Name:	Martin WEIK
Date of birth:	
Place of birth:	
Nationality:	
Marital status:	
Work address:	Institut de Biologie Structurale (IBS) 71, avenue des Martyrs 38044 Grenoble, France http://www.ibs.fr/groups/dynamics-and-kinetics-of-molecular/

Positions

2011 - present	Chairman of the research group Dynamics and kinetics of molecular processes (currently 12 members) at the *Institut de Biologie Structurale* (IBS), Grenoble, France
2010 - 2013	Co-appointment at the European Synchrotron Radiation Facility (ESRF) in Grenoble (responsible for combining X-ray crystallography and online microspectrophotometry)
2009 - present	CEA Research Director at the IBS
1/07 – 12/09	Visiting Scientist at the ESRF, Grenoble
01/01 – 12/06	Visiting Scientist at the Institut Laue-Langevin, Grenoble
1/01 - present	Research team (currently 8 members) leader at the IBS
1/00 – 12/00	Postdoctoral Position (Fellow of the European Molecular Biology Organization), Weizmann Institute of Science, Rehovot, Israel, in the laboratoires of Profs. I. Silman and J. Sussman and Bijvoet Center, Utrecht, The Netherlands, in the laboratory of Prof. J. Kroon. Subject: '*Use of Temperature-dependent X-ray Crystallography to Study the Dynamics of Acetylcholinesterase*'
6/98 – 12/99	Postdoctoral Position, Bijvoet Center, Utrecht, The Netherlands, in the laboratory of Prof. J. Kroon. Subject: '*Acetylcholinesterase: Structure and Function'*

Education

07/06	'Habilitation à Diriger des Recherches' in Biophysics, Université Joseph Fourier, Grenoble
9/94 – 4/98	Ph.D. in Biophysics. Institut de Biologie Structurale, Grenoble, Supervisior: Dr. J. Zaccaï. Subject : '*Rôles des Glycolipides et de l'Hydratation dans la Membrane Pourpre : Etude par Diffraction de Neutrons et Detériation Spécifiques*', honor: 'Très Honorable avec les Félicitations de Jury'
9/93 – 6/94	Université Joseph Fourier, Grenoble, France. 'Diplôme d'Etudes Approfondies' (equivalent to M.Sc.) in Material Sciences, honor: 'bien'
10/89 – 11/95	Universität Karlsruhe, Germany. Study of Physics. 'Diplom-Physiker', honor: 'sehr gut'

Statement of research interests and 10 most important publications

Vision

My research aims at understanding the internal dynamics of proteins in a range from femtoseconds to seconds and how they animate structures to enable biological activity. To this end, I apply neutron spectroscopy and X-ray scattering at free-electron lasers (XFEL) and synchrotrons and complementary experimental and computational techniques. At the crossroad of physics, chemistry and soft matter, my research is highly interdisciplinary.

Background

Proteins are the molecular engines of life. Their broad range of biological tasks and functions is reflected in the large diversity of specific dynamical characteristics they display on a broad time scale. On the femtosecond time scale, atomic bonds vibrate and proteins respond to light stimuli. Amino acid side chains jiggle and wiggle on the pico- to nanoseconds time scale. Within micro- to milliseconds, protein domains change shape and move with respect to each other. Entire proteins are synthesized and fold in seconds to minutes. Unresolved issues in the field of macromolecular biophysics include the mutual influence of protein motions on the various time scales and how they are connected to the dynamics of hydration water embedding soluble proteins. A large number of experimental techniques exist that each opens a specific window onto macromolecular dynamics on a particular time scale. Neutron spectroscopy allows studying protein equilibrium dynamics on the ps timescale and time-resolved crystallography at XFELs and synchrotrons informs about structural changes at atomic resolution on a time scale down to the sub-ps regime.

