Research News

Modulating flow topology in microdroplets to control reaction kinetics

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Abstract

In traditional reaction flasks, the reaction rate of macromolecular compounds is dictated by the concentrations and distribution of reactants along with their intrinsic reaction kinetics. Controlling reaction kinetics in microfluidic droplets has been proposed through the regulation of flow dynamics, but is yet to be demonstrated experimentally. Here, we verify this hypothesis by accelerating or suppressing macromolecular reactant mixing in microfluidic droplets. The control of reaction kinetics through the modulation of flow topology in microdroplets might enable further developments in modelling macromolecular systems.

The emergence of microfluidics and lab-on-a-chip technologies enabled the miniaturization of experimental laboratory procedures onto penny-sized chips. These chips are composed of networks of microchannels and reservoirs, which are analogous to beakers and pipettes in a standard chemistry laboratory. Droplet-based microfluidics allows parallel reactions to take place in compartmentalized droplets with high throughput,[1-3] which is accomplished by downsizing the reaction volumes by several of magnitude into thousands of identical microdroplets.[4-6] Additionally, droplet reactors help reduce cross contamination as the reactants are usually confined by the interface formed between the droplet surface and an immiscible continuous phase.

Numerous experimental and simulation studies have shown the high efficiency that comes with mixing within microdroplets, which is attributed to the unique molecular transport mechanisms occurring at the microscale and the internal flow dynamics generated by the droplet movement.[7-9] This aspect of flow dynamics can be modulated, enabling the precise control of reaction mixing and timings.[10] In a straight microchannel, the fluid within a droplet tends to form two symmetrical hemispheres with continuous flow recirculation divided by a stable interface in the middle. This topology suppresses convection in the direction perpendicular to the flow, which enables the production of Janus particles by independently crosslinking dissimilar polymers contained in each hemisphere.[11] Meanwhile, microchannels featuring curves induce convective mixing in droplets, facilitating the generation of particles with homogeneous compositions.[12-14] Additionally, droplets containing phase-separated liquids are useful to generate anisotropic microstructures.[15,16]

The manipulation of droplet flow topology can be applied in more complex scenarios. For example, the droplet's internal circulation can be increased or suppressed to achieve higher or reduced shear forces and mixing efficiencies. The flow topology is regulated by several physical parameters, including the capillary and Reynolds numbers, surface tension, Marangoni effects, and droplet morphology, with viscosity playing a dominant role over the others.[17-19] Apart from intrinsic reaction kinetics, the rates of chemical and biological reactions are correlated with the local concentration and transport efficiency of reactants. With

this in mind, rapid mixing in microdroplets has been proposed to improve the mixing performance in a sol-gel transition,[9] as well as allowing for more efficient chemical and biological reactions.[20] However, controlling reactions through the regulation of droplet flow topology has not been extensively studied experimentally.

We have previously used centroid location-based ensemble correlation to reduce the noise in velocity vectors obtained from microparticle image velocimetry (μPIV) to investigate the three-dimensional flow topology in two different types of droplets. The flows were characterized by distinct circulation and shear profiles, which were observed to be mainly regulated by the viscosity ratios across the interfaces of droplets. The average flow within the droplet in reference to the droplet itself increases along with the inner-to-outer phase viscosity ratio λ. This work demonstrates that chemical reactions can be controlled by varying the viscosity of the continuous phase.

The two types of droplets ($\lambda = 0.12$ and $\lambda = 0.78$) studied by Ma et al.[17,18] exhibit distinctive flow topologies. One droplet ($\lambda = 0.12$) features a relatively high volumetric internal flow regardless of its size (Figures 1 and 2a), whereas the other droplet ($\lambda = 0.78$) presents a small internal flow, except for symmetric recursive flows along the droplet boundaries (Figure 2b).

Figure 1 shows the axial and transverse flow profiles in droplets of various sizes when $\lambda = 0.12$. The flow topology remains unchanged independently of the droplet morphology, and the dominant velocities are the axial in the center and the transverse in the diagonal corners. However, the droplet morphology does affect the flow magnitude, i.e., larger droplets have a larger contact area with the channel walls, which results in increased friction and enhances internal flow circulation.

