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Review

An NMR database for simulations of membrane dynamics

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ABSTRACT

Computational methods are powerful in capturing the results of experimental studies in terms of force fields that both explain and predict biological structures. Validation of molecular simulations requires comparison with experimental data to test and confirm computational predictions. Here we report a comprehensive database of NMR results for membrane phospholipids with interpretations intended to be accessible by non-NMR specialists. Experimental ^{13}C–^{1}H and ^{2}H NMR segmental order parameters (S_{CH} or S_{CD}) and spin-lattice (Zeeman) relaxation times (T_{1Z}) are summarized in convenient tabular form for various saturated, unsaturated, and biological membrane phospholipids. Segmental order parameters give direct information about bilayer structural properties, including the area per lipid and volumetric hydrocarbon thickness. In addition, relaxation rates provide complementary information about molecular dynamics. Particular attention is paid to the magnetic field dependence (frequency dispersion) of the NMR relaxation rates in terms of various simplified power laws. Model-free reduction of the T_{1Z} studies in terms of a power-law formalism shows that the relaxation rates for saturated phosphatidylcholines follow a single frequency-dispersive trend within the MHz regime. We show how analytical models can guide the continued development of atomistic and coarse-grained force fields. Our interpretation suggests that lipid diffusion and collective order fluctuations are implicitly governed by the viscoelastic nature of the liquid-crystalline ensemble. Collective bilayer excitations are emergent over mesoscopic length scales that fall between the molecular and bilayer dimensions, and are important for lipid organization and lipid-protein interactions. Future conceptual advances and theoretical reductions will foster understanding of biomembrane structural dynamics through a synergy of NMR measurements and molecular simulations.

Contents

Abbreviations: Chol, cholesterol; CPMG, Carr-Purcell-Meiboom-Gill; CSA, chemical shift anisotropy; DDPC, 1,2-didocosahexaenoyl-*sn*-glycero-3-phosphocholine; DLPC, 1,2-dilauroyl-*sn*-glycero-3-phosphocholine; DLPC-d_{46}, 1,2-diperdeuteriolauroyl-*sn*-glycero-3-phosphocholine; *D*, methylene travel; D_M, maximum methylene travel; DMPC, 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine; DMPC-d_{54}, 1,2-diperdeuteriomyristoyl-*sn*-glycero-3-phosphocholine; DMPE, 1,2-dimyristoyl-*sn*-glycero-3-phosphoethanolamine; DMPE-d_{27}, 1-myristoyl-2-perdeuteriomyristoyl-*sn*-glycero-3-phosphoethanolamine; DOPC, 1,2-dioleoyl-*sn*-glycero-3-phosphocholine; DPPC, 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine; DPPC-d_{62}, 1,2-diperdeuteriopalmitoyl-*sn*-glycero-3-phosphocholine; DROSS, dipolar recoupling with shape and sign preservation; DSPC, 1,2-distearoyl-*sn*-glycero-3-phosphocholine; DSPC-d_{72}, 1,2-diperdeuteriostearoyl-*sn*-glycero-3-phosphocholine; GalCer, galactosylceramide; GlcCer, glucosylceramide; H_{II}, inverted hexagonal phase; MAS, magic angle spinning; MD, molecular dynamics; NMR, nuclear magnetic resonance; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PLPE-d_{31}, 1-perdeuteriopalmitoyl-2-linoleoyl-*sn*-glycero-3-phosphoethanolamine; POPC, 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine; PS, phosphatidylserine; PSM, N-palmitoyl sphingomyelin; PI, phosphatidylinositol; SAXS, small-angle X-ray scattering; SLF, separated local-field

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Nuclear magnetic resonance spectroscopy is valuable for investigating membrane structure and dynamics because of the varied experimental techniques and multitude of probe nuclei present in the membrane. There exists a substantial and diverse body of experimental nuclear magnetic resonance (NMR) results for membrane lipid bilayers that provides important structural and dynamic information that cannot be obtained with other experimental methods [1–5]. However, for the non-specialist, NMR results may tend to be inaccessible due to their being distributed throughout the research literature, and rendered opaque by various theoretical treatments invoked in the analysis of the data [5–8]. One further aspect is that the diversity of the NMR measurements and the experimental systems studied may contribute to obscuring of the underlying general principles. Here our aim is to bring together the available experimental NMR results into a comprehensive database that is transparent to all, ranging from NMR practitioners to non-specialists in the field of molecular simulations [9–16].

