Laboratory of Nanoscale Biology (LNB[1])

- a new lab within the BIO department of the Paul Scherrer Institute -

The LNB investigates the molecular structure and dynamics of complex molecular machines and cascades *within the context of the living cell*. Technological developments at the PSI provide novel approaches for studying fundamental, molecular processes of life within their physiological context. Electron diffraction and cryo-electron microscopy of bio-molecular complexes form the technological basis of the LNB, together with electron tomography and X-ray diffractive imaging of larger, nanoscopic structures. We develop these technologies in studies of fundamental, molecular aspects of neuro-degeneration and cell motility, and investigate other fundamental processes of life in collaboration. Intellectual property on novel technologies developed at the LNB may lead to commercial spin-outs.

The molecular foundations of biology

Life is an emergent property of matter. The macromolecular structures that catalyze many of life's fundamental processes are known. But understanding how these processes collectively create life, requires more than knowing their catalytic details. We also need to understand why, where and when these processes occur within the living cell. For example, insight into the structural rearrangement of a myosin molecule is insufficient for understanding how a muscle cell contracts. Living cells are highly organized and intricately controlled, but hardly ever homogeneously ordered in space or time, and their regulating factors are usually scarce and diffusive. This impedes studying most cell types in fundamental detail.

Current research approaches

The study of fundamental cellular processes relies on complementary technologies. Advanced light microscopies can image living cells and selectively locate fluorescently labelled proteins with nanoscopic accuracy; X-ray diffractive imaging yields comprehensive nanoscopic resolution of fixated cells; cryo-electron tomography provides even better resolution but requires frozen cells that are thinly sliced; single particle cryo-EM and X-ray crystallography permit atomic interpretation of isolated or crystallized purified proteins and their complexes. But none of these technologies, nor their combination, offers the characterization of cellular structure that is sufficiently detailed for full functional understanding. A new technology is required that allows us to locate the complex, multi-component molecules of life within a cell, determine their orientation towards each other, identify their crucial, often ephemeral interactions and characterize their resulting structural transitions.

New technologies

Novel types of electron detectors allow measuring electrons with single quantum accuracy. With these hybrid pixel detectors, we confirmed earlier results that electron diffraction data can be measured with a much higher quantum accuracy than electron microscopy images. We could quantitatively explain these observations from first principles, showing that the high signal amplification of electron diffraction (compared to cryo-EM), results from the multiplication of several independent, relatively minor effects.

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[1] Laboratorium für Nanoskalare Biologie; Laboratoire de Biologie Nanométrique

To exploit the signal amplification offered by electron diffraction, we are developing automated procedures for scanning 50 to 100 nm thick samples with a parallel, 10 nm diameter electron beam, whilst recording the diffracted electrons on the fly using a 512x512 hybrid pixel detector at multi kHz frame rates. We are developing phasing algorithms and novel hardware approaches for holographic phasing in diffraction space, allowing structural interpretation of the data. In addition, we are exploring phasing by molecular replacement.

Each observed elastically diffracted electron encodes two ‘bytes’ of information: the displacements in x and in y with respect to the direct beam. Thus, a diffraction pattern of a typical biological sample illuminated with a 10 nm diameter electron beam, encodes up to 15 kb of useful data before radiation damage becomes too severe. Since the three-dimensional scattering potential at 3.5 Å of a 10 nm diameter molecular complex corresponds to only 90 kb of data, we anticipate that just a few hundred diffraction patterns of a protein complex will be sufficient for a full structure determination. Thus, we may be able to distinguish more active states of dynamic complexes compared to current approaches in cryo-EM. In an alternative approach, we consider a diffraction pattern to be complex, highly redundant hash code, that can index a data base of random projections of known molecular structures. This alternative approach will allow the localization and orientation of all molecular complexes of known structure in complex mixtures, ideally within their physiological environment.

With these novel technologies, we anticipate opening a new window into the cell by creating a novel structural biology that studies biological structures at atomic resolution in their complex, natural, cellular context.

Research goals

The human brain consumes about 1/5th of all the energy a human being requires, yet it represents only about 2% of our body mass. This implies that the brain is highly exposed to oxidative (mitochondrial) stress and, as a consequence, to protein breakdown and synthesis. Even slight imbalances in protein quality control will result in build-up of damage, which, given the very long lifetime of nerve cells, results in neuronal disorders.

It is a scientific goal of the LNB to expand fundamental molecular studies on isolated, purified proteins that are associated with neuronal functioning and stress, to include the impact at high resolution of physiological factors and eventually a cellular context. Thus, we anticipate contributing to deeper understanding of the fundamental, molecular causes of a range of devastating diseases associated with aging.

In addition, we study the mechanism of flagellar/ciliary bending motion, which drive cells forward or backward, or generate extracellular flows. The regular structures consist of ~300 proteins, and contain nine microtubule doublets are linked by dynein motor proteins. We are analyzing molecular arrangement of dynein and other proteins by electron tomography and refine high resolution structures by single particle analysis, developing methodologies.

J.P. Abrahams, 7 May 2018