

A State-of-the-Art Review of Mixing in Microfluidic Mixers*

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Abstract Microreaction technology is one of the most innovative and rapid developing fields in chemical engineering, synthesis and process technology. Many expectations toward enhanced product selectivity, yield and purity, improved safety, and access to new products and processes are directed to the microreaction technology. Microfluidic mixer is the most important component in microfluidic devices. Based on various principles, active and passive micromixers have been designed and investigated. This review is focused on the recent developments in microfluidic mixers. An overview of the flow phenomena and mixing characteristics in active and passive micromixers is presented, including the types of physical phenomena and their utilization in micromixers. Due to the simple fabrication technology and the easy implementation in a complex microfluidic system, T-micromixer is highlighted as an example to illustrate the effect of design and operating parameters on mixing efficiency and fluid flow inside microfluidic mixers.

Keywords micromixing, microfluidics, T-shaped micromixer, microfabrication techniques, microreaction technologies, microelectromechanical systems

1 INTRODUCTION

The increasing demands of process industry, pharmacy, analysis and biochemistry, for novel and effective mixing technologies as well as the smooth execution of highly exothermic or explosive chemical reactions have led to the intensive development of the microreaction technologies, and resulted recent years in a considerable variety of microfluidic systems. The term of microfluidic systems refers to systems with characteristic length scales that are in the micrometer range. A tangible effect of this small dimension is that fluid properties become increasingly controlled by viscous forces rather than inertia [1]. On the other hand, the reduced dimensions of the microfluidic system lead to a large surface-to-volume ratio, which increases heat and mass transfer efficiencies. The small dimensions allow rapid diffusive mixing to occur in as little as 100 μs . These lamellar systems achieve surface-to-volume ratios of $30000 \text{ m}^2 \cdot \text{m}^{-3}$, compared to batch reactors with typical surface-to-volume ratios of $4 \text{ m}^2 \cdot \text{m}^{-3}$. In addition, temperature changes and heat transfer coefficients up to $25 \text{ kW} \cdot \text{m}^{-2} \cdot \text{K}^{-1}$ are possible depending on the materials and heat exchanger used [2]. High heat transfer efficiency allows for fast heating and cooling of reaction mixtures within the micromixers whereby reaction under isothermal conditions with exactly defined residence time can be carried out [3].

Mixing in microfluidic systems starts almost exclusively from regular periodical concentration profiles with steep gradient, which is governed by molecular diffusion proceeding in deformed fluid elements. Deformation decreases segregation scales in a mixture, generates contact surface between mixed materials and maintains high local concentration gradient. In these circumstances, molecular diffusion can effectively decrease concentration variances in the

system [4–6]. The rate of deformation of fluid elements depends on the local rate of energy dissipation, the orientation of a contact surface in the local flow field, physical properties of mixed materials, and scaling of microfluidic devices. With dimensions reducing, viscous forces dominate the flow in the fluid handling apparatus, and Reynolds number, Re , decreases with the decrease of cross-sectional area of the channels. Microfluidic systems, when compared to macroscale ones, have advantages such as smaller geometrical size, shorter analysis times, less sample/reagent consumption, and disposability. Taking these advantages in consideration, it can be concluded that, rather than designing a microfluidic system that is just a downsized copy of a macrofluidic system, the microfluidic systems should be designed from the physical design rules of fluid mechanics and diffusion in confined spaces [6]. Micromixer is the most important component in microfluidic systems. They can be classified into two main types: active and passive ones. Each type has its specific mixing concepts, capacity, mixing speed, and operating conditions. Generally two steps occur in the mixing process in these micromixers: heterogeneous mixing created by convection, and homogeneous mixing at the molecular level caused by diffusion between adjacent domains.

An overview on the effects of operating and design parameters on mixing efficiency of microfluidic mixers is presented. General principles of mixing within microfluidic systems are discussed in more detail. Also, an overview of the flow phenomena and mixing characteristics in active and passive micromixers is covered. T-shaped micromixer is the focus of this review.

2 CLASSIFICATION OF MICROMIXERS

Micromixers can be classified into active and

Received 2007-07-12, accepted 2008-04-14.

* Supported by the National High Technology Research and Development Program of China (2006AA030202, 2006AA05Z316).

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passive mixers (Fig. 1). The active mixer requires external forces such as pneumatic or mechanical vibration to enhance mixing efficiency. Also, it requires complex fabrication processes, more complex to package and control, and is difficult to integrate with other fluidic components [8], whereas passive mixers generally have longer mixing length than active mixers, require no external agitation, easy to fabricate and incorporate with other fluidic components [9–12].

