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EDITORIAL

The Coming of Age

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Single-molecule studies and optical spectroscopy of biomolecular dynamics.

The current issue of *ChemPhysChem* highlights the coming of age of two fields with many inter-relationships, both in terms of methodology and in terms of ambition: optical spectroscopy of biomolecular dynamics, hailed by a series of Minireviews, and single-molecule spectroscopy, acknowledged by a broad collection of original contributions.

The compilation of Minireviews in this issue attests to the success of optical spectroscopy in placing itself as a central discipline within biochemistry and biophysical chemistry. It was conceived following a recent German–Israeli conference,^[1] and can be seen as an informal “status report” on the field. An influential review written in 1991 stated that “Studies of biomolecular dynamics today are in some sense where atomic physics was near 1885. A bewildering variety of protein motions has been revealed by fluorescence spectroscopy, nuclear magnetic resonance (NMR), hydrogen exchange, and Raman scattering. Can regularities be found and connected to the structure of proteins, and can the underlying concepts and laws be discovered?”^[2] This by itself could be read, at the time, as a call for the development of even more sensitive spectroscopic methods for the detection of such structural rearrangements in real-time and their correlation with functional properties of biomolecules. Indeed, optical spectroscopists have taken this challenge seriously, and have shown how functional conformational changes can be probed on a variety of time- and lengthscales. Much progress has been made in this field since its inception, which can arguably be traced to Quentin Gibson’s 1956 work

on conformational changes in hemoglobin following photodissociation of carbon monoxide^[3] (for a broad history of the optical method see ref. [4]). Many novel optical techniques have been introduced in recent years to study biomolecules. Among these, single-molecule spectroscopy (SMS) maintains a position of honor (see Figure 1).

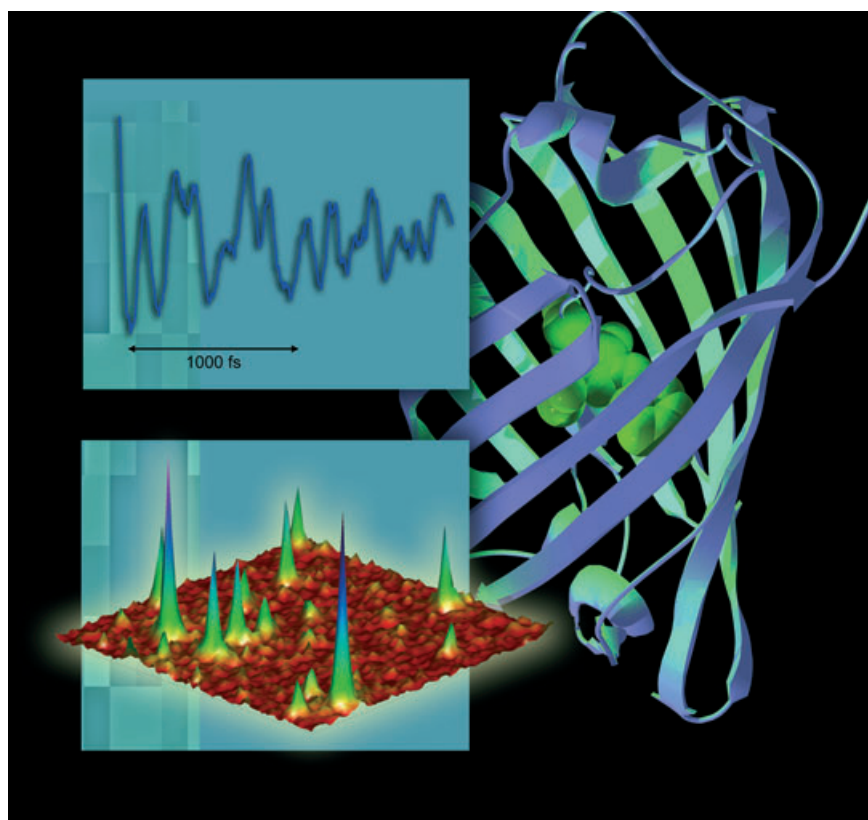


Figure 1. A spectrum of optical spectroscopies is used to probe the dynamics of biomolecules. A good example is provided by the green fluorescent protein, whose photophysics is studied with femtosecond pulses (upper left panel) and single-molecule spectroscopy (lower left panel), among many other techniques.

SMS is the science that attempts to explore the properties of matter through the interaction of electromagnetic radiation with an individual molecular entity.^[5] As is evident from the impressive compilation of original contributions in this topical issue, the scientific questions that can be addressed with SMS are widespread and come from all classical disciplines of the natural sciences, that is, physics, chemistry, and biology.

Historically, though this might cause some debate among the readership, the theoretical foundations for SMS as well as the first bold attempts at identifying spectral fingerprints of single molecules were made in low-temperature chemical physics. The field of SMS was actually born in 1989 with experiments which detected the absorbance of a single organic chromophore in a cryogenic matrix, and was boosted shortly thereafter by introducing the superior technique of laser-induced fluorescence. This pioneering early work, linked to W. E. Moerner and Michel Orrit, was based on the concept of spectrally isolating single molecules in the wings of the inhomogeneous distribution.^[6] It did not take long for SMS to mature beyond the “esoteric” detection of single rigid organic chromophores occupying only low-probability crystal lattice sites. The concept of spatial isolation and hence of imaging of single molecules was introduced into the field of SMS at about the same time as the first heralded detection of a single molecule at room temperature was accomplished.