Past and current research

Effects of X-ray irradiation on biological macromolecules

X-rays are invaluable to study the structure and dynamics of biomolecules. Yet, they leave fingerprints in the sample due to their ionizing character. During my postdoctoral research, I was among those who first described the specific structural and chemical damage that intense synchrotron radiation produces in protein crystals [1]. Since then, the new theme of Radiation Damage to Biological Crystalline Samples grows rapidly, for which I co-organize every other year an international workshop together with Elspeth Garman. In parallel to my activity as a research-group leader at the Institut de Biologie Structurale in Grenoble, I was appointed for three years at the ESRF to establish absorption microspectrophotometry as a complementary tool during X-crystallographic experiments to follow radiation induced changes. Motivated by the results of our neutron scattering studies on the coupling between protein and water dynamics (see below), I developed a particular focus on the (cryo-)temperature dependence of the dynamics of crystalline proteins and their convolution with radiation-induced effects [1]. Interestingly, we were able to identify an ultra-viscous phase of the crystal solvent, similar to the one proposed to occur for super-cooled bulk water. More recently, we have studied the effect of X-ray radiation damage in serial protein X-ray crystallography at the ESRF [2].

Structure and dynamics of acetylcholinesterase, an essential enzyme in the CNS

Acetylcholinesterase (AChE) is an essential enzyme in the central nervous system as it terminates synaptic transmission by hydrolyzing the neurotransmitter acetylcholine. We studied the structural dynamics of AChE involved in the molecular traffic and inhibition by applying X-ray crystallography and complementary biophysical methods and molecular dynamics simulations. Whereas X-ray crystallography in general provides static pictures of a protein, kinetic crystallography unravels its structural dynamics. In particular, temperature-controlled kinetic crystallography offers the possibility to generate, trap and visualize enzymatic reaction intermediates. By substrate-soaking experiments, by recruiting X-ray induced modifications of AChE in temperature-controlled kinetic crystallography experiments [3] and by employing caged compounds, we were able to locate substrate and product binding sites within the enzyme and provided experimental evidence for the existence of a 'backdoor' involved in rapid product clearance from the active site after catalysis. Beyond academic interest,

studying the structural dynamics of AChE benefits the rational design of drugs targeting this medically important enzyme.

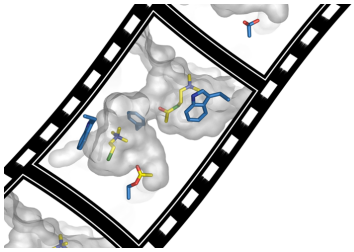

Figure 1: Kinetic X-ray crystallography allowed trapping a substrate and a product within acetylcholinesterase, one of Nature's fastest enzymes [3].

Coupling of protein dynamics with water dynamics in the context of amyloid-fiber formation

What is the molecular secret behind water's role as the *matrix of life* ? I address the molecular aspect of this question by studying the dynamical give-and-take of protein and hydration-water by neutron spectroscopy. A decade-long effort, involving several PhD students and postdocs I supervised, led to the experimental discovery of water-translational diffusion on a protein surface as being the central mechanism enabling macromolecular activity by promoting internal dynamics of the biological solute ([4]; figure 2). Since a few years, I turned my attention to studying the molecular mechanisms of pathological protein aggregation, in particular the changes in the dynamics of proteins and their hydration water that might drive aggregation. We studied hydration water-mobility on the surface of the intrinsically disordered human protein tau in its monomeric form and in its amyloid-fiber form. It has been found that hydration water mobility is enhanced around tau amyloid fibers, a finding that identifies hydration water entropy as a potentially universal driving force behind amyloid-fiber formation ([5]; figure 3).

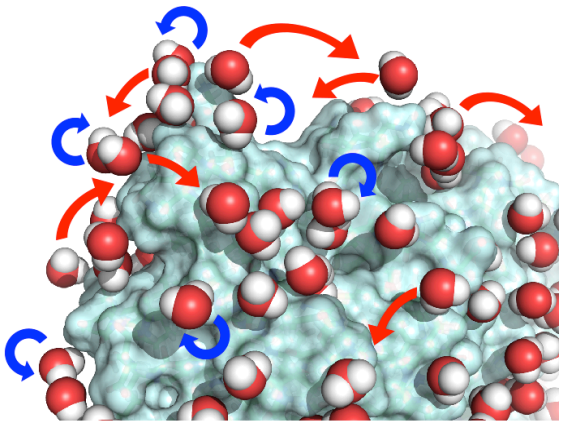

Figure 2: Water molecules undergo rotational (blue arrows) and translational (red arrows) diffusion on the surface of a soluble protein (green). It is the translational motion that is the central mechanism enabling protein activity by promoting internal dynamics of the biological solute [4].