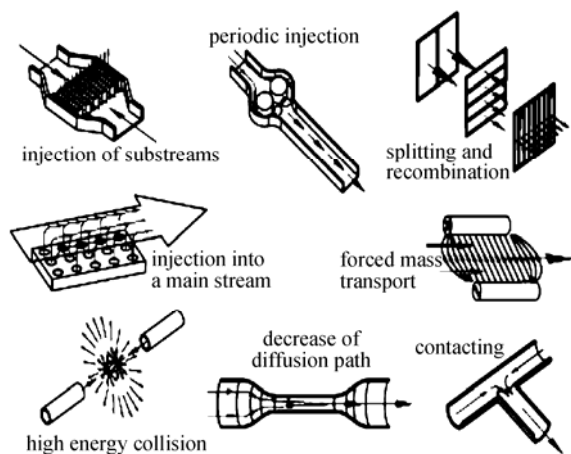


Figure 1 Schematic drawing of selected passive and active micromixing [7]

2.1 Active micromixers

Active mixers use external perturbation to introduce vorticity into laminar flow [13–21]. Ultrasonics [13], pressure field disturbance [14], thermal [15], magnetically [16] and electrokinetics [17] driven mixers are a few examples having been demonstrated to date. Electrokinetics is a branch of electrohydrodynamics (EHD) that describes the coupling of ion transport, fluid flow and electric fields and is distinguished from EHD by the relevance of interfacial charge at solid-liquid interfaces. The fluid flow in this class of devices is often stable and strongly damped by viscous forces (with Re being 1 or smaller). However, heterogeneous ionic conductivity fields in the presence of applied electric fields can, under certain conditions, generate an unstable flow field owing to electrokinetic instabilities (EKI) by which the action of fluctuating electric fields causes the two fluids to stretch and fold rapidly and promote mixing [17, 18]. Oddy *et al.* [17] used fluorescent experiment to observe the performance rapid stretching and folding of a homogeneous fluorescence tracer in EKI mixer (Fig. 2). A mixing time of 2.5 s for a mixing volume of 0.1 μL was achieved. Recently, Posner and Santiago [18] presented a parametric experimental study of convective EKI in an isotropically etched cross-shaped microchannel with three inlets and one-outlet (Fig. 3).

Active mixing can also be achieved by using ultrasonic vibrations generated from piezoelectric materials to introduce turbulence in the fluid flow to enhance mixing. An ultrasonic micromixer was realized and tested by a dilution experiment, and employing the dye uranine [19]. In the presence of ultrasonic

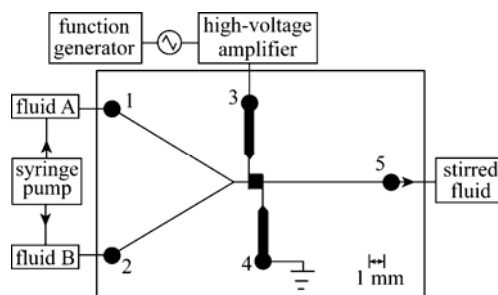


Figure 2 Electrokinetic instability micromixer [17]

(Points 1 and 2 are the inlet ports for fluid A and fluid B, whereas point 5 is the outlet port for mixing fluids. Side channel ports 3 and 4, connected to either side of the mixing chamber, allow for ac excitation)

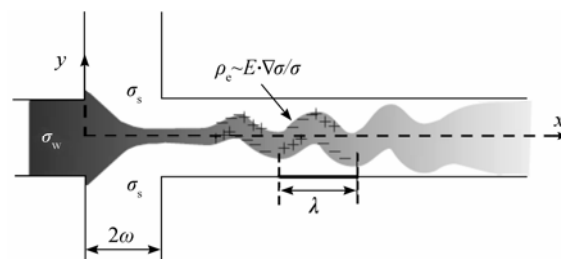


Figure 3 Schematic of unstable flow in a cross-shaped microchannel and the channels have the characteristic D-shape cross-sections of isotropic etching [18]

(E , ρ_e , λ and ω are the electric field, charge density, nominal wavelength and the channel half-width respectively. Whereas σ_s is the ionic conductivity of the inlet streams at the top and bottom inlet of channel, and σ_w is the ionic conductivity of the inlet stream at the left inlet of the channel)

mixing, Magnetic forces can also be used to achieve mixing. By patterning electrodes in a channel under a magnetic field, coupling between magnetic and electric fields induces body forces in fluids. A complex flow was observed using magneto-hydrodynamic mixer [20]. Haeberle *et al.* [21] presented a modular centrifugal micromixer comprising a mixing unit hosting a planar network of low-aspect-ratio microfluidic channels, a fixed rotating drive and contact-free dispensers for continuous feed of educts as seen in Fig. 4. The modular setup allows simple fabrication and exchange of the mixing unit. High-speed micromixing is powered by the Coriolis force at volume throughput up to milliliters per minute. Due to high flow rate attributed to the favorable interplay of the strong centrifugal force with the large channel cross section, the high throughputs at extremely reduced mixing times were reported.

