

We agree with the points raised and the arguments are warranted. Our contribution is conceptual in nature and not yet substantiated by experimental results. However, the proposed measurement of longitudinal $C'/C^\alpha C'$ CCR is by no means speculative. A possible measurement scheme was sketched and preliminary data for human Ubiquitin is presented in Fig. 3 illustrating that the CCR rates can be measured with sufficient resolution.

Based on the distances alone, CCR to remote carbons ($C'C^\beta$ and $C'_i C^\alpha_{i+1}$) would not be completely negligible. However, as the J-couplings $2J(C'C^\beta)$ and $2J(C'_i C^\alpha_{i+1})$ are not resolved, these effects can be expected to average out especially for short and intermediate mixing times. While up to 20% in size of the $CCR(C'C^\alpha)$, the \pm CCR($C'C^\beta$) components contribute to the same line.

Still, we are not at the point to complement our contribution to the Festschrift with definitive experimental data. With the given deadline, the presented concepts and preliminary measurements represent the project's current status. Closely related to Geoffrey Bodenhausen's groundwork, we feel the developed concepts and ideas provide a worthwhile contribution to the Festschrift.

So indeed, by offering a closely connected but differently oriented spin probe complementing the conventional NH^N spin pair, $C'/C^\alpha C'$ CCR can provide a "feel" for the local dynamics of the peptide plane and possible differences on a residue-per-residue basis. As the spectral densities are mapped at the same (i.e. zero) frequency, direct comparisons are straightforward.

If the $J(0)$ s and thus Q s vary noticeably and with a persistent pattern over multiple residues and the size of $J(0)$ implies the presence of slower tumbling motions, we would consider this experimental evidence for the previously evoked image of anisotropic tumbling of helical or chain-like elements in IDPs (Mantsyzov et al.). If the $J(0)$ s/ Q s deviate from the isotropic case in a systematic and correlated manner, it would hint towards different inherent mobilities for $C'/C^\alpha C'$ and N/NH^N . This could result from different librational degrees of freedom and/or the effect of flanking ψ_{i-1}/ϕ_i flips derived from MD (Salvi et al., Bremi et al.). In the somewhat unexpected scenario of pronounced variation of $J(0)$ s/ Q s from residue to residue, it would mean that IDP dynamics are highly anisotropic and heterogeneous. In this case, ^{15}N relaxation alone could not be expected to capture IDP dynamics in adequate detail. If the time correlation function of such closely connected spin-probes were to decay very differently, it would have substantial structural implications.

If the $J(0)$ s/ Q s are very similar and adhere to the isotropic case, it would appear that peptide plane dynamics in IDPs are already well-probed by ^{15}N relaxation alone and peculiarities observed for sequential $H^\alpha H^N$ NOEs should not be attributed to anisotropic dynamics but rather to the additional degree of freedom encoded in ψ (Mantsyzov et al.). In structural terms, diffusive segmental reorientation in IDPs does not correspond to the mental image of isolated helices and chains tumbling in solution.

Of course, the above scenarios might apply differently depending on the protein system. We can highlight these implications further in the Results & Discussion section.