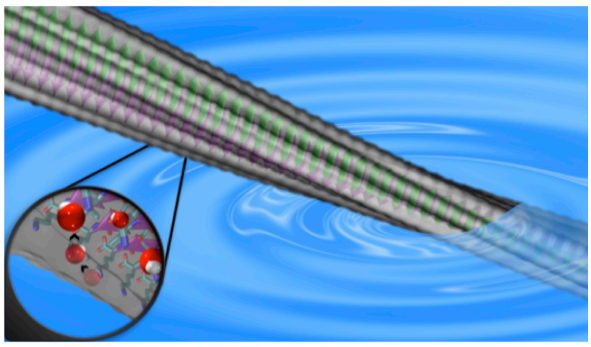

Figure 3: Water translational diffusion is enhanced on the surface of tau fibers compared to tau monomers [5].

Recently, we started deciphering by neutron spectroscopy experiments the molecular dynamics of solvent-free protein-polymer nano-hybrids in which myoglobin surprisingly showed biological activity in the complete absence of hydration water [6, 7]. Myoglobin motions within the nano-hybrid are found to closely resemble those of a hydrated protein, and motions of the polymer coating are similar to those of the hydration water, leading to the conclusion that the polymer coating plasticizes protein structures in a way similar to hydration water.

Studying light-sensitive proteins with time-resolved crystallography at X-ray free electron lasers

The advent of XFEL sources pushes the temporal resolution of time-resolved protein crystallography from 100 ps at synchrotrons to sub-picoseconds, opening up exciting new possibilities to study hitherto unobservable ultrafast processes such as those involved in primary photochemical events in proteins. In an international collaboration, my team has captured for the first time an excited state of a

photoswitchable fluorescent protein 1 ps after *photoexcitation* (figure 4) by time-resolved serial femtosecond crystallography (TR-SFX) [8, 9]. Photoswitchable fluorescent proteins can be reversibly toggled between two stable states, a non-fluorescent *off* and a fluorescent *on* state, a property that is the molecular basis in nanoscopy of biological cells. In the 1-ps switching intermediate, the chromophore within the fluorescent protein is halfway between the *trans* (*off*-state) and the *cis* isomers (*on*-state), in a twisted conformation that has long been predicted by simulations. Based on the intermediate state structure, we were able to design mutants with enhanced photoswitching properties that might be of use in nanoscopic applications. Recently, we have been able to uncover by TR-SFX the structural changes occurring in a new photoenzyme upon photon absorption [10].

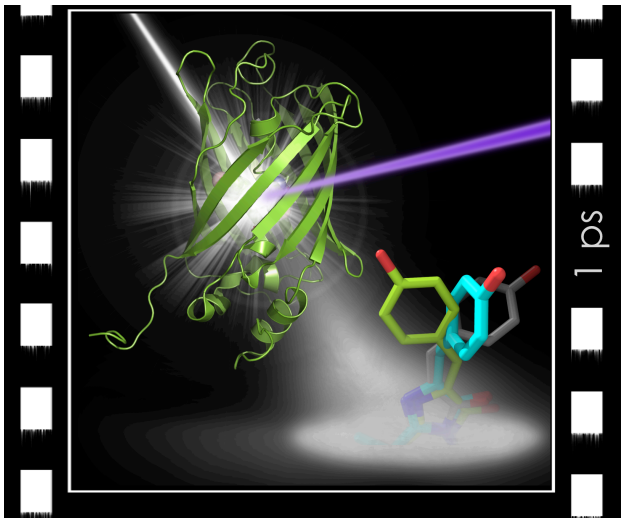

Figure 4: Ultrafast molecular movie of a protein in action [7]. The fluorescent protein (green) is excited by visible laser light (purple) and hit by an X-ray pulse (white) produced by an X-ray free electron laser. One picosecond after excitation, the chromophore (blue) is observed halfway between two stable isomers in the heart of the protein (grey and green).

