MD signal for the $[Fe(H_2O)_6]^{2+}$ complex; the signal in black is the original, and in red it is the compressed signal. It can be observed that the original data set $x(t)$ presents a high oscillatory (noisy) profile while the compressed data set $y(t)$ presents a smoother profile, not equidistantly spaced. Thus, the original signal has a total of 7801 conformations and the compressed signal has 50 conformations, where it is possible to observe that the treatment of the MD simulation signal considerably reduces the number of structures.[26]

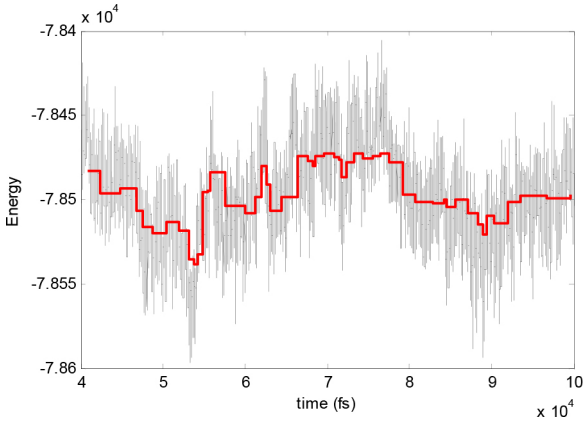

Figure 2. Energy of MD $[Fe(H_2O)_6]^{2+}$ conformations (original and compressed) at each time (fs)

$$\psi_{Haar}(t) = \begin{cases} -1 & 0 \le t < 0.5 \\ 1 & 0.5 \le t < 1 \\ 0 & otherwise \end{cases} \tag{4}$$

In this context, the term MD signal refers to the numerical values of a selected descriptor extracted at each step of the molecular dynamics simulation, as illustrated in Figure 2. As shown, the OWSCA method efficiently compresses MD simulation data by significantly reducing the number of

conformations while preserving essential structural features. This capability not only decreases computational cost but also improves the clarity of data interpretation by filtering out noise and redundant information. Consequently, it enables researchers to focus on the most relevant molecular motions and conformational changes, facilitating more accurate identification of functional states and transition pathways. Additionally, by providing a compressed yet representative subset of structures, OWSCA supports enhanced sampling techniques and subsequent high-level quantum mechanical calculations that would otherwise be computationally prohibitive. The method finds broad applications in biomolecular studies, coordination chemistry, and materials science, where managing large and complex datasets without losing critical information is crucial for accurate modeling, drug design, materials optimization, and the exploration of reaction mechanisms. Moreover, the systematic reduction achieved through OWSCA contributes to improved reproducibility and comparability across simulations, enabling more robust statistical analyses and fostering the integration of MD-derived data with machine learning frameworks. This synergy broadens the potential for predictive modeling and accelerates the discovery and rational design of molecular systems.

3. Conclusion

Quantum mechanics has revolutionized our understanding of the structure of matter by accurately describing the behavior of particles at the atomic and subatomic scales. Its rigorous mathematical formalism enables the investigation of fundamental phenomena such as electronic interactions, bond formation and dissociation, excited states, and processes involving charge and energy transfer.

When applied to the study of biological systems, quantum mechanics provides essential tools for unraveling complex molecular mechanisms, including enzymatic catalysis, molecular recognition, protein-ligand interactions, and spectroscopic properties. However, the high computational cost associated with quantum calculations imposes significant limitations on their direct application to large biomolecules, thus justifying the use of hybrid approaches that combine classical and quantum methods.

The combination of Molecular Mechanics (MM) techniques with Quantum Mechanics (QM) approaches, within a sequential workflow, enables the consideration of thermal effects, solvent effects, and conformational space sampling. Once representative structures are appropriately selected from molecular dynamics simulations, it becomes possible to explore their quantum properties with greater efficiency and precision. This stepwise hybrid strategy, based on QM/MM methodologies, constitutes a powerful approach for multiscale modeling of complex systems.

As demonstrated, the successful application of this hybrid methodology critically depends on selecting the most representative conformations following classical molecular dynamics simulations. This selection step ensures that quantum calculations focus solely on the most relevant structures, thereby significantly reducing the computational cost while maintaining the scientific rigor of the results.

In this context, the methodologies discussed in this review – Clustering, Statistical Inefficiency (SI), and Optimal Wavelet Signal Compression Algorithm (OWSCA) – emerge as complementary and effective tools for reducing the number of conformations subjected to quantum mechanical analysis while preserving structural representativeness.