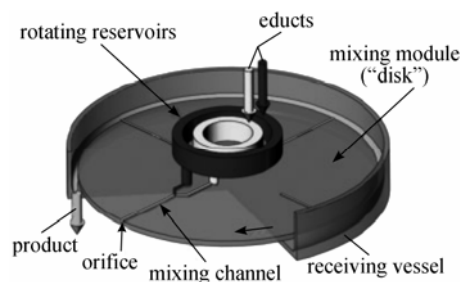


Figure 4 Centrifugal micromixer [21]

Historically, active mixers performed better than passive ones in terms of time and space needed for mixing. These mixers can be activated on demand, leading to reconfigurable devices. However, they suffer from complex fabrication, high cost for active control, and typically high power consumption. Also, some of the active mixing mechanisms such as ultrasonic waves and high temperature gradients can damage biological fluids making them a poor choice for biological processing. Due to these problems, active mixers are seldom used on micro fluidic devices and there are few publications about their optimization.

2.2 Passive micromixers

Mixing in passive mixers usually is induced by driving fluids through channels with cleaved geometries. Repeated lamination and splitting of flows in microfluidic channels were used to increase interfacial area and thus mixing quality [22–25]. An alternative way is to make use of chaos, because chaotic fluid path lines can disperse fluid species effectively, even in smooth and regular flow fields [26–29]. However, the conventional fabrication method is unable to form precisely aligned microchannels in passive mixers. Therefore, these mixers were designed with a simple structure and required longer mixing length. Multi-lamination [29–40], split-and-recombine [41–44], and chaotic [45–50] micro mixers are a few examples of passive micromixers demonstrated to date.

2.2.1 Multi-lamination micromixers

Most micromixers for mixing liquids follow the principle of producing thin liquid lamellae typically in the range of a few to several tens of micrometers and guiding them in contact through a flow-through-chamber [29]. Splitting the inlet streams into n substreams and recombining them increases the contact surface between the two fluids causing diffusion to occur faster [30–38]. Multi-lamination micromixers, such as interdigital, circular, superfocus, split-and-recombine, and chessboard micromixers, are based on the following concepts: (a) bifurcation feeds, (b) interdigital parallel-flow, (c) hydrodynamic focusing, and (d) splitting recombination and rearrangement.

Bifurcation-type feeds create an alternate ar-

range of feeds. Such a laminated feed stream passes into an inverse bifurcation structure and a subsequent folded delay-loop channel where mixing takes place. Interdigital micromixers are the most widely used one and is by now well established for lab-scale investigations and for use in production units [30–33]. These mixers are characterized by feeding structures leading to alternate co- or counter-flow interdigital array of microchannels or a system of fine circular nozzles set into each other to obtain circular slots [Fig. 5 (b)]. Miyake *et al.* [33] designed a mixer using an array of 400 micro nozzles; by forming small plumes after passing through the micro nozzle the contact area between two liquids is increased.

Hydrodynamic focusing concept for a single stream and for, the multi-laminated flows is based on the fact that, thinning of the multilamellae flow can be lead to increasing of mixing speed. Hydrodynamic focusing mixer [Fig. 5 (c)] is thinning the liquid lamellae through micro structured feeding channels additionally by geometric focusing that means by a continuous reduction of the width of the flow-through chamber and thus accelerate the mixing rate. With the aim to overcome the unwanted effect of slight deviation of lamellae thickness observed in the case of triangular interdigital mixer caused by the parallel orientation of the inlets, a novel focusing interdigital micromixer, termed Super focus was developed [29, 36]. In Super focus mixer the various lamellae have different angles with respect to the channel direction. Thereby, lamellae width becomes slightly dependent on the channel position [Fig. 5 (a)].