Ten most important publications (100 in total, ~5400 citations, h-index 42, Google Scholar)

[1] Weik, M., Ravelli, R. B. G., Kryger, G., McSweeney, S., Raves, M., Harel, M., Gros, P., Silman, I., Kroon, J. & Sussman, J. L. (2000). Synchrotron X-ray radiation produces specific chemical and structural damage to protein structures, ***PNAS*** 97, 623-628.

[2] de la Mora E, Coquelle N, Bury CS, Rosenthal M, Holton J, Carmichael I, Garman EF, Burghammer M, Colletier JP, Weik M (2020) Radiation damage and dose limits in serial synchrotron crystallography at cryo- and room temperatures. ***PNAS*** 117: 4142

[3] Colletier, J.-P., Bourgeois, D., Sanson, B., Fournier, D., Silman, I., Sussman, J.L. & Weik, M. (2008) Shoot-and-trap: use of specific X-ray damage to study structural protein dynamics by temperature-controlled cryo-crystallography. ***PNAS*** 105, 11742.

[4] Schiro G, Fichou Y, Gallat FX, Wood K, Gabel F, Moulin M, Hartlein M, Heyden M, Colletier JP, Orecchini A, Paciaroni A, Wuttke J, Tobias DJ, Weik M (2015) Translational diffusion of hydration water correlates with functional motions in folded and intrinsically disordered proteins. ***Nature Commun*** 6**:** 6490

[5] Fichou Y, Schiro G, Gallat FX, Laguri C, Moulin M, Combet J, Zamponi M, Hartlein M, Picart C, Mossou E, Lortat-Jacob H, Colletier JP, Tobias DJ, Weik M (2015) Hydration water mobility is enhanced around tau amyloid fibers. ***PNAS*** 112, 6365-6370

[6] Gallat FX, Brogan AP, Fichou Y, McGrath N, Moulin M, Hartlein M, Combet J, Wuttke J, Mann S, Zaccai G, Jackson CJ, Perriman AW, Weik M (2012) A polymer surfactant corona dynamically replaces water in solvent-free protein liquids and ensures macromolecular flexibility and activity. ***J Am Chem Soc*** 134**:** 13168-13171

[7] Schirò G, Fichou J, Brogan A, Sessions R, Tobias D, Lohstroh W, Zamponi M, Gallat F.-X., Paciaroni A, Perrimam A, Weik M (2021) Diffusive-like motions in a solvent free protein-polymer hybrid. ***Phys Rev Lett*** *in press*

[8] Coquelle N, Sliwa M, Woodhouse J, Schirò G, Adam V, Aquila A, Barends T, Boutet S, Byrdin M, Carbajo S, De la Mora E, Doak B, Feliks M, Fieschi F, Foucar L, Guillon V, Hilpert M, Hunter M, Jakobs S, Koglin J,

Kovacsova G, Lane TJ, Lévy B, Liang M, Nass K, Ridard J, Robinson J, Roome C, Ruckebusch C, Seaberg M, Thepaut M, Cammarata M, Demachy I, Field M, Shoeman R, Bourgeois D, Colletier J-P, Schlichting I, Weik M. (2018) Chromophore twisting in the excited state of a fluorescent protein captured by time-resolved serial femtosecond crystallography, ***Nature Chem*** 10, 31

[9] Woodhouse J, Nass Kovacs G, Coquelle N, Uriarte LM, Adam V, Barends TRM, Byrdin M, De la Mora E, Doak RB, Feliks M, Fieschi F, Guillon V, Hilpert M, Hunter MS, Jakobs S, Joti Y, Macheboeuf P, Motomura K, Nass K, Owada S, Roome CM, Ruckebusch C, Schirò G, Shoeman RL, Thepaut M, Togashi T, Tono K, Yabashi M, Cammarata M, Foucar L, Bourgeois D, Sliwa M, Colletier J-P, Schlichting I, Weik M. (2020) Photoswitching mechanism of a fluorescent protein revealed by time-resolved crystallography and transient absorption spectroscopy. ***Nature communications*** 11: 741