Each method presents unique features that make it particularly suitable for specific scenarios: Clustering excels at grouping similar structures and facilitating the interpretation of conformational space; the SI method ensures statistical independence by selecting uncorrelated structures; and the OWSCA approach offers an efficient signal compression technique that retains essential structural information. The most appropriate method should be selected based on the system under study, the research objectives, and the available computational resources.

Thus, the intelligent integration of these selection techniques into QM/MM workflows represents a significant advancement for computational chemistry applied to biological systems, enabling both cost-effective calculations and a more robust, accurate description of electronic and structural properties at the atomic level.

Author Contributions

All authors contributed equally to the production of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

Bibliographic References

1. Aravind, G.; Goyal, A.; Mukunda, N.; Suri, B.; The Journey from Classical to Quantum Mechanics. *Journal of the Indian Institute of Science* **2025**, *105*, 9. [Crossref]

2. Fedotov, A.; Vakhrushev, A.; Severyukhina, O.; Sidorenko, A.; Savva, Y.; Klenov, N.; Soloviev, I.; Theoretical Basis of Quantum-Mechanical Modeling of Functional Nanostructures. *Symmetry-basel* **2021**, *13*, 883. [Crossref]
3. Raucci, U.; Weir, H.; Sakshuwong, S.; Seritan, S.; Hicks, C.; Vannucci, F.; Rea, F.; Martínez, T.; Interactive Quantum Chemistry Enabled by Machine Learning, Graphical Processing Units, and Cloud Computing. *Annual Review of Physical Chemistry* **2023**, *74*, 313. [Crossref]
4. Robinson, P.; Rettig, A.; Dinh, H.; Chen, M.; Lee, J.; Condensed-Phase Quantum Chemistry. *Wiley Interdisciplinary Reviews-Computacional Molecular Science* **2025**, *15*, e70005. [Crossref]
5. Karmakar, T.; Nobel Prize in Chemistry 2024. *Resonance-Journal of Science Education* **2025**, *30*, 649. [Crossref]
6. Aguéro-Pizzolo, S.; Bettler, E.; Gouet, P.; Nobel Prize in chemistry 2024: David Baker, Demis Hassabis et John M. Jumper. The revolution of artificial intelligence in structural biology. *MS-Medecine Sciences* **2025**, *41*, 367. [Crossref]
7. Doga, H.; Raubenolt, B.; Cumbo, F.; Joshi, J.; Difilippo, F.; Qin, J.; Blankenberg, D.; Shehab, O.; A Perspective on Protein Structure Prediction Using Quantum Computers. *Journal of Chemical Theory and Computation* **2024**, *20*, 3359. [Crossref]
8. Pal, S.; Bhattacharya, M.; Lee, S.; Chakraborty, C.; Quantum Computing in the Next-Generation Computational Biology Landscape: From Protein Folding to Molecular Dynamics. *Molecular Biotechnology* **2024**, *66*, 163. [Crossref]
9. Yukawa, H.; Kono, H.; Ishiwata, H.; Igarashi, R.; Takakusagi, Y.; Arai, S.; Hirano, Y.; Suhara, T.; Baba, Y.; Quantum life science: biological nano quantum sensors, quantum technology-based hyperpolarized MRI/NMR, quantum biology, and quantum biotechnology. *Chemical Society Reviews* **2025**, *54*, 3293. [Crossref]
10. Gonçalves, M.; Andolpho, G.; da Cunha, E.; Ramalho, T.; Exploring 129Xe NMR parameters for structural investigation of biomolecules: relativistic, solvent, and thermal effects. *Journal of Molecular Modeling* **2022**, *28*, 372. [Crossref]
11. Santos, T.; Andolpho, G.; Tavares, C.; Gonçalves, M.; Ramalho, T.; Improving the Path to Obtain Spectroscopic Parameters for the PI3K-(Platinum Complex) System: Theoretical Evidences for Using 195Pt NMR as a Probe. *Magnetochemistry* **2023**, *9*, 89. [Crossref]
12. Öztürk, I.; Gervasoni, S.; Guccione, C.; Bosin, A.; Vargiu, A.; Ruggerone, P.; Malloci, G.; Force Fields, Quantum-Mechanical- and Molecular-Dynamics-Based Descriptors of Radiometal-Chelator Complexes. *Molecules* **2024**, *29*, 4416. [Crossref]
