Nondestructive Optical Assay Method for Nanoscale Biological Particles in Solution

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In this paper, we present an optical system for non-destructive assay of nanoscale biological particles (viruses) in fluids. This method is part of the design of a novel lab-on-chip device[1] that enables microbiologists to purify, isolate and assay mixtures of viruses without the use of destructive labeling techniques or direct observations using electron microscopy. Our approach is based on the fabrication of large (10³ scale) and very dense (100nm scale) electrode arrays using the semiconductor layers of a lab-on-chip die. This array, see Figure 1, is the platform for dielectrophoresis (DEP) based methods for sorting the mixtures of bioparticles and arranging the particles by type into groups at various regions of the electrode array. Based on the DEP field configuration, each group of particles organizes into a set of lines between specific pairs of electrodes with the lines repeated in a spatially periodic pattern. These lines of particles, shown in Figure 2, along with the electrodes themselves, form a diffraction grating, where the efficiency of the grating is directly related to the density of the particles captured between the electrodes. By measuring the optical power in the 1st order diffraction mode of the grating before and after a separation (with and without particles) we can make an indirect measurement of the density of particles trapped in that region of the electrode array. The method works in both reflective mode, for CMOS 3D-IC chip stacks (Figure 1) or transmissive mode for SoS-based transparent substrate devices (Figure 3a).

Dielectrophoresis[2] is a technique for manipulating biological particles in a fluid by exposing them to an electrical field that is spatially non-uniform in amplitude, phase, or frequency. The sensitivity of a bioparticle to a DEP field depends in its morphology and electrical properties. By using a novel DEP field multiplexing technique, particles with small differences in composition can be made to experience different amounts of force, forces in opposite directions, or no force at all based on particular sequences of field frequencies and phases. The specific type of dielectrophoresis that we use is traveling-wave dielectrophoresis (TWDEP), in which a linear array of electrodes is energized by AC signals each with fixed difference in phase. This configuration exerts two orthogonal force vectors on particles within the field, one that levitates particles above the electrode array while the other transports particles laterally across the array. Figure 2 shows a polystyrene bead experiment demonstrating this effect in a four phase TWDEP field with traps configured between every fourth pair of electrodes.

[Figures 1 and 2: Images showing the electrode array and polystyrene beads in a TWDEP field.]

Figure 1: 3D-IC with two DEP chambers fabricated in the polysilicon layer of the top die. Electrode array shown has 1500 electrodes at 480nm pitch.

Figure 2: Polystyrene beads in four phase TWDEP field configured with traps at every fourth electrode on a PCB.
With the particles grouped and aligned in this fashion, our approach to the detection and assay of particle density is shown in Figure 3(a). In this figure, an electrode array is implemented in the polysilicon layer of a transparent substrate, Silicon-on-Sapphire, die. A VCSEL array and collimating optics illuminates individual regions of the array from below. In each region, the electrode array diffracts the light and an array of detectors above the die measure the optical power in the 1st order diffraction angle as each laser is illuminated. After a separation, particles of a particular type are localized and trapped into a specific region of the electrode array creating lines of particles between the electrodes. The presence of these particles changes the diffractive properties and efficiency of the electrode array, moving some or all of the optical power out of the first order diffraction angle and causing it to be scattered or moved into other diffraction orders. In either case, the strength of this effect and the corresponding change in the optical power in the original modes will be proportional to the density of particles in the regions between the electrodes. This provides an indirect assay measurement. Since the effect uses large collections of particles, it will work even if the individual particle size is below the diffraction limit. Moreover, by using an array of laser sources to define isolation regions across the array, multi-channel operation is easily implementable.

As a preliminary demonstration of this effect, we have modeled the system as the superposition of two diffraction gratings[3], the first being formed by the electrode array and the second by the lines of particles. Figure 3(b) shows the results of a calculation where we assume that the electrode width and separation is 500 nm, the incident wavelength is 850 nm and the diameter of the trapped viruses is 250 nm. In the first case, electrodes with no particles above, the dotted blue trace shows optical power in the 0th (non-diffracted light) order and first order at +/- 48 degrees. In the second case, we modeled the presence of viruses trapped in a 4-phase traveling-wave dielectrophoresis configuration that collects particles over every fourth electrode. In this case, new diffractive modes appear at multiples of +/-12 up to +/-84 degrees caused by the presence and periodicity of the viruses (solid red line). Since the periodicity and location of trapped particles is programmable, the angle at which to expect diffracted orders for a given incident wavelength can be predetermined by using the grating equation. The detection of these new diffractive modes by the photodetectors placed above the chip will allow us to correlate the measured optical power to the presence of particles.

References

Figure 3: Optical detection and assay method (a) Cross section view of lasers, electrode array grating, and detectors (b) Diffraction efficiency at observation angles for case of non-trapped and trapped. 