13 Physics of Biological Systems

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13.1 Overview

Since January 18th 2002, a new laboratory building (see Fig.13.1), designed with a special emphasis for carrying out sensitive experiments with coherent low energy electron wave fronts, has become available. Currently, the group works on the following five projects:

- Manipulation of individual DNA molecules in the liquid phase (C. Escher, since February 2001)
- Fermion-statistics (G. Cross, since September 2001)
- Online hologram reconstruction (T. Latychevskaja, since December 2001)
- Methods for preparing individual bio-molecules (M. Drechsler, since December 2001)
- Low temperature LEEPS Microscopy (H. Okamoto, since February 2002)

The overall motivation of all our efforts is to develop methods and tools to gain insight into the structural and electronic properties of individual molecules that is not accessible by other techniques. Apart from these microcopy aspects, we are also interested in using biological molecules as materials to design functional devices. Those functions must not necessarily be related to the natural purpose of these biological systems. A precondition for achieving this is to be able to interface single molecules with appropriate structures, to direct them to defined locations on such a device and to electrically contact them. Eventually, an "automatic" assembly of more complex structures in envisioned by taking advantage of the recognition capabilities that nature provides for biological species.

Figure 13.1: *At left, a view of the new laboratory building is shown. At right, the Low Energy Electron Point Source (LEEPS) microscope, mounted on a vibration damping stage, is shown. A total of four such platforms are available inside the new building. They are embedded in three orthogonal Helmholtz coil pairs used for compensating the local magnetic field to protect the coherence of our low energy electrons.*

We employ optical fluorescent microscopy techniques combined with mechanical manipulation and local electric fields to direct single molecules at will in the liquid phase. Micromachining tools, in collaboration with Clondiag Chip Technologies, are used to fabricate appropriate structures on which the scenario should take place. Conventional electron microcopy allows us to characterise and modify the devices. Coherent low energy electrons are finally employed to characterise the fragile molecules without damaging them. High contrast holographic imaging and in-situ manipulation provides us presently with structural and electronic information on the nanometer-scale. Once routine operation in the new laboratory environment has been established, the resolution limit should move towards the sub-nanometer-scale. In the following an overview about the present status of the individual projects is given.

13.2 Manipulating individual DNA molecules in the liquid phase

By employing video fluorescent microscopy techniques, Conrad Escher [1] succeeded to observe the dynamics of individual DNA molecules in liquid solution. Electric fields were used to stretch out individual DNA molecules, an example of which is shown in Fig.13.2. Alternating electric fields, localised on a device to micrometer dimensions, were used to at-

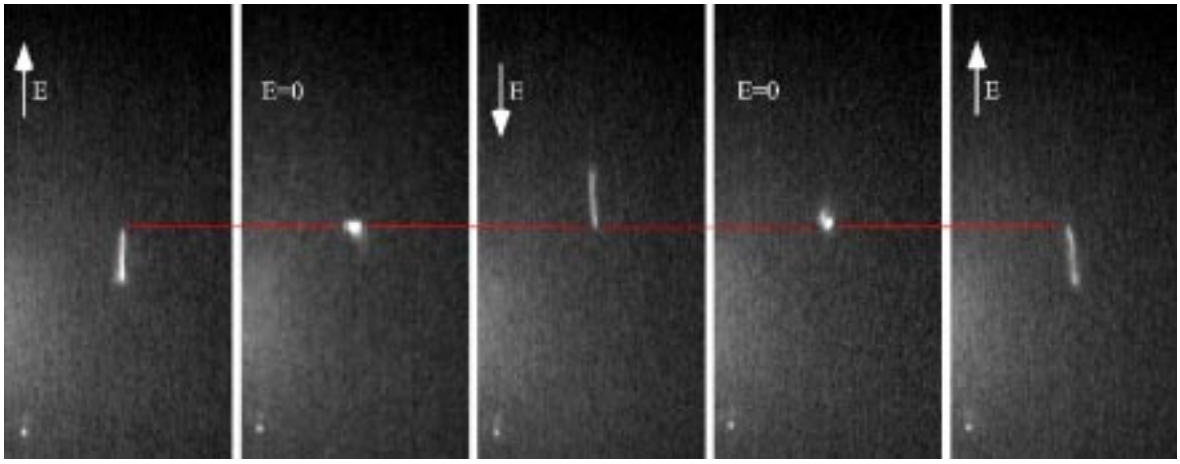

Figure 13.2: *DNA stretching experiment in a liquid film. The 17-micron long molecule is anchored at one end to the substrate. Under ordinary thermal conditions, the Brownian agitation of the solvent leads to a random coil structure of the DNA that corresponds to the minimum of the free energy. This random coil structure, assumed by minimising the entropy of the system, can be transformed into a linear chain structure by applying an external electric field.*

tract the molecules to the high field regions. We consider this ability of controlled in vivo motion of single molecules as an important first step towards interfacing bio-molecules with silicon structures. Future experiments will be carried out using a device that has recently been fabricated for us by Clondiag Chip Technologies in Jena. It is a two-terminal microchip device with an integrated liquid chamber. It has been designed in such a way as to be compatible with both, optical fluorescent microcopy and electron holography.

