Ignored for a long time in high-resolution studies of proteins, intrinsic protein disorder is now recognized as one of the key features for a large variety of cellular functions, where structural flexibility presents a functional advantage in terms of binding plasticity and promiscuity. The properties of intrinsically disordered proteins (IDPs) and protein regions (IDPRs) are highly complementary to those deriving from the presence of a unique and well-defined three-dimensional fold. Structural order, well characterized through the vast number of protein 3D structures present in the Protein Data Bank (www.pdb.org), leading to highly organized protein machines with well-defined binding pockets, lies at the heart of structural biology. However, the functional importance of conformational flexibility, and the characterization of residual transient structure in these protein regions, has only recently attracted the attention of the scientific community and has immediately found widespread interest in molecular biology research.

The tendency of a protein to adopt a stable globular structure such as the number of folds we find in the Protein Data Bank or to be highly flexible and able to sample many different conformations, directly results from the amino acid primary sequence. It is not so surprising that a wide range of properties is needed for proteins to carry out a broad range of functions and the idea that a high extent of dynamics and flexibility provides important functional features nowadays appears quite obvious. Structural disorder is abundant in higher multi-cellular organisms, in particular in regulatory protein regions that orchestrate dynamic cellular functions relying on spatial and temporal malleability. As a consequence, IDPs and IDPRs are overrepresented in key functions of higher eukaryotes, i.e. transcriptional and translational regulation, intracellular signaling, protein homeostasis, inter-cellular communication, cell-fate decisions, and many more.

In this frame nuclear magnetic resonance (NMR) spectroscopy is the unique technique able to provide high resolution information. However the peculiar properties of IDPs do influence the NMR observables raising also several critical questions that should be considered in the design of optimal NMR experiments and in the interpretation of the data in terms of protein’s structural and dynamic properties.
Recent progress in the field has radically changed our perspective to study IDPs through NMR: increasingly complex IDPs can now be characterized, a wide range of observables can be determined reporting on their structural and dynamic properties, computational methods to describe the structure and dynamics are in continuous development and IDPs can be studied in environments as complex as whole cells.

Therefore we felt timely to convey these exciting recent developments in a book and to do this in close interactions with pioneers in the field of IDPs as well as with newcomers able to bring fresh energy and enthusiasm. We hope to be able to communicate the new exciting possibilities offered by NMR and to present open questions to foster further developments.

After an introductory chapter by Dunker and Oldfield describing the key steps opening the field of IDPs, the book focuses on the many aspects that make NMR a unique technique to study IDPs (Chaps. 2–5). Contributions discuss different aspects starting from the first principles of NMR spectroscopy, including hardware requirements, to the design and application of complex NMR experiments, to data interpretation in terms of structural and dynamic properties, to the best ways to achieve snapshots of IDPs in cells. Key to NMR analysis of complex proteins is the possibility to have efficient heterologous protein expression, enabling stable isotope incorporation. The tricks useful for IDPs samples preparation are reported in Chap. 6.

Information at atomic resolution derived from NMR needs to be complemented by information achieved through a variety of different biophysical methods reporting on different properties of IDPs, as discussed in Chaps. 7–8. The use of predictors, which may represent a preliminary step for any investigation, is reported in Chap. 9 while the perspectives for in-cell NMR in this field of research are discussed in Chap. 10. Several examples of recent investigations and open questions are reported in the final part of the book (Chaps. 12–14).

A separated chapter (Chap. 11) is dedicated to the PED, the database that has been designed to deposit experimental data and calculate structural ensembles in order to render these data feely accessible to the scientific community and stimulate discussion and progress in the field.

With this book we hope to provide a useful guide to students and post-docs approaching the field and willing to contribute to the characterization of IDPs through NMR. Recent progress in NMR instrumentation, combined with the development of new methods, has radically changed the perspective of the kind of molecules we can study, the amount of information that we can achieve as well as the time needed to complete an NMR characterization. Therefore we hope that the new NMR tools developed will be increasingly used and contribute a wealth of experimental information on IDPs. Speculating on more long-term perspectives, the development of improved NMR methods to study IDPs is expected to provide a large amount of experimental data on them, contributing to our understanding of the molecular basis responsible for their function and filling a gap of about 50 years with respect to our knowledge on the structural and dynamic behaviour of folded proteins. This is expected to reveal a much larger number of ways in which proteins communicate in the cell. Other expected outcomes of NMR experimental data on
IDPs include the improvement of prediction tools, which still suffer from the bias that they are derived from the missing information in the electron density maps in X-ray crystallography data!

We hope you will enjoy the book, and even more studying IDPs through NMR, as much as we do! A great thanks to all the Authors that we had the luck to work with and to the IDPbyNMR EC Marie Curie Initial Training Network which contributed to make it possible.
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