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Phase-resolved optical Doppler tomography for imaging flow dynamics in microfluidic channels

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Phase-resolved optical Doppler tomography (ODT), an imaging technique based on low coherence interferometry, is presented as a tool to perform high-resolution cross-sectional imaging of fluidic flow in microchannels with high velocity sensitivity. To demonstrate ODT as a tool, electro-osmotic flow (EOF) was investigated, observing cross-sectional images of bidirectional flow within a microfluidic channel and pulsating flow when driven by a pulsed electrical field. ODT demonstrates great promise as a tool for studying the effects of microchannel surface modifications on biological sample flow and optimizing microfluidic device design. © 2004 American Institute of Physics. [DOI: 10.1063/1.1785854]

Recently, chemical and biological lab-on-a-chip applications have attracted significant attention in designing microfluidic devices that are highly efficient, disposable, multifunctional, reproducible, and mass-produced.^{1,2} Various physical and chemical methods for the control of fluids have been presented to meet the performance requirements from the end user.^{3–7} However, these approaches face challenges in the microfluidic domain such as accurate fluidic manipulations, minimization of dead volumes, and enhanced solution-channel wall surface interactions. Although classical flow mechanics still applies at the microscale, the various mechanisms behind are complex and not yet well understood, particularly for nonideal fluids such as biological fluids. For example, surface effects, complex electrokinetics, and manufacturing imperfections will play a significant role and deviate the flow behavior from the ideal case. Better understanding of local flow dynamics can in principle produce efficient designs and ensure good quality control, leading to optimization in the design of microfluidic devices for mixing, separation, and fluid manipulation.⁸

There are existing techniques to measure the microfluidic flow characteristics. In particle imaging velocimetry (PIV), a fluid seeded with particle tracers for imaging over time is used to generate a flow pattern for deducing flow rate. However, only small in-focus areas can be imaged.^{9–11} Fluorescent dye used as tracer to extract flow information has also been developed.^{12,13} Nuclear magnetic resonance (NMR) microscopy was used to image flow, capable of giving a cross-sectional velocity profile.¹⁴ However, its use for imaging the flow in integrated microfluidic devices will become increasingly complicated. It is noted that these techniques are limited to the field study of ideal fluids and may not be applicable to the study of biological fluids such as blood or urine due to lack of faithful tracers and general opacity of the fluid media. An important goal of microchannel devices is to manipulate biological fluids. Thus techniques capable of imaging the biological fluidic flow and determining its effects on microfluidic chip design is worthwhile exploring.

In this letter, we present a flow metrology system based on phase-resolved optical Doppler tomography (ODT) that can produce a cross-sectional velocity image of turbid fluid flow through microfluidic channels with a spatial resolution of 7 μm , temporal resolution of 10 ms, and a velocity sensitivity of 10 $\mu\text{m/s}$.^{15,16} This is done by collecting scattered light from different depths within a sample with its coherent gate. This technique can complement conventional flow metrology methods and may be particularly useful for studying microflow under complex conditions, such as analyses with biological fluids even in semiopaque media and with newly developed materials for microchannel devices.

Phase-resolved ODT is based on a Michelson interferometer and employs a broadband light source to provide a coherence gate to select back-scattered light from different depths. A schematic of ODT system is shown in Fig. 1. Light from a superluminescent diode (SLD) is launched into a 2 by 2 fiber coupler and split into two beams, a reference beam and a sample beam. The reference beam is reflected by a rapid scanning optical delay line (RSOD)¹⁷ and routed back to a detector. The sample beam is directed into a microfluidic channel with moving fluid. The backscattered light is collected by an objective lens and routed back to the same cou-

FIG. 1. Schematic of phase-resolved ODT system: (SLD) superluminescent diode; (C2) coupler; (PC) polarization controller; (EOM) electro-optical modulator; (RSOD) rapid scanning delay line; (C1) collimator; (G) grating; (L) lens; (M) galvo mirror; (OL) objective lens; (PD) photon diode; (MC) microchannel; (R) reservoir; (SS) substrate; (+) anode; (–) cathode; (PS) PDMS; (A/D) analog to digital converter; (DP) data processor.

