Magn. Reson. Discuss.,
https://doi.org/10.5194/mr-2020-32-RC1, 2020

Open Access MAGNETIC RESONANCE Discussions

Interactive comment on "Extending the applicability of P3D for structure determination of small molecules" *by* Alain Ibáñez de Opakua and Markus Zweckstetter

Anonymous Referee #1

Received and published: 19 December 2020

The paper submitted by M. Zweckstetter applies molecular alignment simulations (P3D) to the structure determination of small molecules by comparing predicted residual dipolar couplings (RDCs) with experimental data.

Before I will comment further on the paper I have to say that this manuscript is close to being unreadable without an intense recourse to the first paper on the subject published by the same author in Angew. Chemie. Furthermore, the manuscript does not include any Supporting Information, which additionally compromises the comprehension of its scientific content. This means that this manuscript cannot stand on its own which is a very unpleasant fact for the reader (and the reviewer!). Moreover, the introduction

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Discussion paper

should be rewritten in order to give credit to the people doing pioneering work in the field. Ad Bax may have coined the term RDCs, but this doesn't mean that he invented the technique or that the paper of Bax and Tjandra was a seminal one. Courtieu, Prestegard, Lesot and of course Emsley to name just a few, should be mentioned here. [1-4] In general the citation policy of the manuscript is far from being of good scientific practice (the LLC-phase literature, [5-7] the structure of PBLG – its helicity is known since 1954[8] not 2009 and so on. . .). But apart from these formal deficiencies, the scientific value of the paper is more than questionable.

P3D simulations are based on MD derived PBLG snapshot geometries, around which a cubic grid is placed. The molecular geometries of the analytes under investigation (strychnine, IPC, and sucrose) are placed on this grid, and Boltzmann-averaged RDC sampling is carried out by evaluating the averages over all grid points and all analyte orientations. The interaction between the analytes and the alignment polymer PBLG are evaluated purely on the basis of static (pre-computed grids) interactions that include steric (excluded volume) and electrostatic (based atomic charges) terms. This type of simulation represents a fast, but surely very crude model to simulate the analyte-polymer interactions as well as the alignment process. Not only are vdW-interactions completely ignored, but also all dynamic and entropic contributions to the alignment process are neglected. The rather coarse-grained grid used in the simulations (grid spacing 0.4A) and the rough sampling of molecular orientations (1800 per grid point) must necessarily lead to large uncertainties. It is not even clear, whether a cubic grid superimposed to a rod-shaped, cylindrical polymer may introduce systematic errors. Certainly, the excluded-volume simulations are apt to introduce large degrees of order even at large polymer-analyte distances when first contacts become possible. The Boltzmann-averaging is highly sensitive towards energies used, and simple electrostatic interactions using static molecular models are with some certainty crude oversimplifications. The RDCs obtained from the P3D-PBLG simulation are then compared to experimental data obtained from diverse alignment media (Figure 2), though obviously these media do have vastly differing alignment properties (see Figure 2, RDCs

across different alignment media also differ vastly in their magnitude). It is unclear how the P3D derived RDCs were scaled to account for different degrees of order, and how a PBLG simulation should compare to chemically different alignment media such as PELG, PMMA, PS, PA, etc. Even for the simulated and experimental data of PBLG, there are huge discrepancies between the individual RDCs of up to 115 Hz (Figure 2, strychnine, CH3 RDC)!!! The invalid comparisons are continued in Figure 3, were matrices of Pearson correlations are given in color-coded form. Many of these correlations are negative (marked by dots in Figure 3), and thus raise additional doubts on the assumptions made by the P3D simulations (by the way: the color-code used in Figure 3 is also highly misleading, as “green” color obviously indicate bad correlations). The obviously invalid cross-alignment media / P3D – PBLG comparisons are then continued in Figure 4 for different diastereomers of strychnine, yet it remains unclear how such a crude alignment simulation that neglects almost all relevant interactions (including all dynamic alignment polymer properties) can differentiate the molecular configurations. The investigations are then extended to the more flexible structure of sucrose, were only eight out of 23 RDCs that have been reported in the literature have been used. It is open to speculation why only this small subset of experimental data is used – may be the rest of the data doesn’t fit well? Three different sucrose conformers are evaluated, the geometries of which were taken from the literature. Figure 5 details the results for the three individual sucrose conformers, where large deviations of the experimental and calculated RDCs are observed indicated by significant deviations of the correlations from the diagonal of the plots given in Figure 5c. The relative contributions of the sucrose conformers are then optimized by maximizing the RQ parameter, and an “an almost perfect fit (R=0.996; QS=0.076)“ was finally obtained (Figure 6). However, given the sparsity of the NMR data used, and the number of conformers evaluated, it is clear that a multi-conformer fit represents sort of an over-fitting scenario, which is not supported by an adequate amount of experimental data. Given the wealth of conformational data available for a common compound such as sucrose, a more thorough evaluation against the literature data available is mandatory. The most highly popu-

lated structure of sucrose seems to be close to its solid-state conformation, but this must not necessarily be the correct description for the flexibility of sucrose as the solution conformation may differ significantly therefrom. The claim stated in the conclusion of this paper that “molecular alignment simulations might – with further improvements – become crucial for the determination of the absolute configuration” is, based on these results, an unjustified expectation as these simulations supposedly must treat molecular interactions on a much finer and much more detailed level, which even may be out-of-reach altogether at least in the (near) future. In view of the roughness of the model, the complete neglect of dynamic effects, the over-simplifications of the molecular interactions, and the invalidity of the cross-alignment comparisons employed here I cannot see how these P3D simulations may be used to elucidate even the relative configuration of slightly more complex natural products of unknown configuration beyond reasonable doubt. For these reasons publication in Magnetic Resonance is not recommended.

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