Perspectives: DOD Inkjets at High and Ultra-Brilliant Light Sources

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Abstract

Droplets generated by inkjets can serve as carriers for biological solutions and objects including nanocrystals. X-ray scattering from ballistic droplets loaded with biological matter provides conformational and structural information in the absence of confining walls of microfluidic systems. Such experiments have been performed stroboscopically on a stream of droplets of sub-nL volume using quasi-continuous synchrotron radiation microbeams in order to obtain sufficient counting statistics. We will discuss methodological and scientific perspectives of X-ray scattering with micro- and nanobeams from individual droplets down to nL volumes based on pulsed ultra-brilliant X-ray free electron laser and 4th generation synchrotron radiation sources.

Keywords

Drop-on-demand inkjets, X-ray scattering, Synchrotron radiation, X-ray free electron laser

Introduction

Liquid sample delivery systems for 3rd generation synchrotron radiation (SR) sources are often based on continuous-flow microfluidics. Indeed, microbeam small-angle X-ray scattering (SAXS) provides access to molecular conformational dynamics with sub-millisecond time resolution [1]. In contrast, serial crystallography based on a stream of aqueous droplets carrying protein nanocrystallites intersecting fs pulses has been pioneered at ultra-brilliant X-ray free electron laser (XFEL) sources [2, 3]. Droplets can also serve as wall-free carriers of solutions -including colloidal- of biological molecules or functional objects like viruses and cells. Temporally uncorrelated droplets limit, however, hit rates from XFEL pulses implying high sample consumption and inefficient use of expensive beam time. Here we are interested in the potential of temporally correlated “ballistic” droplets ejected from drop-on-demand (DOD) inkjets [4, 5] enabling stroboscopic to single droplet scattering depending on the source brilliance. While the examples and discussions will be limited to scattering, droplets are also of interest as carriers for single particle imaging [6]. We will discuss preferentially scattering from ballistic droplets in view of maintaining conformational equilibriums which are important for understanding large functional proteins. Deposition of droplets with biological loads on substrates can, however, be of interest for enhancing molecular concentrations or probing particles at specific locations. Although bearing many similarities to inkjets, acoustic droplet ejection methods [7, 8] will not be discussed.
Droplet ejection and propagation

Thermal DOD inks (bubble-jets) used frequently for printing applications allow high-speed, addressable and precise droplet deposition based on multiple print-heads with liquid-filled chambers relied to a common manifold [5, 9, 10]. A heater integrated in each chamber is activated by a μs voltage pulse and the droplet is ejected through an orifice. Experimental science relies, however, generally on single print heads, often based on the piezoelectric compression of a liquid-filled glass capillary due to low fabrications costs [4]. An electronic triggering system allows ejecting a stream of identical, equally spaced droplets of several 10^6 of μm diameter [4, 10, 11] (Figure 1A-1D).

This technology is also adapted to ejecting aqueous droplets loaded with fragile biological objects such as living cells [4]. Particularly compact inks in planar silicon technology use piezoelectric compression of a liquid-filled reservoir with integrated nozzle [13].

Ballistic droplets ejected from a piezo-driven inkjet propagate in air with speeds (v) up to several 10^6 m/s and up to about 10 kHz frequency [4, 11]. The dominance of droplet surface energy $\gamma = \sigma 4\pi d^2$ ($\sigma$: surface tension, $d$: diameter) over kinetic energy $E_{\text{kin}} = 2/3 \rho m v^2 d^3$ ($v$: density, $\rho$: density) of sub-nL volume droplets results in spherical droplets. Ejection into vacuum is accompanied by an increased evaporation rate and cooling of droplets [14] which can even result in freezing [15].

