Ultra-Sensitive High Dynamic Range Label Free Platform for Bioparticle Detection

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Scattering-based imaging has emerged as a suitable technique for detecting and tracking sub diffraction limited bioparticles with excellent resolution and sensitivity. Due to the intrinsically label-free nature of such scattering-sensors they have a large potential for imaging [1] and sizing bioparticles [2]. Albeit these advantages, this approach is intrinsically limited to quantifying nano-objects within a very narrow size-range which is due to the dramatic scattering-signal dependence on the particle size. This dependence drastically reduces its use due to the size heterogeneity of bioparticles.

Here, we present a microscope that is able to image heterogeneous size particles. Traditional microscopes are limited by their camera's single pixels dynamic range, as bright particles locally saturate the camera. Our platform, in contrast, employs all camera's pixels to acquire the signal of all the particles in the image all at once. Thus, the sum of the saturation limit of all pixels define our dynamic range, instead of individual pixels.

Our platform relies on off-axis interference of reciprocal-space representations of the images with a reference wave. Hence, we obtain interferograms that can be digitally processed for obtaining real-space intensity representations, which are equivalents of common images, albeit the dramatic increase in dynamic range. Additionally, we obtain the phase of the image, necessary for the use of digital holography tools. Therefore, we can computationally propagate and refocus the image, which allows single-shot 3D particle tracking and eliminates the need for mechanical focusing units thus dramatically reducing the sensors' cost.

I will show a pure scattering-signal quantification benchmark of 20 250 nm diameter gold nanoparticles as well as a size distribution chart showing the sizing and quantification of extracellular vesicles [3], probing its suitability for imaging heterogeneous biomolecules. Additionally, I will present some proof-of-concept experiments in which we characterize different nanoparticles by performing 3D nanoparticle tracking analysis (NTA), taking advantage of the phase retrieval and the digital holography tools.

References

[1] G. Young et al., "Quantitative mass imaging of single biological macromolecules," *Science (80-.).*, vol. 360, no. 6387, pp. 423–427, Apr. 2018.
[2] M. Liebel, J. T. Hugall, and N. F. Van Hulst, "Ultrasensitive Label-Free Nanosensing and High-Speed Tracking of Single Proteins," *Nano Lett.*, vol. 17, no. 2, pp. 1277–1281, 2017.
[3] U. Ortiz-Orruño, A. Jo, H. Lee, N. F. van Hulst, and M. Liebel, "Precise Nanosizing with High Dynamic Range Holography," *Nano Lett.*, vol. 21, no. 1, pp. 317–322, Jan. 2021.

Figures

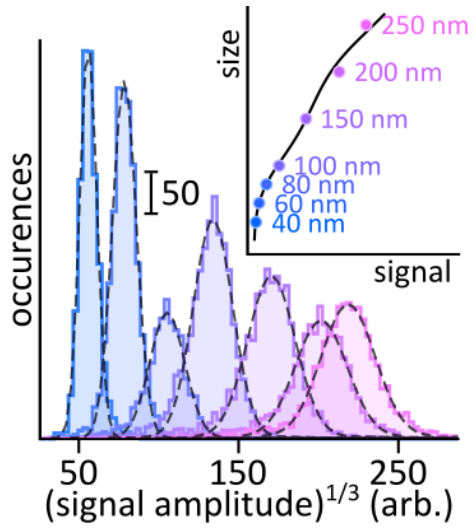

Figure 1: Dynamic range benchmark obtained by the quantification of different size gold nanoparticles scattering-signals

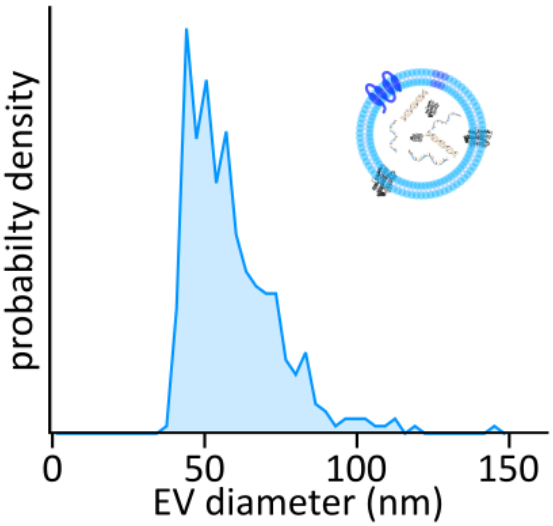

Figure 2: Obtained size distribution of different extracellular vesicles secreted by an ovarian cancer cell line