13. Schmitz, G.; Yönder, Ö.; Schnieder, B.; Schmid, R.; Hättig, C.; An automatized workflow from molecular dynamic simulation to quantum chemical methods to identify elementary reactions and compute reaction constants. *Journal of Computational Chemistry* **2021**, *42*, 2264. [Crossref]
14. Ramalho, T.; Bühl, M.; Probing NMR parameters, structure and dynamics of 5-nitroimidazole derivatives. Density functional study of prototypical radiosensitizers. *Magnetic Resonance in Chemistry* **2005**, *43*, 139. [Crossref]
15. Brooks, C. I.; MacKerell, A. J.; Post, C.; Nilsson, L.; Biomolecular dynamics in the 21st century. *Biochimica et Biophysica Acta-General Subjects* **2024**, *1868*, 130534. [Crossref]
16. Gonçalves, M.; Júnior, A.; da Cunha, E.; Ramalho, T.; Investigating an efficient and accurate protocol for sampling structures from molecular dynamics simulations: a close look by different wavelet families. *Theoretical Chemistry Accounts* **2021**, *140*, 109. [Crossref]
17. Lanjan, A.; Moradi, Z.; Srinivasan, S.; Computational Framework Combining Quantum Mechanics, Molecular Dynamics, and Deep Neural Networks to Evaluate the Intrinsic Properties of Materials. *Journal of Physical Chemistry A* **2023**, *127*, 6603. [Crossref]
18. Daura, X.; Gademann, K.; Jaun, B.; Seebach, D.; van Gunsteren, W.; Mark, A.; Peptide folding: When simulation meets experiment. *Angewandte Chemie-International Edition* **1999**, *38*, 236. [Crossref]
19. De Paris, R.; Quevedo, C.; Ruiz, D.; de Souza, O.; Barros, R.; Clustering Molecular Dynamics Trajectories for Optimizing Docking Experiments. *Computational Intelligence and Neuroscience* **2015**, *2015*, 916240. [Crossref]
20. Shao, J.; Tanner, S.; Thompson, N.; Cheatham, T.; Clustering molecular dynamics trajectories: 1. Characterizing the performance of different clustering algorithms. *Journal of Chemical Theory and Computation* **2007**, *3*, 2312. [Crossref]
21. Lyman, E.; Zuckerman, D.; Ensemble-based convergence analysis of biomolecular trajectories. *Biophysical Journal* **2006**, *91*, 164. [Crossref]
22. Coutinho, K.; Canuto, S.; Zerner, M.; A Monte Carlo-quantum mechanics study of the solvatochromic shifts of the lowest transition of benzene. *Journal of Chemical Physics* **2000**, *112*, 9874. [Crossref]
23. Coutinho, K.; Canuto, S.; Solvent effects from a sequential Monte Carlo - Quantum mechanical approach. *In Advances in Quantum Chemistry* **1997**, *28*, 89. [Crossref]
24. Coutinho, K.; Georg, H.; Fonseca, T.; Ludwig, V.; Canuto, S.; An efficient statistically converged average configuration for solvent effects. *Chemical Physics Letters* **2007**, *437*, 148. [Crossref]
25. Gonçalves, M.; da Cunha, E.; Peixoto, F.; Ramalho, T.; Probing thermal and solvent effects on hyperfine interactions and spin relaxation rate of δ-FeOOH(100) and $[MnH_3buea(OH)]^{2-}$: Toward new MRI probes. *Computational and Theoretical Chemistry* **2015**, *1069*, 96. [Crossref]
26. Gonçalves, M.; Santos, L.; Prata, D.; Peixoto, F.; da Cunha, E.; Ramalho, T.; Optimal wavelet signal compression as an efficient alternative to investigate molecular dynamics simulations: application to thermal and solvent effects of MRI probes. *Theoretical Chemistry Accounts* **2016**, *136*, 15. [Crossref]
27. Gonçalves, M.; Gonçalves, A.; Franca, T.; Santana, M.; Da Cunha, E.; Ramalho, T.; Improved Protocol for the Selection of Structures from Molecular Dynamics of Organic Systems in Solution: The Value of Investigating Different Wavelet Families. *Journal of Chemical Theory and Computation* **2022**, *18*, 5810. [Crossref]
28. Gao, R.; Yan, R.; Em *Wavelets: theory and applications for manufacturing*; Gao, R.; Yan, R.; eds.; Springer: Boston, 2011, cap 2. [Link]
29. Salomon, D.; Motta, G.; *Handbook of Data Compression*, Springer: London, 2010. [Link]