1. Membrane lipids and biomembranes are liquid-crystalline materials with a hierarchy of time scales

The nature of phospholipid membrane dynamics is highlighted in this contribution, where we present and interpret NMR measurements of ^{13}C–^{1}H and ^{2}H NMR segmental order parameters and spin-lattice relaxation frequency dispersions for a comprehensive series of saturated, unsaturated, and biological phospholipid membranes. Experimental NMR methodologies and closed-form biophysical models are provided in order to demonstrate how this benchmark experimental technique enables molecular dynamics to be observed. Nuclear spin-lattice (T_{1Z}) relaxation studies show that the rates recorded as a function of magnetic field for unsaturated and saturated phosphatidylcholines follow a single frequency dispersive trend that spans the MHz regime (correlation times in the nanosecond to microsecond range). This trend suggests that experimentally determined rates of anisotropic rotational diffusion and molecular order fluctuations are determined by the viscoelastic nature of the liquid-crystalline membrane ensemble. Global perspectives from model-free and model-dependent interpretations of the comprehensive set are presented in the context of comparison to other experimental and computational methods to foster understanding of biomembrane structural dynamics.

Another of our main goals is to develop the notion of phospholipid membrane dynamics within a hierarchical framework that includes a large sampling of the experimental data sets. Interpretation of the data within the framework of a simple heuristic structural and dynamic picture involving closed-form analytical expressions allows us to illustrate general features that can be further refined through consideration of molecularly specific interactions. Various NMR studies of the structural and dynamic features of membranes are conceptualized, whereby spatial dimensions such as local segmental order, molecular orientation, and continuum geometries are considered. The temporal dimension involves the correlation times of the motions associated with the geometrical transformations of each spatial frame in accord with a hierarchy of the timescales for the various possible lipid motions.

Equilibrium and dynamical properties of membrane lipid bilayers correspond to a multi-dimensional energy landscape that may be probed with diverse biophysical techniques (cf. Fig. 1). Equilibrium properties are due to segmental, molecular, and collective fluctuations averaged over appropriate time scales, and can be explored with methods like X-ray scattering [17–20], neutron scattering [21–26], and spectroscopic techniques encompassing Fourier transform infrared [27–29] or Raman spectroscopy [30–32]. Examples of equilibrium properties for a planar membrane include the mean cross-sectional lipid area $\langle A \rangle$ and the volumetric thickness D_C, as well as the corresponding compressibility moduli such as the area (lateral) compressibility modulus k_a as discussed in the excellent reviews by Nagle and Tristram-Nagle [20,33] and Zimmerberg and Gawrisch [34]. Membrane curvature is described by the spontaneous (intrinsic) curvature H_0 and the bending modulus k_c together with the saddle (Gaussian) curvature modulus and compression modulus, and affords a means of conceptually understanding membrane deformation and lipid–protein interactions [35,36].

By contrast, dynamical properties correspond to the magnitudes and rates of fluctuations of the structural quantities about the equilibrium average, and are probed by techniques such as neutron scattering [24] and NMR relaxation [5–8,37–39]. Examples include local isomerizations of the lipid related to the microviscosity of the membrane interior, diffusional (rotational and translational) lipid motions, and collective fluctuations of the membrane. It follows from the fluctuation–dissipation theorem that the macroscopic relaxation rates are essentially manifestations of dynamical processes with contributions from mobility of the reference frames that also express the equilibrium (static) picture of the membrane. Hence, dynamics measurements in conjunction with equilibrium studies can provide a comprehensive view of the lipid properties that underlie membrane deformation and protein conformational changes [40,41], as well as membrane remodeling [42,43] and curvature sensing [35,41,44]. Further interpretation at a fundamental level in terms of molecular forces entails either simplified models that are more or less exactly solvable [45–47], or more exact models whose approximate solution requires numerical methods [9,48,49]. Knowledge of the molecular forces implicated in membrane deformation in turn can give a deeper understanding of the material properties, as well as lipid–protein interactions implicated in various key biological functions.

According to the hierarchy depicted in Fig. 1 arranged from smallest to largest time scale, we first focus on the individual C–H bonds. These segmental sites fluctuate with correlation times in the range of femtoseconds to nanoseconds due to vibrational motion, *trans–gauche* isomerizations, and restricted segmental reorientation. One step up in the temporal hierarchy, one may consider the orientational fluctuations of the lipid molecules. Anisotropic motion