SR microbeam scattering of ballistic droplets

The high spatial and temporal repeatability of droplets from DOD inks enables stroboscopic SR microbeam scattering [16]. Indeed, the stroboscopic optical image of $d = 80 \mu m$ (268 pL) water droplets ejected at 2 KHz with $v = 1.7$ m/s is shown in figure 2A. Droplets traversing the 3 μm X-ray focal spot within about 50 μs were probed with $t_f = 5 \mu s$ in order to avoid blurring of the stroboscopic composite image derived from the sequence of SAXS patterns (Figure 2B) [12, 17]. To obtain sufficient counting statistics $\sim 2 \times 10^4$ patterns corresponding to $\sim 100$ ms overall exposure with $\sim 10^7$ photons were accumulated at each mesh-position [12]. X-ray optics and ESRF source improvements allow currently obtaining the same statistics for about 100 patterns per mesh-position [18]. SAXS patterns from aqueous droplets loaded with biological molecules such as cytochrome C (Figure 2C, 2D) [12] or wide-angle X-ray scattering (WAXS) patterns from molten paraffin droplets [19] were obtained in the same way.

This approach can be extended to the synchronization of two inks providing access to droplet coalescence. Indeed, the stroboscopic optical image of droplets ejected from two inks is shown in figure 3A [20]. Excess kinetic energy resulting in damped shape oscillations of the merged droplets resemble chaotic advection in plugs with two components moving through winding microfluidics channels, enhancing mixing and providing access to sub-ms reaction kinetics [21].
Figure 3B shows stroboscopic composite images (heat maps) at two times after the contact of pH 2 solution droplets of cytochrome C with pH 4.6 buffer droplets resulting in protein folding [20]. Protein density redistribution is observed at the ms time-scale as the pixels of the composite images correspond to the integral protein scattering. Indeed, the heavier protein molecules appear to be pushed at 2 ms to the rim, presumably involving chaotic advection [21]. At 4 ms the protein is nearly homogeneously redistributed with a central hole remaining. Such experiments are limited, however, at the ESRF - a 3rd generation SR source- by rather long set-up times and the few heat maps obtained thus far do not reaching the time-scale of protein chain condensation. Indeed, two kinetic phases at the sub-ms scale with the smallest at < 160 μs lifetime have been identified by SAXS using continuous flow microfluidic mixing [22].

Figure 3: (A) Stroboscopic optical image of droplet ejection from two inkjet heads at an approximate angle of 45° [20]. (B) Stroboscopic composite images of the coalescence of pH 2 Cytochrome C and pH 4.6 buffer droplets. The pixels in the images corresponding to the integrated SAXS intensity reveal the protein location. The buffer droplet can be localized by mapping the interface refraction (adapted from [20]). Red contours are guides for the eye and do not show the anisotropy of the merged droplets. The time is defined relative to the contact point.

Perspectives for droplet probing by single pulses at ultra-brilliant light sources

Probing droplets by X-ray pulses (or flashes) from ultra-brilliant light sources allows reducing droplet volumes, sample consumption and provides access to ultra-short time-scales of coalescence processes. We will consider two state-of-the-art light sources providing hard X-rays: (i) the linear electron accelerator-based EuXFEL (European XFEL) in Hamburg (Germany) and (ii) the upcoming (2020) electron storage ring-based ESRF/EBS (Extremely Bright Source) in Grenoble (France) [23] as an example for a 4th generation SR source.

The EuXFEL is based on pulse-trains of 2700 pulses of 50 f, fwhm (full-width-half-maximum) with an inter-pulse separation of 220 ns (Figure 4). The flux for the fully commissioned SPB/SFX (Single Particles, Clusters, and Biomacromolecules & Serial Femtosecond Crystallography) instrument is expected to be 1-8 x 10^{13} photons/pulse in 0.1/μm focal spots [24]. ESRF/EBS will provide variable filling patterns for an upper limit of 932 bunches of electrons in the storage ring (Figure 4). Inter-pulse distances and pulse-trains can be changed according to specific filling patterns. The strongest undulator harmonics will provide a flux of ~10^{10} photons/pulse for a Δλ/λ = 2.8*10^{-2} band-width (pink beam) [25, 26], enabling single pulse scattering with μm to sub-μm spots for the size of droplets shown in figure 2A-2C. Scaling with the volume suggests that droplets of d = 8 μm (268 aL) for EBS/ESRF and d = 1.7 μm (2.5 aL) for EuXFEL should show equivalent scattering with a single pulse as d = 80 μm droplets (268 pL) at the ESRF-ID13 beamline (Figure 2B and 2C).

