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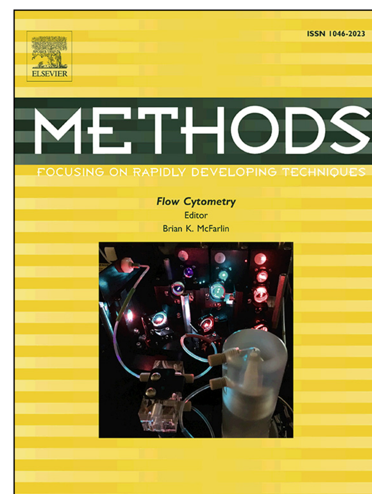

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Irina Oganesyan, Cristina Lento, Derek J. Wilson

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ACCEPTED MANUSCRIPT

Contemporary Hydrogen Deuterium Exchange Mass Spectrometry

Irina Oganesyan[1], Cristina Lento[1] and Derek J. Wilson[1,2,3]

[1]Department of Chemistry, York University, Toronto, M3J 1P3, Canada
[2]Centre for Research of Biomolecular Interactions, York University, Toronto, M3J 1P3, Canada
[3]Centre for Research in Mass Spectrometry, York University, Toronto, M3J 1P3, Canada

Abstract

Hydrogen/deuterium exchange (HDX) mass spectrometry (MS) emerged as a tool for biochemistry and structural biology around 25 years ago. It has since become a key approach for studying protein dynamics, protein-ligand interactions, membrane proteins and intrinsically disordered proteins (IDPs). In HDX labeling, proteins are exposed to deuterated solvent (usually D_2O) for a variable 'labeling time', resulting in isotope exchange of unprotected labile protons on the amide backbone and amino acid side chains. By comparing the levels of deuterium uptake in different regions of a protein, information on conformational and dynamic changes in the system can be acquired. When coupled with MS, HDX is suitable for probing allosteric effects in catalysis and ligand binding, epitope mapping, validation of biosimilars, drug candidate screening and mapping membrane-protein interactions among many other bioanalytical applications. This review introduces HDX-MS *via* a brief description of HDX-MS development, followed by an overview of HDX theory and ultimately an outline of methods and procedures involved in performing HDX-MS experiments.

1. Introduction

1.1 The history of HDX

The origins of HDX as a bioanalytical approach with a well-developed underlying theory can be traced to the work of Linderstrøm-Lang and colleagues at the Carlsberg laboratories, which focussed on HDX at the amide backbone of peptides/proteins [1]. Initially, Linderstrøm-Lang and coworkers were interested in using HDX rates to measure the stability of the hydrogen bonds involved in the formation of secondary protein structures[2–10]. Later, they recognized that exchange in the amide backbone of the protein relates to conformational changes which were the first study of protein dynamics using this method [1,11,12]. In what is arguably their most critical contribution, Linderstrøm-Lang developed the essential theory for the analysis of HDX kinetics that is still the dominant framework for understanding how HDX data related to the dynamics of macromolecules [1,12–16]. Up until the late 1980's, HDX in macromolecules was mainly monitored by nuclear magnetic resonance (NMR), as no method existed at the time for transferring macromolecules into the gas phase [17–24]. In 1988 and 1989, this problem was overcome by the introduction of soft ionization methods – Matrix Assisted Laser Desorption/Ionization (MALDI) and Electrospray Ionization (ESI), respectively [25–28]. Combined with improvements in LC separations and pH-based HDX quenching [29–31], this was the last critical advance that set the stage for HDX-MS to become a viable a bioanalytical tool. The rapid rise of HDX-MS related publications over the last 20 years is a testament to it's broad applicability in biochemistry, and its complementarity to the classical tools of structural biology [32–36]. Compared to HDX-NMR, for instance, HDX-MS has the advantage of having virtually no size limitation and can require substantially less protein material, but it typically does not provide atomic resolution[37–39]. HDX-MS is also ideal for

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