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https://doi.org/10.1017/S1551929500069029 Published online by Cambridge University Press

Attaboy! Attoboys, or the new Zeptoscopists

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As the year ends there is a bumper crop of announcements of advances that I find absolutely amazing. First of course is the continued clever use of light as a veritable tool in manipulating everything from atoms (entrapping them in "atomic molasses") to having tugs of war with biological motors (using "light tweezers"). But these developments will be for discussion another time. What I want to talk about in this installment are advances in Near Field Scanning Optical Microscopy (NSOM), which has now been used by Chichester and Betzig[1] to visualize single molecules.

In classical (far field) optics, resolution is limited by diffraction to about 1/2 the wavelength of the radiation used for imaging. Near field optics overcome this limitation by use of scanning techniques similar to those employed in Scanning Tunneling or Scanning Force Microscopy. Each point on the sample is successively illuminated by a light source of very small physical size, say 100 nm wide, placed 10 nm from the sample, thus ensuring that the light does not spread far from the tip and illuminates only a very small area, of a size comparable to that of the light source itself. The light emitted from the sample (in the case of fluorescence as in the experiments described) is picked up by a detector in the far field below the sample by a photon counting avalanche photodiode with a small active area, confocal with the aperture in the image plane of the objective used to collect the light.

Such devices have previously been used to detect molecules with numerous (~30) chromophores. The paper under discussion shows that it is actually possible to detect a single chromophore when well separated from its neighbors. The compound used are molecules of the commercially available (Molecular Probes, Inc.) carbocyanin dye dilC12. Carbocyanin dyes are fluorescent. For the experiments under discussion molecules of dilC12 were embedded in a thin film of of poly methyl methacrylate (PMMA) at a calculated density of 23 molecules/m^2. Betzig and Chichester show that not only can they detect individual molecules but that by analyzing the polarization of the signal they can obtain information about the orientation of the individual molecules in space.

Betzig and Chichester are well aware of the potential applications of their technology. They chose dilC12 not only because it is photostable and has a large absorption cross section but also because carbocyanine dyes are lipophilic which makes them very useful as stains for cell membranes. They are used extensively for tracing cells in both living and fixed tissues.

Single molecule detection the authors say "represents the ultimate goal in trace chemical analysis and has been proposed as a tool for rapid base sequencing of DNA". They suggest in addition that attaching fluroophors to membrane proteins would permit one to study the behavior of individual as opposed to populations of molecules. This would obviously be a very useful complement to patch clamping studies by which physiological properties of individual membrane channels can often be elucidated. This and other similar approaches will or already have allowed spectral analysis of single molecules. Kopelman and Tan[2] point out that another unexpected bonus will be "rugged, ultraslim, ultrasensitive and ultrafast fiber optic sensors", which will "require only attoliters of sample, zeptomoles (10^{-21} moles) of the unknown substance, and milliseconds or faster response times". Zut alors! Zeptomoles and attoliters, what! Attaboy Betzig and Chichester, Tan and Kopelman and all of you Zeptoscopists (obviously microscopists and microanalysis are about to be left in far field)! And so to all, Microscopists, Zeptoscopists, and others wherever you are along the optical spectrum, a very happy and very fruitful New Year. May all of your best dreams come true. ■

References:

1. Betzig, E. and Chichester, R.J. (1993) Single molecules observed by Near Field Scanning Optical Microscopy. Science (262), 1422-1425.

2. Kopelman, R. and Tan, W. (1993) Near-field optics: Imaging single molecules. Science (262), 1382-1384.

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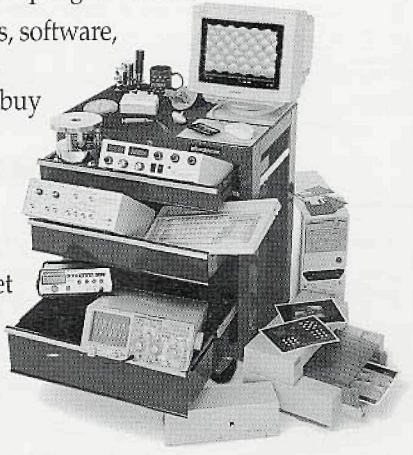

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