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pler. An interference pattern is produced by the superposition of the reference beam and sample beam, but only at that point where the path-length difference matches the coherence length of the light source. This in turn determines the axial resolution of a phase-resolved ODT system, namely, broader light source spectrum provides higher axial resolution. When the RSOD scans (axial scanning), the coherence length selects different backscattered light from different depths of the moving fluid. The intensity of the signal is used to form the structural images of a sample, which is called optical coherence tomographic (OCT) image. The Doppler frequency shift caused by moving fluid is extracted by calculating the phase changes of two axial sequential scanning signals at the same location within a scanning period. The sign of the phase change determines the direction of a flow. Assuming the angle (Doppler angle) between a flow and sampling beam is θ , the flow velocity v is decided by

$$v = \frac{\Delta\phi\lambda_0}{4\pi T \cos \theta},$$

where $\Delta\Phi$ is the phase change between two sequential axial scans, λ_0 is the center wavelength of the light source, T is the interval between two sequential axial scans. Scanning the sample arm performs lateral scans. Performing the axial scan followed by a lateral scan forms a two-dimensional, cross-sectional image. Therefore, axial resolution is determined by coherence length of the source, and lateral resolution is determined by the numerical aperture of the sample focus lens.

The SLD used in our experiments had center wavelength of 830 nm with a FWHM of 45 nm, corresponding to a coherence length of 7 μm in air and about 5 μm in water. The optical power from the light source was about 1 mW and the light incident on the channel is about 0.4 mW. Two polarization controllers (PC) were used to control polarization states of two beams. An electrical-optical modulator (EOM) was used to introduce a carrier frequency of 500 kHz in order to reduce low frequency noise. A microscope objective lens ($\times 10$) that produces a spot size about 10 μm was used to focus light on the sample and collect backscattered light. In the experiments to be described here, the interval between two sequential scans was 2 ms, which provided a velocity range about ± 1 mm/s at a Doppler angle of 83.6° ($\pm$ denotes two opposite flow directions).

The ODT system was used to measure electro-osmotic flow of biological fluid in polymer and glass microchannels. Microchannel devices were built using standard microfabrication methods.² Fluidic channels, 250 μm wide and 50 μm deep, were imprinted onto polydimethylsiloxane (PDMS). The PDMS fluidic channels were pressed against two substrates (PDMS and glass) to form two different microchannels, glass slides (PDMS-glass channel) and PDMS (all-PDMS channel). In both cases, the PDMS device sealed reversibly against the flat surface. No surface treatments such as oxygen plasma or UV grafting were performed. A mixed buffer containing 20.0 mM phosphate in water and 20% intralipid (20.0 mM phosphate: 20% intralipid, 3:1 by volume) was prepared as a model biological fluid. Phosphate buffers (20.0 mM phosphate, pH 7.0) were made from potassium dihydrogenphosphate and adjusted to pH 7.0 with NaOH. The resulting solution was a turbid, milky solution containing lipid and phosphate micelles. The solution could not be readily imaged through with a conventional microscope.

FIG. 2. (Color) Cross-sectional velocity measurements of flows through all-PDMS and PDMS-glass channels by ODT: (a) cross-sectional velocity image of flow in all-PDMS channel; (b) cross-sectional velocity image of flow in PDMS-glass channel; (c) comparison of flow profiles at the center of both channel. Channel dimension: 50 $\mu\text{m} \times 250 \mu\text{m} \times 30$ mm (depth $\times$ width $\times$ length). Working fluids: mixture of intralipid and phosphate solution. Applied electrical field: 100 V/cm.