Not far from lamination concept, Cha *et al.* [38] reported a novel micromixer, named a chessboard mixer, to expand interfaces between mixing fluids. A mixing length of only 1400 μm was reported for complete mixing, and the total flow rate can be increased easily using multiple arrays of this mixer without any loss of performance. Circular micromixers are another type of multi-lamination mixers (Fig. 6), which utilizes self-rotation of the sample fluids from multiple injection channels to produce three-dimensional vortices in the circular mixing chamber at low Re , thereby enhancing mixing performance [39]. Chung *et al.* [40], Sundaram and Tafti [41] also proposed a passive micromixer utilizing self circulation of the fluid in the mixing chamber. Their numerical results

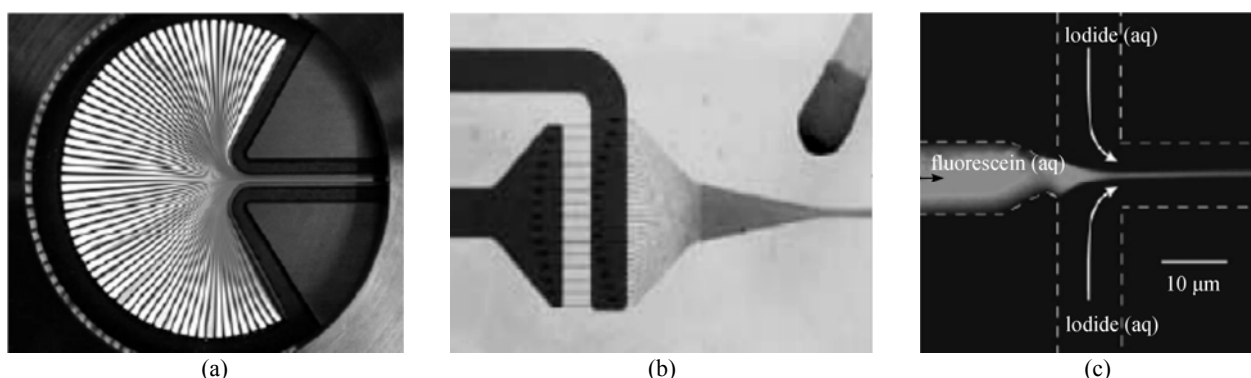


Figure 5 Passive mixers: (a) SuperFocus mixer [12]; (b) Triangular interdigital micromixer [37]; (c) Hydrodynamic focusing mixer [12]

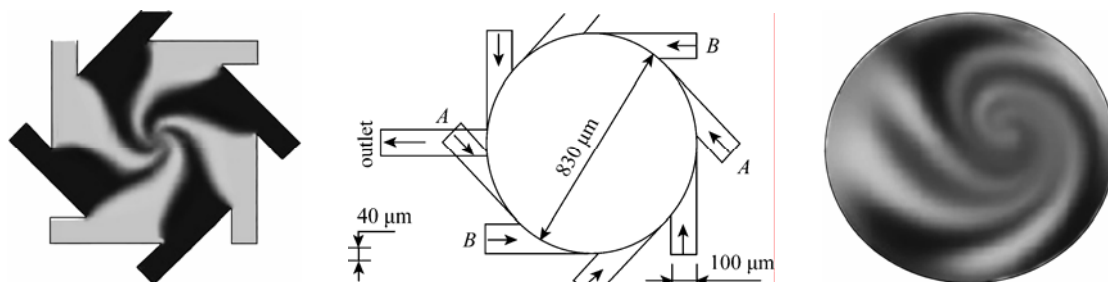


Figure 6 Circular mixer [39]

indicated that this type of micromixer was capable of delivering enhanced mixing performance, particularly at Re in the range of 20–400. Böhm *et al.* [42] reported a rapid vortex micromixer for studying chemical reaction. Lin *et al.* [43] proposed a novel three-dimensional vortex micromixer which also utilizes self-rotation effects to mix fluids in a circular chamber at low Re . The micromixer is fabricated in a three-layer glass structure for delivering fluid samples in parallel into the circular mixing chamber by 8 individual ports tangent to a 3D circular chamber. The mixing performance as high as 90% within a mixing chamber of 1 mm diameter was reported.

2.2.2 Split-and-recombine mixer

This kind of mixer creates sequentially multi-laminae patterns which differ from the parallel approach of the interdigital feeds. For this purpose, basically three steps are required: flow splitting, flow recombination and flow rearrangement (SAR) [44–48]. Branebjerg *et al.* [44] studied theoretically the diffusion in SAR mixers with horizontal lamination of unmixed fluids by successively separating and recombining the flow. An analytical solution for the width-wise concentration profile within the last unit was developed by neglecting the effect of its preceding SAR units. Bessoth *et al.* [47] presented a passive mixer which reduced the diffusion path between the fluid streams by first splitting and then recombining the flow. Bertsch *et al.* [48] presented micromixers with geometries very close to conventional large-scale static mixers used in the chemical and food-processing industry (Fig. 7). Two kinds of geometries have been studied. The first type is composed of a series of stationary rigid elements that form intersecting channels to split, rearrange and combine component streams. The second type is composed of a series of short helix