Figure 2 shows the droplet flow topology at different cross-sectional planes and velocities (axial U and transverse V). Since gravity has negligible effects in microfluidic systems[16] and the boundary conditions are constant along the interface, it can be assumed that the flow topologies in the mid-xz and mid-yz planes are identical to the topology in the mid-xy plane. The flow topology is totally different for the two droplets

($\lambda = 0.12$ and $\lambda = 0.78$) in Figure 2. For example, the $\lambda = 0.78$ droplet is composed of fluids with significantly reduced axial and transverse velocities in the bulk volume, thus the positive axial flow observed on the lower planes are possibly a result of the gutter flow between the water-oil interface and the rectangular channel boundaries.[21]

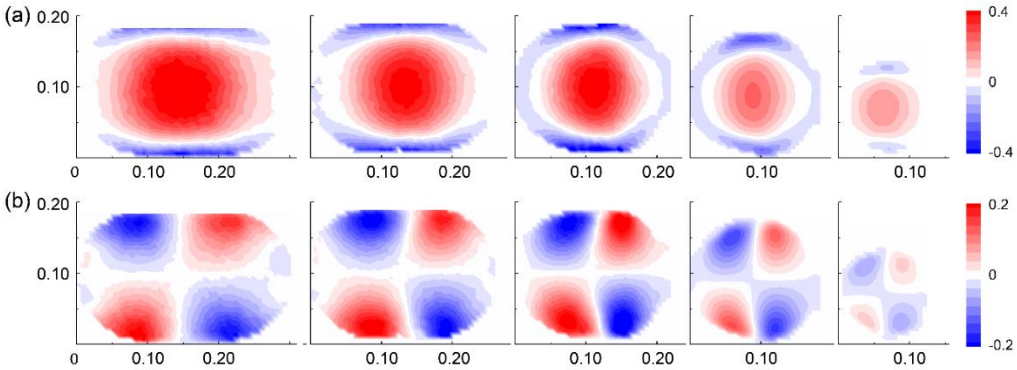

Figure 1. Cross-sectional view of flow topologies at the center of droplets of various sizes flowing through a rectangular microchannel when $\lambda = 0.12$, showing the (a) axial and (b) transverse velocities U and V, respectively. Both components are normalized to the droplet velocity v_d (i.e., $U = {}^{u}/_{v_d}$ and $V = {}^{v}/_{v_d}$). The axial and transverse velocities are positive when the velocity component points in the direction normal or perpendicular (pointing down) to the flow, respectively.

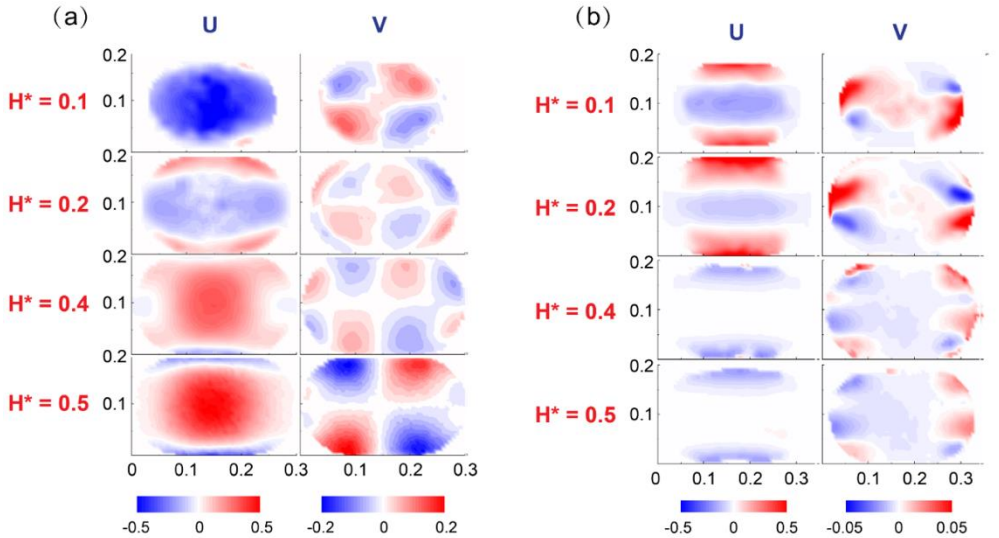

Figure 2. Visualization of U and V at four cross-sectional focal planes in droplets of the same size, when (a) $\lambda = 0.12$ and (b) $\lambda = 0.78$. $H*$ represents the position of the focal plane in relation to the height of the droplet, where $H* = 0.5$ represents the focal plane across the middle of the droplet. The axial and transverse velocities are positive when the velocity component points in the direction normal or perpendicular (pointing down) to the flow, respectively.

It has been shown that the mixing efficiency is directly related to the magnitude of the flow components U and V.[9] Therefore, it must be possible to control the mixing efficiency of chemical reactions by modulating the viscosity ratio across the droplet interface. To our knowledge, the control of reaction kinetics through the modulation of flow topology has not been demonstrated experimentally. In a static microdroplet, molecular diffusion acts as the only mass transport mechanism. Therefore, to evaluate mixing performance as modulated via flow topology, one must use a system with negligible passive mixing (diffusion), so that the droplet internal flow circulation acts as the sole mixing mechanism. Recently, ultra-long single-strand DNA and its complementary sequence has been employed to control the crosslinking of collagen.[22] The reaction remains suppressed in static conditions and is only initiated when the mixture starts flowing through a microfluidic channel. The crosslinking occurs when the nucleic acid bases on the DNA form electrostatic bonds with the complementary sequence (Figures 3a and 3b).

