Distinction of nucleobases – a tip-enhanced Raman approach

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DNA sequencing refers to determine the order of the four nucleotide bases (adenine, cytosine, guanine, and thymine) in DNA strands. It is central to modern molecular biology and molecular diagnostics, because identification of a particular disease is based on nucleic acid identification. Established DNA sequencing approaches are mostly based on PCR amplification or invasive fluorescence labeling. Reading the base sequence of individual molecules without the need of amplification or other modifications of the molecule is one of the greatest challenges in biotechnology. [1]

Here we investigate the intrinsic properties of tip-enhanced Raman scattering (TERS) towards the development of a novel label-free direct sequencing method. It is known that TERS allows the acquisition of spectral information with high lateral resolution (~10nm) and single molecule sensitivity. [2]

In preliminary experiments single stranded adenine and uracil homopolymers were immobilized on different kinds of substrates (mica and gold nanoplates, respectively) and TERS experiments were conducted, which demonstrate the high reproducibility of the technique. In order to characterize different signal distributions of distinct Raman bands TERS spectra were collected on single stranded calf thymus DNA with arbitrary sequence. The results show that although the Raman scattering cross section of the four nucleobases differs remarkably, specific bands can be determined for each respective base.

The combination of sensitivity and reproducibility shows that crucial demands for a possible sequencing procedure using TERS are met. Due to the size of the tip, 20-60 bases are detected in one TERS spectrum hence the sequence of the DNA single strand underneath the tip can be obtained by laterally shifting the tip in intervals of one base-to-base distance and then deduce the spectra. [3, 4]

References

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