The first experiment for demonstration of the capability of ODT was to image electro-osmotic flow (EOF) in microchannels with intralipid solution. In this case, all-PDMS and PDMS-glass microchannels were used, both with a dimension of 50 $\mu\text{m} \times 250 \mu\text{m} \times 30$ mm. When a mixed intralipid buffer went through the all-PDMS channel, a uniform EOF was expected. On the other hand, a nonuniform flow may occur in the PDMS-glass channel due to different dynamic coatings induced by added surfactants against the PDMS and glass wall.^{18–20} Figures 2(a) and 2(b) show the EOF cross-sectional velocity profiles of the mixed buffer in the all-PDMS and PDMS-glass microchannels, respectively. In this image, the velocity direction is coded by color (red and blue represent two opposite directions, respectively). Positive flow (red) indicates fluidic movement towards the cathode. The driving electrical field was 100 V/cm. While a unidirectional, plug flow is observed in all-PDMS channel, a clear bidirectional flow pattern with a well-delineated transition from positive to negative flow is observed in PDMS-glass microchannel. These results suggest that the PDMS and glass acquire opposite zeta potentials when interacting with the mixed phosphate-intralipid buffer.² According to the arrangement of electrodes, the polarities of zeta potential for PDMS and glass with mixed phosphate-intralipid solution are negative and positive, respectively. A comparison of two flow profiles at the center of the channels is shown in (c). The flow through all-PDMS channel shows the unidirectional, nonparabolic velocity profile while the flow through PDMS-glass channel shows two opposite directional flows. A

FIG. 3. (Color) Monitoring of EOF responding to applied pulsed electrical field for 4 s: (a) time-evolutionary image of EOF taken by ODT at the center of channel, (b) driving electrical field: 1 Hz square wave with an amplitude of 800 V and changing of velocity. Channel dimension: $50\ \mu\text{m} \times 250\ \mu\text{m} \times 45\ \text{mm}$ (depth $\times$ width $\times$ length). Working fluids: mixture of polystyrene beads and phosphate solution.

slightly greater volumetric flow is seen near the PDMS side. This is likely due to relative differences in zeta potentials at different walls, and the fact that three of the channel walls were PDMS compared with only one glass wall. The profiles are slightly tapered near the maximum velocity, due to the limited axial resolution of the system.

The second experiment was performed to monitor time varying EOF by phase-resolved ODT. Figure 3 shows a real-time image of EOF of fluid driven by a pulsed field. For this experiment, an all PDMS microchannel with a dimension of $50\ \mu\text{m} \times 250\ \mu\text{m} \times 45\ \text{mm}$ was used. A mixed buffer containing phosphate (7.0 mM, pH: 7.0) and polystyrene beads (0.5%, 0.35 μm diameter) was prepared as working fluid. The EOF was driven by a square wave, with a period of 1 s and a voltage of 800 V. The sampling arm of the ODT system was fixed at the center of the microchannel. Figure 3(a) shows how the measured EOF velocity changed with time according to the driven electrical field. As expected, the fluid started to move immediately when the electrical field was applied and slowed immediately when the electrical field reduced to zero. The fluid did not completely stop between two movements due to residual pressure in the channel. Figure 3(b) plots the waveform of applied alternate electrical field and the resulting velocity of flow along with time. The profile was extracted from the middle of Fig. 3(a).

The ODT system discussed in this letter has spatial resolution of 7 μm and an axial scanning rate of 500 Hz. This limits current studies to relatively large microchannels and slow flow dynamics. However, high spatial resolution (micrometer or submicrometer) can be achieved with newly developed broadband light sources.^{21,22} The imaging speed can be improved by replacing the galvo mirror with a resonant galvo mirror which can operate at 8 kHz. In addition, with the recent development of spectral domain ODT,²³ axial scanning rate as high as 30 kHz can be achieved. With these improvements, ODT will enable the studying of mixing, pumping, and other fast phenomena within microchannels. Because the ODT signal is derived from scattering, ther-

mocapillary pumping can be minimized if appropriate wavelength can be selected for imaging.

In summary, a phase-resolved ODT system has been demonstrated as an imaging tool for the study of complex fluid flows through microfluidic channels. This technique takes the advantage of the coherence gate of a broadband light source to construct cross-sectional images of flows with high resolution. It can rapidly and noninvasively image and quantify flow in turbid solutions without the need for additional tracers. This provides a significant benefit for flow imaging since it does not depend on the seeding of tracers. We have demonstrated its capability and usefulness to study complex flow caused by the dynamic electrokinetic interactions between channel wall surface and solutions, and real time EOF responding to applied electric field. Since the control of flow in microfluidic channels is fundamental to the operation of microfluidic devices, such a metrology system is of significant importance. We anticipate that phase-resolved ODT will be a useful tool for performing detailed analysis of microfluidic systems in future development efforts.

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