

Studying the conformational dynamics of intrinsically disordered proteins at atomic resolution using high field NMR spectroscopy

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Scientific description.

Structural biology is undergoing a rapid and unexpected revolution. In the last few years it has been predicted that up to 40% of proteins encoded in eukaryotic genomes are intrinsically disordered, and function without a stable three dimensional fold. Remarkably, these highly flexible proteins are able to form membraneless organelles, by liquid-liquid phase separation within human cells, revealing a new dimension to our understanding of their role in biology. These highly dynamic proteins cannot be studied using classical methods of structural biology such as X-ray crystallography, and new methods need to be invented, that allow us to describe their function at a molecular and even atomic level. Nuclear magnetic resonance (NMR) spectroscopy, in combination with molecular simulation, is the method of choice for studying disordered proteins, because even in the absence of structure, their behaviour can be studied in exquisite detail. The Blackledge group at the IBS is at the forefront of development of these techniques that allow us to describe this vast, and as yet poorly understood family of proteins. In particular we are interested in the dynamic behaviour of flexible proteins in conditions close to physiological – all the way to the live cell.

The candidate will develop **new methods** to measure and analyze experimental NMR data to understand the behaviour of intrinsically disordered proteins in physiological environments – a major new challenge for contemporary biology. The group uses six state-of-the-art NMR spectrometers at the IBS (600 MHz, 700MHz, 850MHz et 950MHz with cryoprobes).

Recent publications:

An ultraweak interaction in the intrinsically disordered replication machinery is essential for measles virus function. Milles S, Jensen MR, Lazert C, Guseva S, Ivashchenko S, Communie G, Maurin D, Gerlier D, Ruigrok R, Blackledge M *Science Advances*, 4, eaat7778 (2018)

Analytical Description of NMR Relaxation Highlights Correlated Dynamics in Intrinsically Disordered Proteins. Abyzov, A., Salvi, N., Blackledge M *Angew Chemie Intl Edition*, 129, 14020-14024 (2017)

Identification of Dynamic Modes in an Intrinsically Disordered Protein using Temperature Dependent NMR Relaxation. Abyzov, A., Salvi, N., Schneider, R., Maurin, D., Ruigrok R, Jensen MR, Blackledge M *J Am Chem Soc*, 138, 6240–6251 (2016)

Visualizing the molecular recognition trajectory of an intrinsically disordered protein using multinuclear relaxation dispersion NMR. Schneider R, Maurin D, Communie G, Kragelj J, Hansen F, Ruigrok R, Jensen M, Blackledge M *J Am Chem Soc* 137, 1220 (2015)

Direct observation of hierarchical protein dynamics. Lewandowski J, Halse M, Blackledge M*, Emsley L* *Science* 348, 578 (2015).