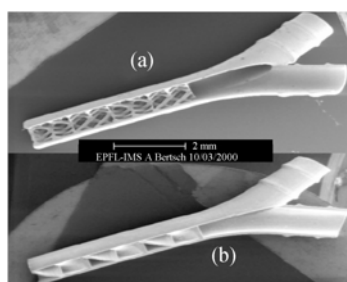


Figure 7 Cut-out view of the micromixer structures built by microstereolithography: (a) Micromixer made of intersecting channels; (b) Micromixer made of helical elements [48]

elements arranged in pairs, and each pair comprised of a right-handed and left-handed element arranged alternately in a pipe. CFD program FLUENT is used to evaluate the mixing efficiency. With a low pressure drop and good mixing efficiency, these truly three-dimensional micromixers can be used for mixing of reactants or liquids containing cells in many microfluidic applications. The formation of the multi-lamellae was proven by both of dilution-type and reactive imaging. It was further noted that SAR flows, although ideally highly regular, have features of chaotic mixing as they benefit from an exponential increase in interface similar to the chaotic stretching.

2.2.3 Chaotic micromixers

Chaotic micromixers are related to imposing perturbation within the flow by generating a transversal velocity component of chaotic advection increasing the macroscopic mixing. This can be achieved by using three-dimensional helical channels, bas-relief structure on the floor of the channel, or EKI. Chaotic micromixers such as cross-channel micromixer and staggered herringbone mixer (SHM) are based on the fact that chaos is remarkably efficient at mixing low Re flow. In essence, the efficiency relies on the fact that, in chaotic regimes diffusive fluxes across interfaces are enhanced at exponential rates in time, accompanied by a corresponding reduction of the striation thickness [28, 49–53]. The first design of a chaotic micromixer was by Evans *et al.* [28], who developed a planar active micromixer based on chaotic advection resulting from a source/sink system, where unmixed fluid is pumped into a mixing chamber, and then two source/sink systems are alternately pulsed. Other configurations featuring perpendicularly intersecting channels (grooves) allow hydrodynamic focusing under pressure driven flow *via* submerged fluid jets or parallel and serial mixing under electroosmotic flow *via* an array of cross intersections. The net effect of the grooves is the entrainment of fluid near the structured surface along the direction of the grooves; this motion is perpendicular to both the principal axis of the channel and the applied pressure gradient. To drive and control fluids inside a microchannel, especially liquids, a very high pressure gradient is required. Surface forces dominate at small dimension and, thus, the friction increases dramatically. Therefore, the study and application of surface-driven electro-osmotic flow become important. Stroock *et al.* [49] exploited three-dimensional vertical flows to produce chaotic regimes along a grooved channel, which creates a

transverse velocity component in the flow field. The mixer is composed of several mixing cycles, whereby a mixing cycle comprises two sequential regions of grooves, *i.e.*, two half-cycles. The grooves were shown to be particularly adept at creating chaotic advection and thus increasing mixing potential compared to straight grooves for both pressure driven flow and electrokinetic flow. A few years later, Liu *et al.* [50] and Park *et al.* [12] fabricated passive chaotic microfluidic mixers incorporating three-dimensional serpentine microchannels at high flow rates. They provided an effective mixing performance at *Re* of approximately 70. Lee *et al.* [51] and Dodge *et al.* [52] realized cross-channel micromixers which consists of one or more channel intersections, operating by using an external oscillatory flow excitation. Based on the design proposed by Stroock *et al.* [49], Hessel and Zimmerman [53] introduced a new mixer named a staggered herringbone micromixer (SHM). This mixer used alternating cycles of asymmetric herringbone grooves to create increased mixing as a result of cross channel fluid movement through the grooves.

