

Statement of Interest for a Collaborative Project

Development of Biological NMR into a High-Throughput Technique

NMR spectroscopy has established itself as an invaluable tool in the investigation of the structure, dynamics, and intermolecular interactions of biomolecules (bio-NMR). Within a vast portfolio of applications in Structural Biology, NMR has also made an important contribution in Structural Genomics by allowing the determination of the structure of a significant number of proteins. Notwithstanding these successes, which also constitute the result of many important technical and methodological advancements achieved in the last five-ten years, structure determination based on NMR data is still a relatively lengthy process whose results are quite dependent on the specific laboratory where the project has been carried out.

The application of NMR spectroscopy to Structural Proteomics and Structural Biology in general could be even more productive if a massive, collaborative effort is deployed by the major European laboratories and research teams in the field in order to make structure determination by NMR a truly high-throughput, fully automated endeavor whose outcome is assessed through a thorough, standardized quality evaluation. This would open up bio-NMR to a large audience of European researchers e.g. in biology or biomedicine, contributing towards the unraveling of the complex network of weak transient interactions that constitute cellular processes and that must be characterized both at the atomic level and within a systems biology approach. The latter represents a frontier for Life sciences, which is only just starting to produce its first results. Indeed, the development of bio-NMR into a high-throughput technique would have a major impact on scientific topics ranging from the understanding of biochemical processes and metabolic pathways to the regulation of gene expression. The successful completion of the present Collaborative Project will not only boost the performances of the EC-funded program for trans-national access to NMR Research Infrastructures, but also enhance the productivity of national and regional NMR facilities.

We want to pursue the above objectives by directly tackling the following key steps in the workflow for NMR-based protein structure determination (most steps are actually interlinked):

1. rapid acquisition of NMR experiments
2. optimization of the requirements in terms of NMR data sets
3. automated processing methods for multidimensional (3D and higher) spectra
4. automated resonance assignment for backbone and side chains
5. automated peak picking, including pattern identification techniques
6. automated structure calculation and validation methods

In brief, the presently proposed Collaborative Project will develop a fully integrated methodology that couples acquisition of an optimized ensemble of NMR data (i.e. NMR spectra) based on recently developed fast acquisition schemes with the use of completely automated software tools that cover all steps from data processing to analysis as well as structure calculation. Labeling strategies will be addressed as long as they aim at enabling high-throughput structural characterization. By simultaneously addressing the necessary experimental and computational advancements in a single project, it will be possible to optimize both aspects in a **concerted** manner, thus maximizing the impact of the project. At the end of the project, a scientist not expert in NMR will be able to obtain a protein structure from a sample through a protocol that minimizes his/her intervention through the selection of optimal acquisition schemes that are also a function of the sample properties, followed by application of automated software tools for data analysis and structure calculation.