13.3 Fermion statistics

Besides the more technical and application oriented aspects of our electron point source, an ensemble of free electrons with an unprecedented high phase space density is of interest of

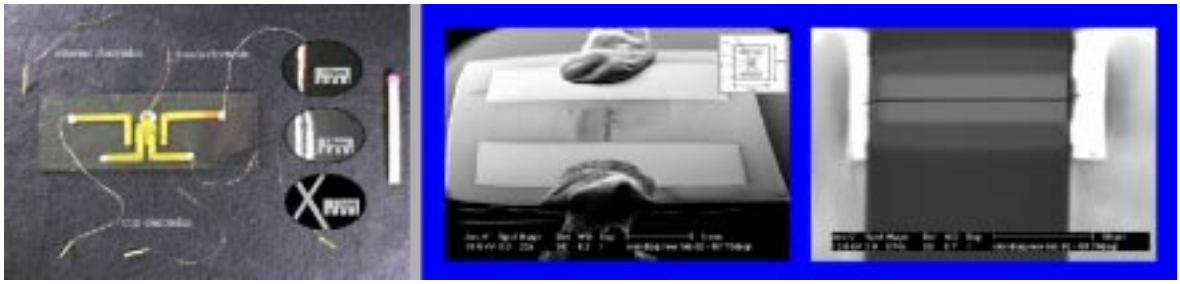

Figure 13.3: *Left: "Home-made" simple device for manipulating DNA molecules in liquids [1]. Right: Integrated chip structure, fabricated by Clondiag Chip Technologies.*

its own right in as much as it provides us with the possibility to observe interference effects of higher order. All electron interference effects observed so far, including our holograms, are brought about by a single electron at a time: "loosely speaking", this implies that an electron interferes with itself. In a high-density ensemble of electrons in a vacuum, they should however feel each others presence and their fermion character must show up. Since we are in the unique situation to create such beams, we shall try to explore their statistics by carrying out cross correlation experiments within a pulsed coherent electron beam.

13.4 Numerical reconstruction of electron holograms

Our involvement in the "National Center of Competence Research for Nanoscale Science" in collaboration with the Bio-Chemistry Institute of the University of Zurich is focused on exploring the potential of holography with low energy electrons for the structure determination of individual bio-molecules. A vital aspect of this endeavour is the ability to be able to reconstruct the high-resolution holographic information on-line. In December 2001 we have started a project aiming at a fast numerical hologram reconstruction routine. This work is done in close collaboration with CNRS researchers in Marseille.

13.5 Preparing individual bio-molecules for holography studies

In the same context, namely that of structural biology, an effort was initiated to prepare individual bio-molecules in such a way that they can be exposed to our coherent electron wave front without being attached to a substrate. As a first approach to this problem we are currently investigating the preparation of freestanding bacteria phages that could later serve as a template by assembling the proteins of interest to the elongated protein-shell of the virus.

13.6 Low temperature LEEPS microscopy

Once all system related aspects to optimise the coherence of our point source and the detection ability for the electron holograms are in place, the intrinsic thermal fluctuations of the molecules become resolution limiting. To minimise those, the construction of a liquid helium cooled LEEPS microscope has been started in February 2002. Ultimate 3-dimensional resolution in molecular imaging is one aspect of this effort. Another one is related to interesting low temperature physics problems, like the dynamics of single electron effects in nanometer-sized objects. Those should directly be accessible with such a new tool.

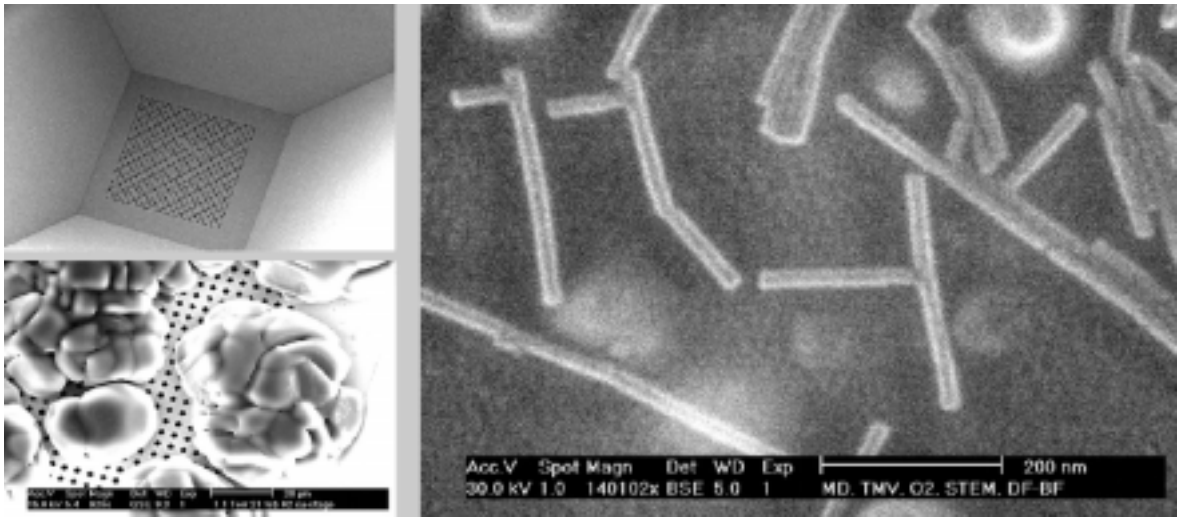

Figure 13.4: *Preliminary experiments, carried out in our environmental scanning electron microscope for controlling various preparation steps for single bio-molecules. Left: Formation of water droplets while cooling down a silicon microstructure. Right: Viruses deposited on a perforated film observed in the scanning transmission mode.*

References

[1] Conrad Escher, *Manipulating $\lambda-DNA$ molecules in aqueous solution*, Diploma Thesis Zurich University (2001), unpublished.