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Biophysical Reviews’ “Meet the Editors Series”: a profile of Christina Sizun

Christina Sizun¹

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Abstract

This edition of the continuing “Biophysical Reviews Meet the Editors Series” introduces Dr. Christina Sizun, physical chemist, member of the Biophysical Reviews editorial board and current Treasurer of the International Union for Pure and Applied Biophysics (IUPAB).



Biophysical Reviews (BREV) is the journal of the International Union for Pure and Applied Biophysics (IUPAB). When I was elected treasurer of IUPAB in October 2022, after having been active in the French Biophysical Society, I also joined the editorial team of BREV. As a mid-term career scientist, I was particularly pleased to be invited to

participate to the Michèle Auger Award jury. It offers recognition and provides a showcase to young scientists who are gaining their independence and building their own projects. It is my pleasure to introduce myself here to the readership of BREV.

Unlike other biophysicists, and although I felt attracted to life and medical sciences, I graduated in chemistry and physics. These disciplines were considered to be more challenging than biology, when I was a student in France in the early 1990s. Nevertheless, I had the opportunity to attend several lectures at the Ecole Normale Supérieure of Lyon, which gave me a glimpse into the world of biology and geology. These graduation years later became an asset to work in a multidisciplinary field. At the same time, I discovered nuclear magnetic resonance (NMR), as an application of the laws of nuclear magnetism and as a tool for chemical analysis. I strongly liked the idea of studying spectroscopic methods at the interface between physics and chemistry, mixing theory and experiments. I therefore prepared a PhD degree in physical chemistry at the University of Strasbourg, specializing in NMR. I worked on a variety of samples, ranging from inclusion complexes to cobalt clusters and mesoporous silica, used for chemical catalysis (Sizun et al. 2000, 2003). Although seemingly unrelated, all these samples displayed dynamics occurring at different time scales, which could be revealed by liquid and solid state NMR methods.

My next move was to the Max Planck Institute for Biochemistry in Martinsried, as a post-doc fellow in the junior research group of Burkhard Bechinger. I started investigating membrane peptides and model membranes by solid-state NMR (Bechinger and Sizun 2003; Sizun and Bechinger 2002), and thereby entered the world of biophysics. I had been advised earlier to focus on a specific research topic,

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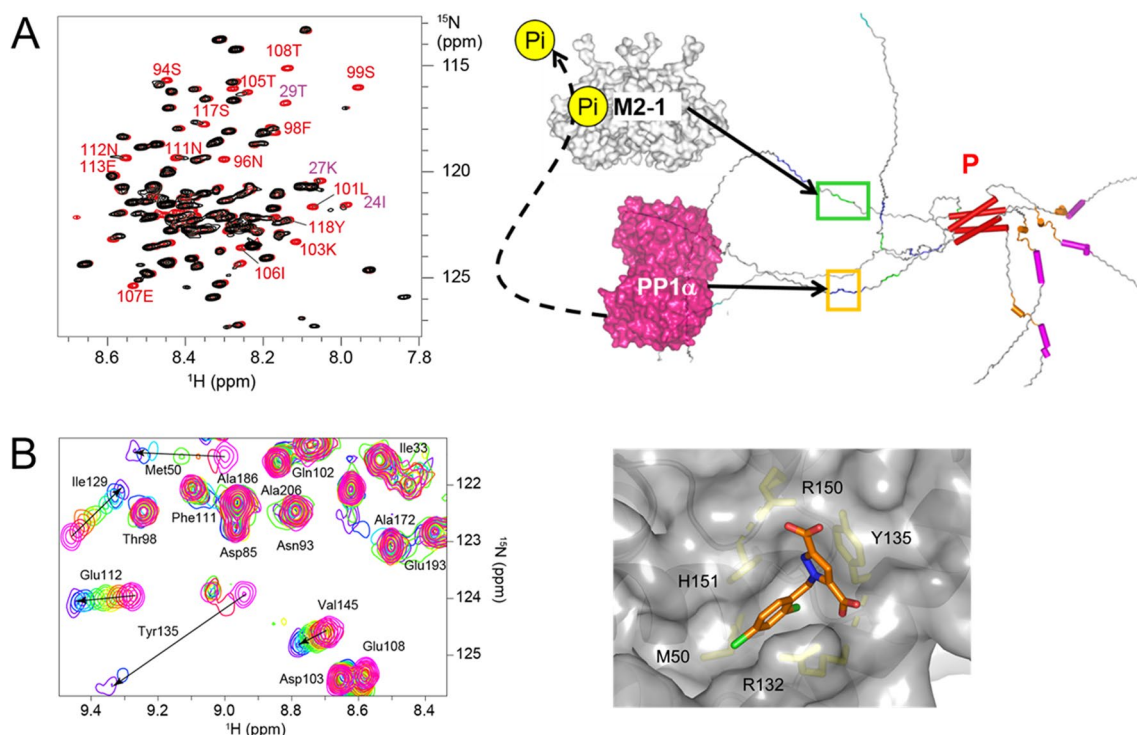


Fig. 1 Contribution of NMR spectroscopy to the structural characterization of respiratory syncytial virus (RSV) protein complexes. **A** Intensity perturbations in the ^1H - ^{15}N HSQC spectrum of ^{15}N -labeled RSV phosphoprotein P pointed to a small linear motif that is the main binding site of RSV transcription co-factor M2-1 (red labels on the spectrum). It is highlighted by a green box on the representation of the P protein on the right-hand panel. The same type of experiment was used to determine the binding site of the PP1 α phosphatase, which is adjacent (yellow box). These data were validated by biochemical methods and led to a model, where P serves as a platform

to accommodate both PP1 α and M2-1. The proximity of the two proteins leads to dephosphorylation of M2-1 and binding of M2-1 to viral RNA. **B** Titration experiments of the ^{15}N -labeled N-terminal domain of the RSV nucleoprotein N by a 11-mer peptide mimicking the C-terminal tail of RSV P protein reveal the binding site of P on N (reference spectrum in magenta; from red to purple: spectra measured with 0.2–6.2 equivalents of P peptide). The N–P interaction can be inhibited by small molecules like M76, which occupies the P-binding site of N as shown by the X-ray structure of N in complex with M76 (PDB 4ucc).

and not only to define myself through NMR as a method. This is why I made a second post-doc in the group of Erick Dufourc at the European Institute for Chemistry and Biology in Bordeaux, on similar a project (Sizun et al. 2004).