[10] Sorigué D, Hadjidemetriou K, Blangy S, Gotthard G, Bonvalet A, Coquelle N, Samire P, Aleksandrov A, Antonucci L, Benachir A, Boutet S, Byrdin M, Cammarata M, Carbajo S, Cuiné S, Doak RB, Foucar L, Gorel A, Grünbein M, Hienerwadel R, Hilpert M, Kloos M, Lane TJ, Légeret B, Legrand P, Li-Beisson Y, Moulin S, Nurizzo D, Peltier G, Schirò G, Shoeman RL, Sliwa M, Solinas X, Zhuang B, Barends TRM, Colletier J-P, Joffre M, Royant A, Berthomieu C, Weik M, Domratcheva T, Brettel K, Vos M, Schlichting I, Arnoux P, Müller P, Beisson F. (2021) Mechanism and dynamics of light-driven decarboxylation in fatty acid photodecarboxylase. ***Science***, *in press*

Supervision of students and postdoctoral researchers: (12 PhD students, 7 postdoctoral researchers)

• PhD supervision of Ronald Rios-Santacruz, since September 2020. Molecular movie of light-sensitive proteins by time-resolved serial femtosecond crystallography at X-ray free electron lasers and synchrotrons.
• Advisor of Tadeo Moreno (Postdoctoral Researcher), since September 2019. Structural dynamics of acetylcholinesterase.
• Advisor of Nicolas Foos (Postdoctoral Researcher), since September 2019. Serial X-ray crystallography.
• PhD supervision of Kyprianos Hadjidemetriou, since October 2017. Time-resolved serial femtosecond crystallography to study light-sensitive proteins at X-ray free electron lasers.
• PhD supervision of Kevin Pounot, since November 2016. Dynamics of pathological protein aggregates and fibers.
• Advisor of Eugenio de la Mora (Postdoctoral Researcher), since January 2015. Structural dynamics of acetylcholinesterase.
• PhD supervision of Joyce Woodhouse, since October 2014. Studying light-sensitive proteins at work with X-ray free electron lasers.
• Advisor of Giorgio Schiro (Postdoctoral Researcher), since January 2013. Coupling between protein and hydration-water dynamics.
• PhD supervision of Yann Fichou, since October 2011. Structural dynamics of intrinsically disordered proteins.
• PhD supervision of Gianluca Santoni, since April 2011. Structural dynamics of acetylcholinesterase.
• PhD co-supervision of Chady Nasrallah, September 2010 – January 2014. Structural dynamics of porins.
• Advisor of Eugénie Carletti (Postdoctoral Researcher), November 2009 – December 2011. Structural dynamics of acetylcholinesterase.
• Advisor of Colin Jackson (Postdoctoral Researcher), January 2009 – April 2011. Relation between directed evolution and protein dynamics.
• PhD supervision of François-Xavier Gallat, September 2008 – September 2011. Dynamics of intrinsically unfolded proteins.
• Advisor of Kathleen Wood (Postdoctoral Researcher), March 2007 – January 2008. Coupling between protein and hydration-water dynamics.
• Advisor of Andreas Frölich (Practical course, level 'Masters'), March-July 2007. Coupling between protein and hydration-water dynamics.

• PhD supervision of Benoit Sanson, September 2005 – October 2009. Structure-dynamics-function relationships in cholinesterases.
• Advisor of Emanuela Fioravanti (Postdoctoral Researcher), November 2004 – January 2006. X-ray radiation damage to crystalline proteins.
• Advisor of Benoit Sanson (Practical course, level 'Masters'), February-July 2005. Structure-dynamics-function relationships in cholinesterases.
• PhD supervision of Jacques Colletier, September 2002 – July 2006. Structure-dynamics-function relationships in cholinesterases as studied by X-ray crystallography and neutron scattering.
• PhD co-supervision (with Dr. G. Zaccai) of Kathleen Wood, 2004 – February 2007. Dynamical heterogeneity of the purple membrane : a study combining isotope labelling, neutron scattering and molecular dynamics simulations.
• Advisor of Jakob Meineke (Practical course, level 'Licence'), April-July 2004. The study of water in lipid membranes at cryo-temperatures.
• Advisor of Jacques Colletier (Practical course, level 'DEA'), January-June 2002. Structure-dynamics-function relationships in cholinesterases as studied by X-ray crystallography.
• Advisor of Petra Neff (Practical course, level 'DEA'), August-September 2001. Super-cooled water in stacks of purple membranes from Halobacterium salinarum.
• Advisor of Daniela Stoica (Practical course, level 'Licence'), July-August 2001, Temperature-dependent fluorescence studies on crystals of halophilic malate dehydrogenase.
• PhD co-supervision (with Dr. G. Zaccai) of Frank Gabel, January 2001 – October 2003. The effect of solvent composition, inhibition, and structure on cholinesterase molecular dynamics: A neutron scattering study.

