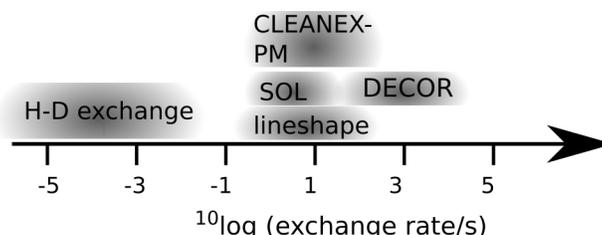


A New NMR Technique to Measure Very Fast Hydrogen Exchange Rates in Proteins: Are High Protection Factors for Alpha-Synuclein a Sign of Structuration?

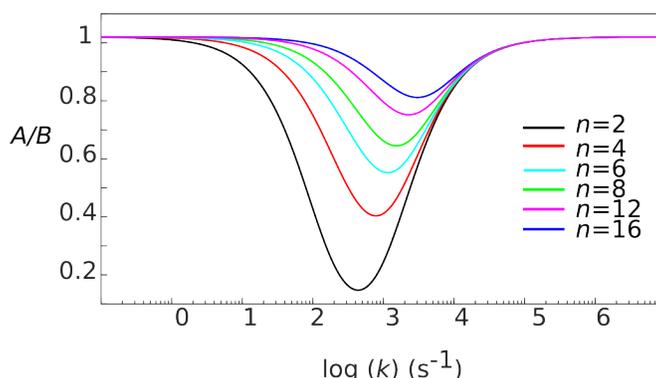
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We describe a novel approach to measure peptide hydrogen exchange rates in the range 10 – 10,000 s⁻¹ [1]. Although several methods exist to measure chemical exchange, these are limited to the determination of very slow to slow processes:



The new application relies on the principle of decorrelation of spin order reported by Skrynnikov and Ernst [2], applied to anti-phase operators, as elegantly described by Pelupessy and colleagues [3]. Briefly, the technique uses spin-echoes to generate different admixtures of in-phase and anti-phase operators, where only the latter are subject to decorrelation by intermolecular hydrogen exchange. The signal loss is therefore a function of the pulse spacing (or, equivalently, the number of refocusing pulses in a constant time period), as follows:



Measuring a series of 2D HA(CACO)N spectra with different pulse spacings allows the exchange rate for individual amides in proteins to be determined through numerical fitting of the evolution of the density matrix in a Liouville subspace [1]. Applying this technique to the intrinsically disordered protein alpha-synuclein revealed surprisingly high protection factors at the C-terminus. This can be interpreted as a sign for structure formation [4]. However, an alternative explanation involving electrostatic effects is also possible. We present conclusive evidence for the latter interpretation, by making use of co-solute Paramagnetic Relaxation Enhancement.

- [1] Measurement of Very Fast Exchange Rates of Individual Amide Protons in Proteins by NMR Spectroscopy. Dass R, Corlianò E, Mulder FAA. ChemPhysChem. (2019) doi: 10.1002/cphc.201801044. [Epub ahead of print]
- [2] Detection of intermolecular chemical exchange through decorrelation of two-spin order. Skrynnikov NR, Ernst RR. J Magn Reson. (1999) 137(1):276-80.
- [3] Measuring fast hydrogen exchange rates by NMR spectroscopy. Kateb F, Pelupessy P, Bodenhausen G. J Magn Reson. (2007) 184(1):108-13
- [4] Okazaki H, Ohori Y, Komoto M, Lee YH, Goto Y, Tochio N, Nishimura C. FEBS Lett. (2013) 587(22):3709-14.