The interaction of a 70 fs fwhm XFEL pulse focused to 1 μm with a d~40 μm (~33 pL) inkjet droplet at the LCLS XFEL (Stanford) results in liquid explosions producing fragments perturbing the shape and trajectory of neighboring droplets [27]. Indeed, a droplet absorbs during exposure an energy of about E_X α_X d while the energy density (proportional to the internal droplet pressure buildup) is E_X α_X d/(2n d^3/3) where E_X is the X-ray pulse energy and α_X the X-ray absorption coefficient [27]. The effects of fragmentation can be reduced by probing smaller droplets and maximizing the ejection speed. The smallest diameters of droplets from print-heads based on piezo-compression of capillaries are around 30 μm (~14 pL). The ejection of smaller droplets is an active R&D topic in view of high-resolution printing applications [28]. We mention as example electrohydrodynamic jet (E-jet) printing with droplet trajectories defined by the electric field due to an applied voltage between conducting nozzle and substrate. Indeed, 3-5 μm (14-65 aL) aqueous droplets ejected at 1 KHz printing speed [29] and 200 nm droplets (4.2 aL) have been demonstrated [30]. Charging can pose problems for fragile proteins and other ejection technologies for reducing droplet volumes will have to be explored [28]. The practical lower droplet size is set by aerodynamic effects perturbing the trajectory (see also below). Reduction of air drag by He-environment or reduced pressure will increase droplet speed and travel range. Limitations of reduced pressure are set by an
increased evaporation rate resulting in droplet cooling.

Droplet ejection can be triggered by the ~10 Hz EuXFEL pulse-trains but not by the ~4.5 MHz pulse-frequency in a pulse-train. The number of droplets from a single inkjet-head interacting with a single pulse-train could be maximized by increasing speed and frequency. Future R&D should, however, aim at MEMS fabrication, integrating multiple ink-jet heads connected to a common manifold, analogue to high-speed printers. This would for example allow distributing droplets along the about 6 mm long Rayleigh length of the 1 μm focal spot of the SFB/SFX instrument [24], minimizing perturbations by liquid explosions. The effect of liquid explosions will be far less for a pink beam at ESRF/EBS and the flexibility of ESRF/EBS filling patters allows triggering droplet ejection to individual pulses. The impact of radiation damage by factor 10^4 longer pulse-length is difficult assessing as photoelectron escape probability will increase with decreasing droplet size [31].

The correlated sequence and trajectory of pL ballistic droplets allows anticipating novel sample environments. We will use as example a nanocalorimetry chip with a thin Si3N4 membrane (Figure 5) allowing modulating the temperature of a sample on the active area for heating rates up to about 2 x 10^4 K/s [33]. This could be used for rapid heating of a droplet with a biological load deposited on the active area. One could also adapt the geometry of the active area for continuously heating of droplets propagating along a trajectory close to the membrane surface by the ascending hot air (Figure 5) providing access to variations of molecular conformational equilibriums in successive droplets. The open geometry is attractive as it permits coupling other fields (electric/magnetic) or laser flashes to biological loads.

![Figure 5: Nanocalorimetry chip based on Si3N4 membrane with sputtered resistance heaters and thermopiles on a Si-frame (adapted from [32]).](image)

Probing the onset of coalescence in ultra-small, wall-free volumes is of considerable interest for practical and fundamental studies on topics such as thin film coatings, non-equilibrium thermodynamics of small-scale systems [34, 35] or transformations of biochemical molecules in the presence of local chemical and shearing gradients [36]. Indeed, microscopic models could be developed based on SAXS providing access to molecular shapes and aggregations. Although fluidic simulations on ballistic droplet coalescence have been reported [37, 38], microscopic details on early stages remain largely unknown.

