Nanofluidic scattering microscopy

Understanding chemical and biological processes at the single molecule level is crucial for numerous fields, such as biochemistry, biotechnology or medicine. However, the investigation of small biomolecules at the single-molecule level is highly challenging and has long relied on involving steps which leads to undesirable modification of a biomolecule, e.g. fluorescent labelling or attachment of a molecule to a surface. We have recently developed a new technique – Nanochannel Scattering Microscopy (NSM) – which enables direct imaging of a freely moving small biomolecule in real-time.

The key components of the method are fluidic channels nanofabricated in glass that are smaller than the wavelength of light in two dimensions and imaged by means of dark-field microscopy. In this arrangement, as biomolecules flow and diffuse along a nanochannel, light scattered by a biomolecule interferes with light scattered by the channel. This results in an optical contrast large enough to enable the direct optical detection of the molecules’ motion. In this way, the device not only allows the precise counting of the number of molecules present, but also to determine their molecular weight. The latter is possible both by tracking of single-molecule Brownian motion and by quantitative analysis of the optical contrast. In combination, this ensures the robustness and versatility of the method. Here we demonstrate its applicability and versatility on several examples including detection and analysis of single DNAs and proteins with molecular weights ranging down to tens of kDa.