The internal flow circulation in droplets is regulated by λ (Figure 2). At higher λ, with HFE7000 (3M, US)[23] as the continuous phase, the internal circulation is reduced and the internal flow velocity becomes uniform. Crosslinking is restricted, resulting in a lack of gelation in the droplets (Figure 3c). Using HFE7500 (3M, US)[24] reduces λ over 2 orders of magnitude, greatly improving droplet gelation (Figures 3d and 3e). The reaction speed takes place about 30 times faster than in native collagen, with gelation times as short as 40 seconds at room temperature.

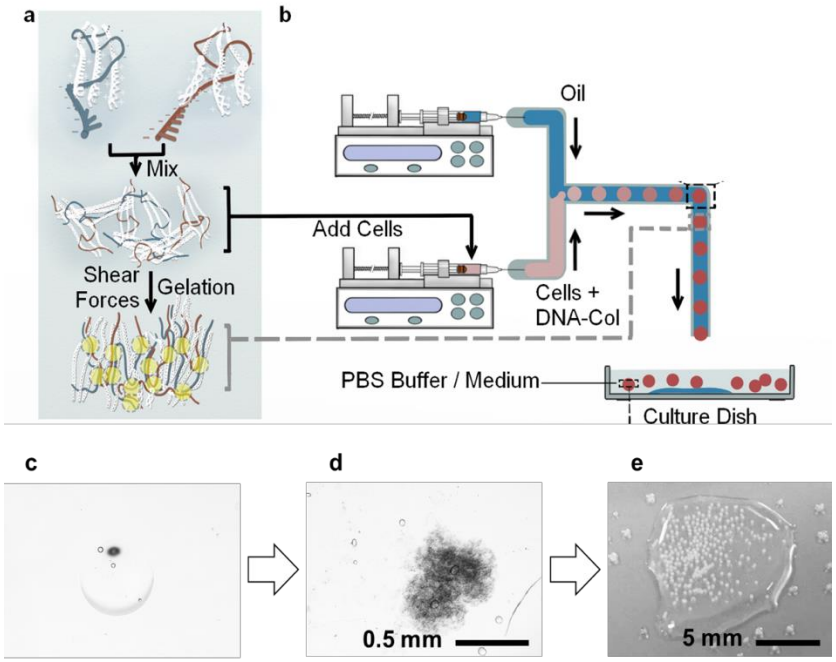

Figure 3. Ultra-long single-strand DNA (ssDNA) was used as the crosslinking agent for collagen fibrils. (a) Mixing of ssDNA with its complementary sequence is suppressed in static conditions and only initiated when the mixture is set to flow. (b) Mixing efficiency increases with flow magnitude in microfluidic droplets, which can be controlled through the modulation of λ by varying the viscosity of the continuous phase. The modulation of crosslinking efficiency can be evidenced by the scenarios where (c) the collagen mixture fails to gelate, (d) accomplishes gelation, and (e) achieves homogeneous shapes. The samples were obtained by circulating collagen droplets through a microfluidic channel for 5 minutes at a rate of 1 m min^{-1} using (c) HFE7000 and (d and e) HFE7500 as the continuous phase.

We demonstrated the control of reaction kinetics through the modulation of flow dynamics in microdroplets as proof-of-concept experiment. This mechanism is yet to be demonstrated in a pragmatic scenario. It is noted that the proposed method is most efficient in macromolecular reactions where diffusion is negligible, since diffusion as a mixing mechanism is intrinsically efficient in small volumes. We believe that the modulation of flow topology could be useful to probe intracellular activities (e.g., transcription or signal transduction) in living cells, although their composition is much more complex than the homogeneous

droplets used here. Future work could focus on developing more complex droplet models that could translate to modelling the contents of cells (e.g., different organelles and cytoskeleton compartments). Additionally, the further exploration of this method might open up new routes to modulate in vitro macromolecular reactions such as the synthesis of antibodies. This could contribute to design efficient biomimetic microreactors. And, although not guaranteed, it is possible that new types of reactions can be designed based on the control of reaction kinetics as demonstrated here.

Acknowledgment

The work was supported by the national natural science foundation of China (Grant Number: 61971255) and Shenzhen Science and Technology Innovation Committee (Grant Number: KQJSCX20180327143623167 and KCXFZ202002011010508).

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