3 FABRICATION MATERIALS

As sequence of a unique characteristics and applications of microfluidic devices, properties of materials are critical for both fabrication and successful application of these devices. Different materials have different electric potential introduced by the wall and also quite different effects on the flow medium and on the characteristics of the mixing. Two approaches to flow manipulation are prevalent in passive micromixers: the first relying on channel geometry to generate chaotic advection and increased circulation, and the second on channel surface properties. Micromixer wall with electrically charged surface heterogeneities may increase mixing efficiencies by creating localized regions of flow circulation. Surface charge heterogeneities have been suggested as a mechanism for enhanced mixing in electroosmotic flows [54–56]. Electroosmotic flow is generated by the surface charge on the microchannel walls in combination with an electric field along the microchannel. For example, polymer materials exhibit a wide range of charge and charge densities, electroosmotic flow in microchannels made from different polymer materials is highly variable. Electroosmotic flow has been measured in various polymer microchannels fabricated by laser ablation [57], and imprinting [58], and in poly-(methylmethacrylate) (PMMA) channels fabricated by LIGA (X-ray lithography, electroforming and moulding techniques) methods [59]. These fabrication methods, as well as the material itself, can affect the surface charge density and therefore have profound effect on the electroosmotic flow. On the other hand, in some applications such as mixing of electrokinetic flows, silicon cannot be used because of its electrically conducting properties [60]. Typically, silicon oxide (or glass) surfaces are negatively charged at neutral pH due to deprotonated silanol groups ($\equiv\text{Si}-\text{O}-$). When these surfaces come in contact with a solution containing ions, positive ions will be attracted to the

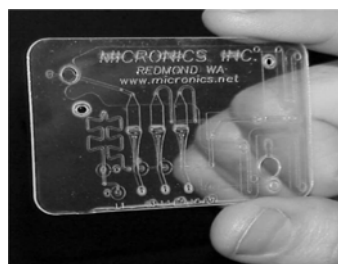
surface forming an immobile layer and a diffuse layer on the surface. If an electric field is applied, the positive ion diffuse layer will move along the field. Consequently, the rest of the fluid is dragged by this diffuse layer *via* shear stress, resulting in bulk motion.

Thermal conductivity also is one of the important properties should be taken into account when electroosmotically driven systems is fabricated. It is well established that Joule heating can be substantial in systems employing electroosmotic flow. Therefore, heat removal in the selected material is a very important consideration when electroosmotically driven systems is utilized, particularly when plastics are used for construction. For these reasons, material properties such as surface charge, machinability, molecular adsorption, electroosmotic flow mobility, thermal conductivity, toxicity, purity, and optical properties are very important considerations.

Metals, silicon, glass, and polymer, as seen in Fig. 8, are the main four types of materials used for microfluidic fabrication [62]. Although metals, glass, and silicon are widely used materials in industries [63, 64], there are many limitations, such as, micromachining, opaque, absorption of biological molecules to silicon surface, and electrically conducting properties which prevent the extensive use of metal and silicon. The limitations due to fabrication difficulty, toxic chemicals involvement, and the cost of glass machining have directed commercial producers to seek other materials such as polymer [65].



(a)



(b)

Figure 8 Slit-type (a) interdigital micromixer made in stainless steel [7], and Microfluidic Lab Chip (b) manufactured by plastic thin film lamination [61]

Polymers have major advantage over glass and silicon; it is being optically clear, non-toxic and low cost. Also, it is easy in fabrication and the varieties of surface modification methods are available to improve the efficiency of these devices. Consequently, many researchers employed polymer materials such as polycarbonate, polymethylmethacrylate, polyethylene,

polypropylene, polystyrene, poly(dimethylsiloxane) (PDMS), and poly(methyl methacrylate) (PMMA) as main materials in all fields of research and industries [66–70].

4 DEVIATION FROM MACROMIXER

It is widely accepted that, in microfluidic scale, the continuum approach can still be applied for modeling liquid flow. However, there are many situations where fluid flow behavior in microfluidic scale can considerably deviate from those in macrofluidic scale [71, 72]. Xu *et al.* [72] investigated viscous dissipation effects for liquid flows in micro-channels. They stated that deviations from predictions using conventional theory that neglects viscous dissipation could be expected because viscous dissipation tends to be significant due to the high velocity gradients existing in channels with small hydraulic diameters. They also suggested that the limit of the viscous dissipation effects has to be linked to a temperature rise of 1 K between inlet and outlet of microchannel.

Since the fluid viscosity is a function of temperature, as the temperature changes along the tube, the fluid viscosity varies along the tube and therefore the viscous shear force changes. This means the pressure distribution in the tube and the Re changes also along the flow direction. Therefore, characteristics of the flow in microchannels could be different, in terms of the friction factor and Re , from those used in the conventional macro-systems. As a result, when the dimensions of microfluidic channels approach the micro level, viscous dissipation becomes too significant to be neglected, and the energy conservation consideration becomes necessary, not because of external heat sources, but because energy comes from the viscous dissipation effects within the flow in the micro-channels, causing the fluid temperature change, especially in the wall region with a high rate of viscous dissipation. As shown in Fig. 9, the local average temperature increases along the flow direction, and the temperature difference between the inlet and outlet increases as the diameter of microfluidic channels decreases. Koo and Kleinstreuer [74] investigated numerically the viscous dissipation effects on the temperature field and friction factor in circular and rectangular micro-channels. They demonstrated that viscous dissipation is strongly dependent on the hydraulic