![Figure 6: (A) Optical images of the head-on coalescence of two, 1 mm diameter (0.5 μL) water droplets on a planar EWOD device observed by a camera with 200 μs frames just before (t = 0) and after (t = 200 μs) liquid bridge formation (adapted from [39]). The reflecting silicon surface mirrors the droplets. (B) Model of liquid bridge formed during onset of coalescence of hemispherical drops (d = 40 μm) moving with v = 1 m/s at an angle of about 45°. The internal frame shows the droplets at rest for three flight times through the focal spot: (i) separated (ii) contact (iii) coalescence (not to scale). The projections of the pulses are depicted as circles for part of the 2700 pulses of a pulse-train. Full circles correspond to pulses hitting the liquid, open circles are outside the liquid. A 2nd pulse-train is shown to the left.](image)
like accessing to sub-μs time scales for observing the first aggregation steps in-situ. This holds also for conformational states at the onset of enzyme/substrate reactions [36]. One can estimate the lowest accessible time-scale (\(t\)) for a freshly created interface of diameter \(d\) between two droplets for a diffusion process from:

\[ t = d^2 D^{-1} \]

For \(d = 100\, \text{nm}\) and a water self-diffusion coefficient of \(D \approx 10^{-5}\, \text{cm}^2\, \text{s}^{-1}\) one obtains \(t \approx 10\, \text{ns}\). This time-scale corresponds to the onset of protein folding accessible to molecular dynamics (MD) simulations, laser-induced temperature jump and dynamic NMR [1].

The practically attainable time-scale depends, however, on the stability of the inkjet setup, droplets trajectory as well as focal spot position and size. X-ray focusing optics at the ESRF has reached the 10 nm scale [45] and the 100 nm focal spot of the EuXFEL SPB/SFX instrument is expected having a drift of less than the beam width [24]. We identify, however several inkjet-related issues to be addressed for reaching stability at sub-μm scale. Indeed, piezo-driven inkjets maintain the droplet trajectory at least to a few microns constant (Figure 2B) but the lower limit is unknown. Compact inkjet-heads in silicon technology with pre-oriented nozzles and a common liquid-filled manifold should be more stable than a mechanical assembly of two inkjets. Active trajectory correction could become necessary for reducing perturbations by air movements or from particles aggregating at the exit of the print-head. This could be based on a superhydrophobic surface [46] where the quasi-contact-free condition between the droplet and the material would result in droplet reflection towards precise trajectories (Figure 7, Supporting Information: Video) by tip-tilt control using piezo-actuators, analogue to astronomical mirrors [47]. The EuXFEL pulse-train in combination with the ultrafast-framing AGIPD detector [24, 48] allows probing the coalescence area of a pair of droplets at a specific coalescence time after their contact without moving the inkjet-heads. Indeed, a pair of 40 μm (33.5 pL) droplets flying with \(v = 1\, \text{m/s}\) through a 100 nm focal spot would be mapped by a single pulse-train with a spatial resolution of 220 nm along a 600 μm trajectory (Figure 6C). Probing droplets at different coalescence times will require, however, changing the nozzle-to-focal spot distance. By displacing the inkjet-head laterally one could map a larger area depending on the stability of the droplets in the beam.

We refrain from a more detailed discussion of the advantages of XFEL versus 4th generation SR sources but we note that the higher XFEL flux/pulse values should allow probing molecular transformations at very early stages of droplets coalescence or serial crystallography with very small droplets. The lower energy deposited for an ESRF/EBS pulse will enable, however, extended mesh-scans in particular at later stages of coalescence. For both types of sources, replacing stroboscopic by single droplet probing will considerably reduce sample volumes and experimental beamtime, enhancing also the stability of the setup.

**Conclusions**

The use of DOD inkjets at advanced light sources is a largely unexplored area at 3rd generation SR sources but could be particularly interesting for probing droplets loaded with particles or solutions with single pulses at ultra-brilliant light sources. pL to sub-pL liquid sample volumes coupled to fast heating or jumps in chemical potential will enable probing conformational equilibriums or reactive processes down to sub-μs time-scales. We note the wide spread use of CCDs and more recently pixel detectors at SR and XFEL sources, enabled by technology developed for the digital photography mass market. The upcoming of MEMS-based inkjets in high speed graphics and printing applications including 3D bioprinting could facilitate the development of inkjets for scattering applications at ultra-brilliant light sources.

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