In 2003, I was appointed to a permanent researcher position at the French Center for Scientific Research (CNRS) in Gif-sur-Yvette, and later became a research director. I joined the Institute for Chemistry of Natural Substances (ICSN). ICSN hosts one of the high field NMR facilities in France. It is a member of the Infranalytics network (<https://infranalytics.fr>), which gives access to high-field NMR spectrometers to scientists throughout France. I first started as a member in the group of Jean-Yves Lallemand. He was interested in ATP Binding Cassette (ABC) transporters, more particularly in the cystic fibrosis transmembrane conductance regulator, and had formulated, together with Gérard Lenoir, the hypothesis of a functional complementation by other multidrug resistance ABC transporters (Lallemand et al. 1997). Complete ABC transporters have at least 12 transmembrane helices, and represent a challenge for structural biology, all

the more so for NMR. The group thus concentrated its effort on the catalytic cycle of Multidrug Resistance Protein 1 (Ramaen et al. 2006).

My leitmotif remained NMR, but I switched to solution NMR of proteins. Although NMR is an old method, progress is still ongoing. Especially sensitivity of NMR is continuously increasing. New magnet technology gives access to ever higher magnetic fields. Modern pulse sequences allow fast acquisition (Lescop et al. 2007), and overall less material is needed for investigations. I completed my initial education as a physical chemist by new knowledge and expertise in biochemistry, molecular biology, and structural biology. I teamed up with François Bontems at ICSN and Javier Perez from the Soleil Synchrotron to develop the DADIMODO software that combines small-angle X-ray scattering (SAXS) and NMR data to investigate the structure of multi-domain proteins and protein complexes (Evrard et al. 2011). Over the years, I supervised several master internships and PhD students. I also got involved in teaching of biological NMR at Sorbonne Université and Université Paris-Saclay, as well

as in NMR and structural biology summer schools (<https://www.renafobis.fr/ecoles-thematiques/>).

Presently, I am leading a small group that investigates interactions of proteins with different ligands at the atomic level, or at least in a residue-specific manner, mainly by NMR. Our aim is to contribute to understanding protein function by providing structural and dynamic information of proteins in isolation and in complex. This is done in an integrated manner: we complement NMR by biochemical methods, e.g. mutagenesis to probe interactions, and other biophysical techniques to access different spatial and temporal scales, often in collaboration with other groups. For example, the group of Benoît d'Autr aux from CEA Saclay unraveled the sequential steps of the mitochondrial multi-protein iron-sulfur cluster (ISC) assembly machinery, and NMR provided insight into the structured versus disordered states of the ISCU protein, as well as into its Fe²⁺-binding site (Srouf et al. 2022).

Our main focus is the characterization of the proteins of respiratory syncytial virus (RSV), of the *Mononegavirales* order, *Pneumoviridae* family. We established a close collaboration with the group of virologists led by Jean-Fran ois El ou et from INRAE Jouy-en-Josas. Such a collaboration is important, as we need to compare our in vitro measurements to data obtained in a cellular context. RSV encodes 9 structural and two non-structural proteins. Several of these proteins are amenable to solution NMR, as they can be produced as soluble recombinant proteins with isotope labels. They fall into different functional categories: components of the viral replication complex, including the main polymerase co-factor P, the nucleoprotein N, and the transcription antitermination factor M2-1, proteins involved in budding, including P and the matrix protein M, and the NS1 protein that is a key player in evasion of the host immune response (Dong et al. 2022). Among these proteins, RSV P stands out as a protein of low structural complexity (Pereira et al. 2017). Many virus-encoded proteins contain intrinsically disordered regions (Mishra et al. 2020). They harbor small linear binding motifs for different protein partners, thus compensating for the small number of viral proteins. In RSV P, only a small tetramerization domain is stably folded (Fig. 1A). P was shown to be a multi-functional multi-partner protein (Cardone et al. 2021). Its main function is the recognition by the polymerase of the viral genome via a specific N – P interaction (Fig. 1B). It also plays an essential role during RSV transcription, by serving as a platform that brings two proteins, RSV M2-1 and the cellular phosphatase PP1 , into close proximity, required for the dephosphorylation of M2-1 (Fig. 1A) (Richard et al. 2018). In all cases, NMR provided valuable information about protein interactions.

Finally, based on preliminary results about the in vitro inhibition of the RSV N – P interaction by small commercially available molecules (Fig. 1B) (Ouzougou-Oubari et al. 2015), I recently started, together with Philippe Durand, a medicinal chemist colleague from ICSN, to search for RSV-specific antivirals based on the inhibition of the RSV N – P complex. This is carried out by structure–activity relationship to optimize hits as well as de novo screening of small compound libraries, in particular the Fr-PPIChem library dedicated to protein–protein interaction (Bosc et al. 2020).

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Conflict of interest The author declares no conflict of interest.

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