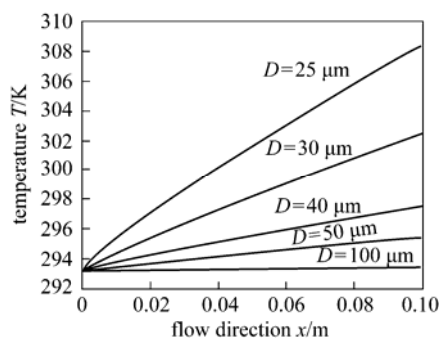


Figure 9 Average temperatures along the flow direction considering the viscous sipation effect [73] ($Re=800$)

lic diameter and the channel aspect ratio. Morini [75] confirm this result, as seen in Fig. 10. It is evident that the effects of the viscous dissipation are more important for decreasing aspect ratios (γ) of the micro-channel (aspect ratio is defined as $\gamma=W/H$, where W is the width and H is the height of microchannel). The viscous heating increases when the aspect ratio decreases; in a trapezoidal micro-channel 1 cm long, the temperature rise between the inlet and the outlet is equal to 5°C for $\gamma=0.05$; if the trapezoidal cross-section degenerates in a triangular cross-section ($\gamma=0.707$) the temperature rise becomes equal to 3°C.

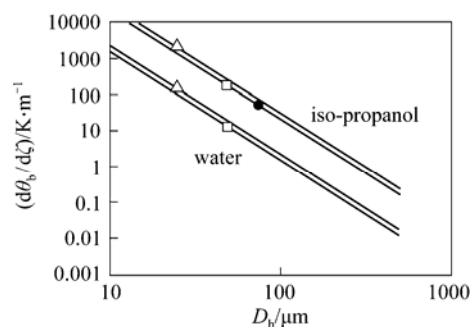


Figure 10 Temperature gradient as a function of the hydraulic diameter and aspect ratio (γ) for square and rectangular microchannels [75] ($Re=300$)

● Judy *et al.* [76]; $\triangle \gamma=0.1$; $\square \gamma=1$

Judy *et al.* [76] confirmed experimentally that viscous dissipation can be invoked to explain the deviation from Stokes flow behavior repeated in many other works on micro-channels; they evidenced that viscous dissipation has the significant effect of increasing the temperature of the flowing fluid along the micro-channel axis. Temperature rising of 6.2°C has been reported for microchannel with a hydraulic diameter of 74.1 μm , and 11.4 cm long, when iso-propanol was employed as working fluid with $Re=300$.

Recent studies exist which aim to identify the scale at which classical flow theory and the Navier-Stokes set of governing equations cease to accurately describe fluid flow systems. Commercial numerical packages (CFX5, FLUENT6, CFD-ACE, DNS, FIDAP), based on the Navier-Stokes equations have been widely applied to the analysis of fluid flow in microfluidic systems [77–87]. Although, it is intensively discussed to which extent and on which scales “micro-effects” occur in micro-channels, an unquestionable conclusion has not yet been reached [88–94].

5 REACTION RATE AND RATE OF MIXING

Before a reaction between any two reagents can occur, intimate contact between component molecules must be realized through mixing, because mixing on molecular scale can only be accomplished by diffusion, rather than through convective transport that dominate in turbulent systems. Diffusive mixing efficiencies for continuous flow systems can be measured using the Fourier number (defined as t_r/t_m , where t_r is the average residence time and t_m is the diffusive

mixing time), which indicates that mixing time scales increase with the characteristic dimensions of the reactor [95]. The ability to controllably and rapidly create a homogenous reactant mixture at the commencement of a reaction is desirable. Indeed, the effect of mixing on the extent of a reaction and product distribution is crucial in reactor design. However, in the case of fast reactions in which two or more reagents are initially present in separate streams, the reaction rarely occurs uniformly throughout the whole volume. The rate of reaction is no longer defined by inherent kinetics, but is limited by diffusional rates. Thus, for fast reactions yielding a single product, the yield is regarded as a direct measure of the mixing degree [96].

The relationship between reaction and mixing rates can be reduced to one of the following three general categories: chemical, diffusional, and mixed chemical/diffusional regimes [95, 96]. In chemical regime, mixing is faster than reaction rate, and it is complete before a significant amount of product is generated. In diffusional regime, reaction is fast, with the rate being limited by the mixing speed. In this situation, the formation of secondary products is greatest. Finally, in a mixed chemical/diffusional regime the greatest interaction between chemical reaction and fluid dynamics occurs, and the product distribution depends on both chemical factors, such as reaction rate, and on diffusional factors, such as mixing degree.