Teaching experience

With an education in physics and research activities in a structural-biology environment, I enjoy teaching molecular biophysics to undergraduate and graduate students. Since I direct a group in a pure research institute (*Institut de Biologie Structurale*, IBS), I did not have the opportunity to develop an extensive research repertoire. However, whenever given the opportunity to teach, I gladly accepted and enthusiastically prepared.

During my PhD at the IBS, I taught the following classes:

• Problem classes 'Small Angle Scattering', Maîtrise de Biochimie, Université Joseph Fourier, Grenoble (6 hr/year), 1995 - 1998
• Problem classes 'Detergents', Licence de Biochimie, Université Joseph Fourier, Grenoble (4 hr/year), 1995 - 1998

As a permanent research scientist, I taught the following classes:

• Practical classes 'Small Angle Neutron Scattering', HERCULES, European Doctoral Course, Institut Laue-Langevin, Grenoble (8 hr/year), 2003 - 2010
• Course on 'Neutron scattering and structural biology' in the French-Swedish School on Neutron Scattering: Applications to Softmatter (1 hr), 2016
• Course on 'Opportunities for using X-ray free electron lasers in structural biology' in a series entitled "New advances and applications in structural biology" for Master students (3 hr/year), since 2017
• Course on 'Opportunities for using X-ray free electron lasers in structural biology' in a series entitled "Introduction to Advanced & Emerging Biophysical Methods for Integrative Biology" for doctoral students (1 hr/year), since 2013
• Course on 'Opportunities for using X-ray free electron lasers in structural biology' in the RéNaFoBIS French School on Integrated Structural Biology (1 hr), 2015

As a main organizer of the biennial international *Protein Dynamics Workshop* that is held since 2014 at the *Ecole de Physique des Houches* in France, I made sure to include a strong focus on teaching PhD students and postdocs in the application of state-of-the-art experimental techniques (including, but not limited to, optical spectroscopy, NMR spectroscopy, Mössbauer spectroscopy, time-averaged and time-resolved X-ray crystallography, X-ray free electron lasers, electron microscopy, and neutron

scattering methods) and theoretical/computational approaches to studying protein dynamics.
In my research group, I had the privilege to instruct 12 PhD students and advise 7 postdoctoral researchers so far. My main focus is to teach them an unbiased and self-critical way of designing and carrying out research. Furthermore, each PhD student is given the possibility and task to write the first draft of two of their publications. I invest effort and time into transmitting my enthusiasm for preparing pedagogic research lectures that follow a carefully established *fil rouge* and contain visually arresting elements.