By the mid-90s, the main principles of all the tools of SMS were already fully established, and they are nowadays being brought to effective use all over the world in areas ranging from quantum optics and photophysics to materials science and biophysics.

Pioneering work on single molecules is linked to W. E. Moerner and Michel Orrit.

This topical issue pays ample tribute to the diversity of scientific problems that can be tackled by SMS. The papers by Hohng and Ha on resonant energy transfer between a single quantum dot and a single molecule, by Bell et al. on electron transfer at the single-molecule level, or by Schindler and Lupton on the identification of single emissive chromophores in conjugated polymers illustrate this fascinating variety of research on individual particles.

But it is in particular the field of biophysical chemistry that has no doubt been most fertilized from the advent of single-molecule methodologies. This is simply because an understanding of biophysical and biochemical processes at a molecular level requires the input of experimental methods, such as optical spectroscopies, that are able to raise the curtain and disclose detailed information at exactly this molecular level. As biological molecules often show complex and heterogeneous dynamics, SMS becomes a method of choice to study them by virtue of its ultimate sensitivity limit and its ability to overcome the “ensemble average” problem. The publication by Langowski and co-workers describing fluorescence cross-correlation spectroscopy of protein–protein interactions in vivo is a prime example for the utility of SMS in addressing scientific questions on biological samples.

Interestingly, and fortunately for biophysical chemistry, the development of SMS into a powerful research tool occurred in parallel to major breakthroughs in optical spectroscopy of ensembles of molecules. In fact, the mid-to-late 1980s mark the early stages of femtochemistry, whose goal is to resolve in real-time the elementary events of chemical reactions.^[7] At that time, its well-known offspring devoted to biochemical phenomena—nowadays termed “femtobiology”—was still in its infancy. It is only five years ago that femtosecond spectroscopy received the highest distinction, by the award of the Nobel Prize in chemistry to Ahmed Zewail.

This particular field of science brings along a temporal resolution sufficient to resolve even the fastest processes imaginable in nature. Thanks to ultrafast lasers, we now appreciate the primary atomic motions in retinal isomerization and hence the mechanisms initiating the process of vision. Thanks to ultrashort flashes of light, we come to grasp with the elementary supramolecular events responsible for harvesting of light and its conversion into chemical energy—the ingredients of the central process of photosynthesis, reviewed in this issue in detail by Zinth and Wachtveitl. In the same spirit, the Minireview by Larsen and van Grondelle shows how sequences of multiple femtosecond pulses can be used to uncover the early light-triggered dynamics of the photoactive yellow protein, a protein that is responsible for bacterial phototaxis.

But beyond the simple observation of chemical or biomolecular processes, physical and theoretical chemists have understood the importance of the optical phase function in determining the evolution of a molecule following its interaction with an ultrashort laser pulse. Not only can we observe the dynamics of a polyatomic molecule in real-time, we can also control its fate by shaping the resonant electromagnetic driving field. In a most instructive Minireview written by a team of researchers around M. Motzkus, these coherent control concepts are described in depth. The selective steering of the energy flow dynamics within a bacterial photosynthetic light-harvesting complex underlines the immense potential of coherent control for manipulating even the most complex biological dynamics.

While remarkably successful efforts in the fields of time-resolved X-ray^[8] and electron diffraction^[9] are currently being undertaken, still a long road lies ahead for these techniques to excel over the tremendous utility of Fourier-transform infrared (FTIR) spectroscopy in unravelling structural details of protein dynamics and protein function. As impressively demonstrated here by Kötting and Gerwert, FTIR spectroscopy—like no other time-resolved method—is able to reveal an unprecedented molecular detail of reaction mechanisms of proteins in action, and it can do so over an unbelievably broad observation window that ranges from seconds to nanoseconds. Furthermore, on even shorter timescales, IR spectroscopy is becoming a phenomenally promising vibrational analogue of NMR spectroscopy^[10] with novel pulsed infrared laser sources serving as the spectrometer’s console, controlling, for example, the power, bandwidth, duration, stability and phase of the resonantly driving radiation. But instead of exploiting proton reso-

Biophysical chemistry is fertilized from the advent of single-molecule methodologies.

Femtosecond spectroscopy received the highest distinction by the award of the Nobel Prize in chemistry to Ahmed Zewail.

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the excitement devoted to
optical spectroscopy.**

nances, their chemical shifts and nuclear couplings, multidimensional IR makes use of vibrational resonances, their anharmonic shifts and excitonic couplings to record the dynamical evolution of the structure of polypeptides.^[11] The fulfillment of the dream of disentangling the structure of a protein at work in real-time from femtoseconds to seconds is now within the scientist's reach.

Clearly, all practitioners of optical spectroscopies, both at the single-molecule and the ensemble level, will have to work hand-in-hand to make this dream come true. We very much hope that this topical issue will be able to send out some of this striving spirit to the broad readership of *ChemPhysChem* and transmit the current excitement in the community of researchers devoted to optical spectroscopy of biomolecular dynamics.

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