



The nuclear Overhauser effect from a quantitative perspective



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ABSTRACT

The nuclear Overhauser enhancement or effect (NOE) is the most important measure in liquid-state NMR with macromolecules. Thus, the NOE is the subject of numerous reviews and books. Here, the NOE is revisited in light of our recently introduced measurements of exact nuclear Overhauser enhancements (eNOEs), which enabled the determination of multiple-state 3D protein structures. This review encompasses all relevant facets from the theoretical considerations to the use of eNOEs in multiple-state structure calculation. Important aspects include a detailed presentation of the relaxation theory relevant for the nuclear Overhauser effect, the estimation of the correction for spin diffusion, the experimental determination of the eNOEs, the conversion of eNOE rates into distances and validation of their quality, the distance-restraint classification and the protocols for calculation of structures and ensembles.

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1. Introduction

1.1. The NOE

The dipolar interaction between two spins, named for its discoverer, the nuclear Overhauser enhancement or effect (NOE) [1], has arguably become the most important phenomenon in nuclear magnetic resonance (NMR) spectroscopy. Two of the most popular and important books in the field stand for two important development stages of the NOE and NMR as a whole. The monolog by Noggle and Schirmer summarizes the state of the 1970s [2] when NMR was recorded in one dimension and the NOE was used to characterize small molecules. The second one by Wüthrich represents the leap in the 1980s when two-dimensional spectroscopy allowed protein and nucleic acid structure calculation from NOEs [3].

Since these groundbreaking discoveries, the application of the NOEs branched into many dedicated fields. This may be mirrored by a list of reviews in the Progress of Nuclear Magnetic Resonance Spectroscopy in which the NOE is the main subject from 1990 onward (making no claim to be complete): Ref. [4, 1990] covers the full relaxation matrix approach for structural studies; Ref. [5, 1994] reviews NOE and rotating-frame Overhauser enhancement (ROE) theory and models for the description of motions; Refs. [6, 1994,7, 1997] review the intermolecular interactions observed by NOEs; Ref. [8, 1998] presents the theory of dipolar interaction in liquid- and solid-state NMR; Ref. [9, 1998] reviews the use of ambiguous NOE restraints in structure calculation, and finally Refs. [10, 2005,11, 2006] review again the intermolecular interactions observed by NOEs.

The NOE was first described in 1953 when it was observed that saturation of the electron spin resonance causes a polarization of nuclear spins to an extent given by the ratio of the gyromagnetic ratios of the two spins [1,12,13]. Although later extended, the simple theoretical description known as the Solomon equations formulated 2 years later remains the most practical formulation of the NOE [14]. It took another 10 years until the dependence of the NOE on the distance between the two nuclear spins was used for conformational studies of small molecules in solution [15]. In 1972, it was observed that the NOE also transfers magnetization between molecules [16] and thus may serve as a tool to study bound ligand conformations [17].

The subject of this review is mostly the transient nuclear Overhauser effect as observed in two proton dimensions [3,18–22] or more. A quantitative analysis of the NOE is also key in techniques such as the saturated NOE (usually one-dimensional experiments with selective irradiation) [23,24] or the transferred NOE (trNOE) [6,25,26] but these topics are beyond the scope of the present work. As this review addresses the extraction of very accurate distances [27,28] and motional effects [29], strong focus is laid on the impact of dynamics on the spectral density function and exact understanding of the approximations that are employed.

1.2. Back to the future: the eNOE

What started out as “a new method for polarizing nuclei, applicable only to metals” 60 years ago [1] lead to the recent characterization of structural ensembles indicating the presence of correlated motion in a protein by the collection of many exact NOEs (eNOE) [30–32].

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