Conference organization

• Protein Dynamics Workshop, May 2021, Les Houches, France (Co-organizer with P. Schanda)
• LINXS Time-Resolved Structural Biology workshop, November 2020, Lund, Sweden (Co-organizer within the LINXS working group)
• Eleventh International Workshop on X-ray Radiation Damage to Biological Crystalline Samples, October 2020, Paul Scherer Institute, Switzerland (Co-organizer with E. Garman)
• Protein Dynamics Workshop, 27 May - 1 June 2018, Les Houches, France (Main organizer)
• Protein Dynamics Workshop, 3 - 8 April 2016, Les Houches, France (Main organizer)
• Ninth International Workshop on X-ray Radiation Damage to Biological Crystalline Samples, March 2016, Max IV Lund, Sweden (Co-organizer with E. Garman)
• 12th International Meeting on Cholinesterases, September 2015, Alicante, Spain (Member of the Scientific Advisory Board)
• Protein Dynamics Workshop, 19 – 23 May 2014, Les Houches, France (Main organizer)
• Eight International Workshop on X-ray Radiation Damage to Biological Crystalline Samples, April 2014, Desy Hamburg, Germany (Co-organizer with E. Garman)
• Water at Interfaces, 15 – 26 April 2013, Les Houches, France (Member of the Local Organizing Committee)
• French – Japanese Seminar on Protein Dynamics, 6 – 11 January 2013, Spring-8, Japan (Co-organizer with M. Nakasako)
• SFBBM – SFB congress, 21-23 November 2012, Grenoble, France (Member of the Local Organizing Committee)
• XFEL School 2012, 4 – 8 June 2012, Annecy, France (Member of the Scientific Advisory Board)
• 11th International Meeting on Cholinesterases, 4 - 9 June 2012, Kazan, Russia (Member of the Scientific Advisory Board)
• Seventh International Workshop on X-ray Radiation Damage to Biological Crystalline Samples, 14 - 16 March 2012, Diamond Light Source, UK (Co-organizer with E. Garman)
• Sixth International Workshop on X-ray Radiation Damage to Biological Crystalline Samples, 11 - 13 March 2010, Stanford Synchrotron Radiation Laboratory, USA (Co-organizer)
• Telluride Science Research Center Workshop on Protein Dynamics, August 2009, Telluride, USA (Main organizer)
• French – Japanese Seminar on Protein Dynamics, 15 – 19 January 2007, Grenoble, France (Co-organizer with A. Kidera)
• Telluride Science Research Center Workshop on Protein Dynamics, July 2007, Telluride, USA (Co-organizer with A. Palmer, A. Markelz, Y. Mizutani)

Positions on advisory boards and referee activities

• Member of the expert committee of health related issues of the League of advanced European Neutron Sources (since 2020)
• Fellow of the Lund Institute of Advanced Neutron and X-ray Science (since 2019)
• Member of the Proposal Review Committee of the SwissFEL (since 2018)
• Member of the Scientific Council of the Institut Laue-Langevin (2017 – 2022)

- Co Guest Editor of special issues on *Radiation Damage in Protein Crystallography* of the *Journal of Synchrotron Radiation* (May 2011, January 2013, January 2015, January 2017)
- Member of the International Advisory Board, Master in Bioinformatics, Universidad de Murcia, Spain (2012 - present)
- Nominated member of the Board of Directors, Telluride Science Research Center, Colorado, USA (2011 - present)
- Member of the Executive Committee of the European Division of Physics in Life Sciences (2009 - present)
- Elected board member of the French *Societé Française de Biophysique* (2007 - 2016)
- Proposal evaluation committee of the FRMII neutron reactor in Munich (2010 - 2015)
- Proposal evaluation committee of the Laboratoire Léon Brillouin (2007 - 2010)
- Proposal evaluation committee of the Institut Laue-Langevin (2003-2006)
- Advisory Editorial Board *European Biophysics Journal* (2006 - present)
- *Ad hoc* referee for *Science, Nature Methods, Nature Commun., PNAS, JACS, Phys Rev Lett, PLOS ONE, Structure, Biophys. J., Biochemistry, Proteins, Eur. Biophys. J., J. Synchrotron Radiat., J. Appl. Cryst., HFSP J., BBA*
- *Ad hoc* referee for grant proposals: NSF (USA), HKUST (China), ANR (France), Royal Society (UK), NWO (The Netherlands), OTKA (Hungary), NSERC (Canada), FCT (Portugal)

Context and outline of proposed course on
'X-ray and neutron scattering methods for the study of biological macromolecules'

Italy is a member country of all European neutron and X-ray large scale facilities, *i.e.* of the European Synchrotron Radiation Facility (ESRF) and the Institut Laue Langevin (ILL) Neutron Facility in Grenoble, France, the European X-ray Free Electron Laser (EuXFEL) in Hamburg, Germany and the European Spallation Source (ESS) in Lund, Sweden. These facilities offer unique opportunities to study the structure and dynamics of biological macromolecules, including proteins and DNA, a research topic of both academic and medical interest. The course intends to equip advanced physics students for a master or PhD thesis at or in collaboration with European X-ray and neutron large scale facilities to study biological macromolecules. Besides its focus on X-ray and neutron based methods, the course will provide a survey of complementary biophysical methods, including single particle cryo electron microscopy, electronic and vibrational spectroscopies, NMR, AFM, etc. The course is intended to be embedded into an exchange program between the University of Parma and the *Institut de Biologie Structural*e and its ESRF and ILL partners at the European Photon Neutron Campus in Grenoble that Prof. Cristiano Viappiani and Dr. Martin Weik intend to initiate (cf. next section).

