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Direct single-particle detection and sizes recognition of adenovirus with whispering-gallery mode resonances

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Abstract: We demonstrate detection of single particles of adenovirus under attaching to a whispering gallery mode resonator without linkers and antibodies. Instead of conventional ways of achieving selectivity via antibody we propose to distinguish viral particles through correlation of resonance line changes with sizes of virus.

1. Introduction

The COVID-19 pandemic has revealed urgent demand on high-sensitive, reliable and cheap medical tools for diagnostics of viruses. To date, a huge set of sensors of viral particles has been proposed. They include both conventional medical tests such as PCR-based assays and many emerging devices based on mechanical, electrical, optical effects. The basic principle of sensor devices is recording of changes of their characteristics: oscillation frequency, conductance, spectral changes etc. The basic procedure of all viral particle sensors includes the development of three steps: fabrication of sensing elements, immobilization of biorecognition elements and registration scheme for tracking their own parameters. In this contribution, we propose a technique based on whispering-gallery mode (WGM) resonators that could be simpler, namely, we are aimed to avoid biorecognition elements replacing them with fast-speed assessment of sizes of single viral particles.

2. Materials and methods

1.1. Sensor fabrication

For virus detection we exploited microresonators supporting whispering-gallery modes. Microresonators were fabricated via melting silica fibers with a focused CO_2-laser beam. For this, fibres were cleaned mechanically and washed with acetone. The spheres were fabricated with controllable sizes of 80-100 μm and placed in a PDMS chamber (typical volume of 290 μL). To excite WGM inside the sphere a prism coupler was used. All experiments were performed with a diode pumped laser (642 nm emission, 300 μW power). A detector synchronized was a laser was connected to a PC with data acquisition card allowing to measure frequency shifts and full width at half maximum (FWHM) changes under particle attachments events during time.

1.2. Sensor calibration procedure

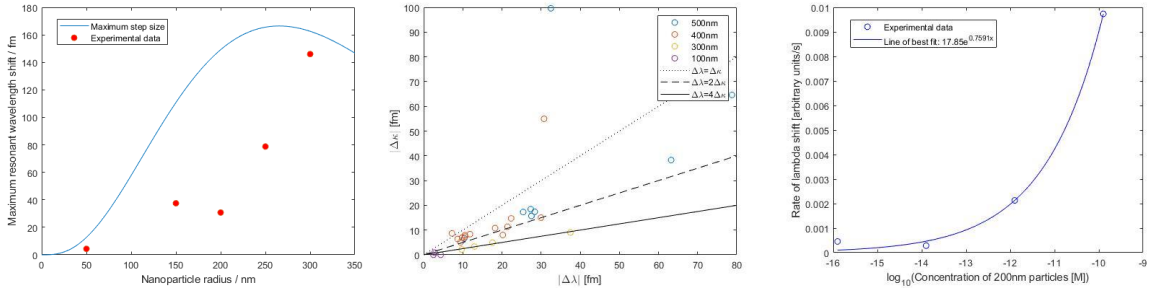
To investigate a relation between sizes of particles and frequency shifts (and FWHM changes), we used polysterene particles of known diameters, thus the WGM sensor was calibrated with 50, 100, 150, 200, 250, and 300 nm spheres. Adding these polystyrene spheres we measured WGM shifts for two series of samples. First series revealed the dependence of wavelength shift on particles size. And second, we investigated the dependence of sensitivity on concentrations, 100 aM, 10 fM, 1 pM, 100 pM, of nanoparticles which supposed to have roughly the same sizes, 100 nm radius, as the adenovirus investigated. All experiments were carried out with PBS buffer solution.

1.3. Adenovirus preparation

For single particle sensing particles of adenovirus vector strain Ad5-GFP were chosen. Adenovirus is a common virus that typically cause colds or flu-like symptoms and was used as the vector for the ChAdOx1 COVID-19 vaccine which has played the crucial role in combat of COVID-19. It was used by the team Oxford-AstraZeneca to develop a vaccine which comes out of decades of research on chimpanzee adenovirus vector-based vaccines. Typical sizes of adenovirus are 100 nm in diameter. The virus was produced by the Jenner Institute at the University of Oxford, UK and obtained via collaboration. The samples were inactivated via germicidal UV-C light at a wavelength of 253.7 nm. The concentration of viral particles was of 1×10^9 pfu/ml.

3. Results

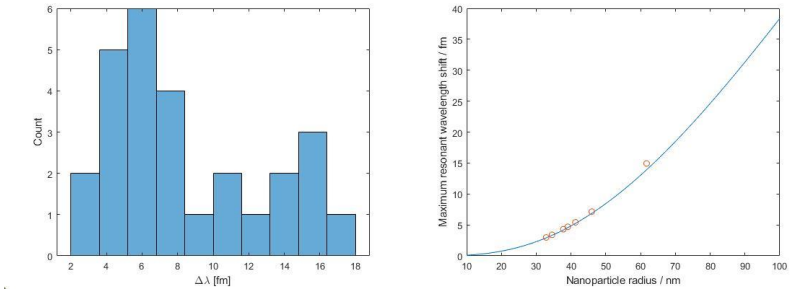
Figure 1 plots the results of the calibration procedure. Figure 1a represents the dependence of WGM resonance wavelength shifts on sizes of nanoparticles. Blue curve was calculated using the formula/theory [Eleanor]; it corresponds to the maximum wavelength shifts under attaching particles. Experimentally observed shifts are usually have lower value due to the variation of the refractive index of the buffer solution [Eleanor, what do you think?]. Since polystyrene particles attachment introduces losses in the resonator via scattering, the FWHM values are also changed. In contrast to wavelength shifts, changes of FWHM does not reveal clear dependence on particle sizes. Figure 1c shows the rate of wavelengths changes for 100 nm particles, that confirmed the attachment events have higher probability when particle concentration is higher [Eleanor, do I understand it correctly. If not could you please correct it?], and gives primary information about dynamic ranges of concentrations which can be detected, single particles to 100 pM.



a) b) c)

Figure 1. a) WGM resonance wavelength shift vs polystyrene particle radius; b) absolute values of FWHM changes vs wavelength shifts; c) rate of wavelength shifts under attachment events. [Eleanor, it would be nice to add 100 nm particles to Fig.1a]

After testing the sensor, the virus attachment events were investigated. For this, it was added to the PDMS chamber in proportions of 30 µL of the viral particle colloid to 260 µL of the PBS buffer. Figure 2 represents the result of single viral particles detected. First, it shows that viral particles are reliably detected without adding lincers and antibodies. Second, the most frequent wavelength shift detected was of 6±2 fm that corresponds to 45 nm particles radii in average. Wavelength shift distribution represents the natural difference of viral particles.



a) b)

Figure 2. a) Adenovirus particles detected vs wavelength shift; b) Dependence of maximum wavelength shift on viral particles sizes. Approximation represent the dependence calculated according [Eleanor?]

In conclusion, we proposed and investigated the method of sensing the particles of adenovirus which does not require additional linkers. This method can be quickly implemented in sensors for preliminary test on different viruses.

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