Course outline (48 hrs in total):

Part I (Teaching – 26 hrs)
- Introduction to the structure and dynamics of biological macromolecules (4 hrs)
- Interaction of X-rays and neutrons with matter (2 hrs)
- Large scale X-ray facilities (synchrotron, XFEL) (2 hrs)
- Large scale neutron facilities (reactor, spallation source) (2 hrs)
- Conventional X-ray crystallography (crystallization, data collection, analysis) (4 hrs)
- Serial X-ray crystallography at synchrotrons and XFELs (2 hrs)
- Time-resolved X-ray crystallography (2 hrs)
- Small angle neutron and X-ray scattering (2 hrs)
- Neutron crystallography, reflectometry and spectroscopy (2 hrs)
- Complementary biophysical techniques (4 hrs)

Part II (22 hrs)
- Virtual tour of a synchrotron/XFEL/neutron facility
- Remote crystallography data collection at ESRF (assuming ESRF to be supportive)
- Crystallography data processing and analysis

- Representation of protein structures (Pymol)
- Presentation of current state-of-the-art research publications by students
- Quizzes
- Presentation of collaborative (U Parma / IBS) research projects

Intended long-term collaboration and exchange program between U Parma and the Institut de Biologie Structurale

Prof. Cristiano Viappiani (U Parma) and Dr. Martin Weik (Institut de Biologie Structurale – IBS) intend to establish a long-term collaboration that will allow both institutions to carry out joint research projects and exchange Master and PhD students.

Briefly, the Institut de Biologie Structurale (IBS) in Grenoble, France, is a joint research unit of the Université Grenoble Alpes and CEA/CNRS. Besides carrying out basic and applied research in integrated structural biology, the IBS provides technician-supported access to some of the highest level structural biology instrumentation in France (http://www.isbg.fr). These include facilities/services for construct design, protein preparation and quality control, biophysical characterization (e.g. CD, SEC-MALLS, fluorimeter, etc.), protein crystallization, a cryo-bench (for spectroscopic studies on crystals/solutions) and an X-ray diffractometer (for testing crystals before experiments at synchrotrons and to collect data sets). The IBS is one of four institutes on the European Photon Neutron Campus in Grenoble, together with the European Synchrotron Radiation Facility (ESRF), the Institut Laue Langevin (ILL) Neutron Facility and the European Molecular Biology Laboratory (EMBL) outstation of structural biology. The IBS forming together with the ESRF, the ILL, and the EMBL a Partnership for Structural Biology, has privileged access to synchrotron and neutron beamlines in Grenoble. In addition, IBS scientists are active in the training of undergraduate, master and PhD students in structural biology and several teach as professors and assistant professors at the University Grenoble Alpes. IBS scientists participate also in the organization of international workshops (EMBO, INSERM, HERCULES, ESSONN) or meetings (SFBBM, GTBio).

The research group of Prof. Cristiano Viappiani is renowned for its cutting-edge studies of proteins by electronic, vibrational and optoacoustic spectroscopies. The groups of Prof. Cristiano Viappiani and Dr. Martin Weik intend to establish a research program to study phytochromes (ubiquitous photoreceptors in plants, fungi and bacteria) by a combination of spectroscopic methods mastered by the Parma group and by structural methods mastered by the IBS group and its collaborators. The activity will build also on the expert collaboration of Dr. Wolfgang Gärtner, now at University of Leipzig and honorary professor at the University of Parma. Examples of systems the research will concentrate on are the 3rd GAF domain from a G1-G2-G3-HK protein from cyanobacterium *Synechocystis* PCC6803 and the protein All2699 from cyanobacterium *Nostoc punctiforme* whose structure (G1-G2-(GGDEF-EAL)-G3-(GGDEF)) comprises two chromophore bearing domains (G1 and G3). These systems have the peculiar property of carrying a phycocyanobilin chromophore.
Students at the Universities of Parma and Grenoble-Alpes will have the opportunity to engage either in this phytochrome research project or in various other structural-biology related projects ongoing at the IBS in collaboration with the ILL and/or the ESRF.