Due to sufficient mixing in microreactors compared to conventional reactors, reactor productivity or reaction rate can be increased greatly in a microreactor over conventional reactors for a multiphase reaction in which reaction is limited by mass transfer [97–99]. As a result, reactions can be carried out significantly faster than those in batch, typically with increases in both yield and selectivity. The difference in reaction time is dramatic in some cases. Wiles *et al.* [97] have demonstrated that the aldol reaction between an aldehyde and a silyl enol ether in the presence of tetrabutyl ammonium fluoride reaches completion in only 20 min when using a microreactor, *versus* 24 h in a typical reactor. Wiles *et al.* [98] demonstrated the formation of a series of enolates within a micro reactor using the organic base, diisopropylethylamine. They observed that, the conversion within a micro reactor is greater than that obtained in batch, in one instance an increase of 22% was observed. In order to compare microreactor systems with batch reactions, Kumada reaction kinetics were studied by Haswell *et al.* [99]. Enhanced reaction rates of this type have previously been demonstrated where enhancements of the order of 3.4×10^3 were reported as a result of miniaturization.

The influences of degree of mixing on product composition have also been investigated for micro reactors [84, 86, 100–103]. Generally, there are two directions in increasing the productivity of reaction product, (1) the construction of reaction modules, so called numbering-up, and (2) the improvement of a reactor itself. Okamoto *et al.* [100] studied the later direction, two methods are proposed, (a) a planar pumping method, and (b) an alternating pumping method. As for method (a), two thin liquid layers can react each other in the vicinity of their interface. Reaction yield as greater as 10% than that in conven-

tional batch reactor using mechanical stirrer reported. Method (b) is based upon the diffusive mixing through the liquid-liquid successive interfaces which are perpendicular to the flow direction. Alternating pumping of two different liquids was realized by using of, a piezoelectric driven system, and a mechanically pumping system. They reported that, if the reaction yield is proportional to the frequency of the alternating pumping, the reaction can be assumed as diffusion-controlled reaction. On the other hand, if the yield does not change according to the increase of alternating frequency, the reaction is assumed to be activation-controlled reaction (Fig. 11).

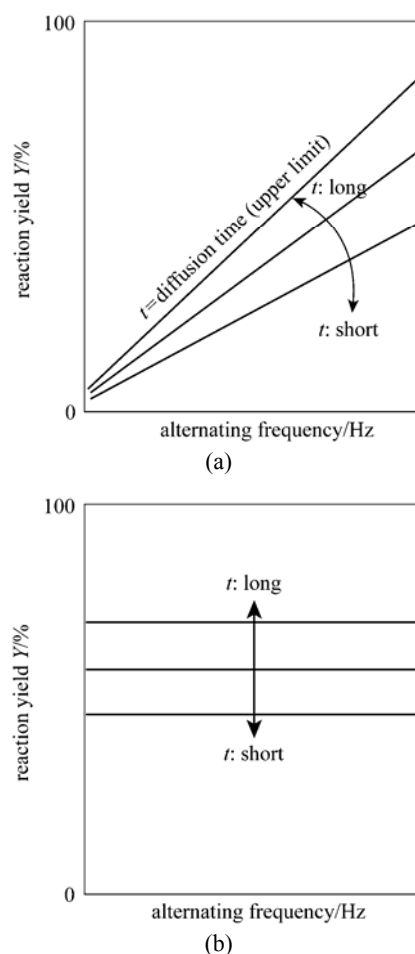


Figure 11 Criteria for distinction between (a) diffusion-controlled process, and (b) activation-controlled process [100] (t : residence time)

Aoki *et al.* [86] used the principle of lamination segments to study the effects of lamination width and rate constant on the relation between the conversion of reactant and the yield of desired product. They concluded that, feeding reactants with wider lamination width provides higher yield and selectivity of desired product at the same conversion when both the reaction order and the rate constant for the reaction producing by-products are higher than those of the reaction producing desired product. So, the selection of proper lamination width is essential for the microreactor to increase the mixing efficiency and thereby increase the productivity.

6 EFFECTS OF OPERATING AND DESIGN PARAMETERS

6.1 The effect of flow velocity

Flow velocity is one of the important factors which can influence mixing efficiency in microfluidic channels. It was found that, with increasing flow velocity, the laminar flow starts to form symmetrical vortices thereby enhancing the mixing quality. Furthermore, flow velocity variation leads to generate different stationary flow regimes (Fig. 12) such as, laminar, vortex, and engulfment flow [90, 104–107].

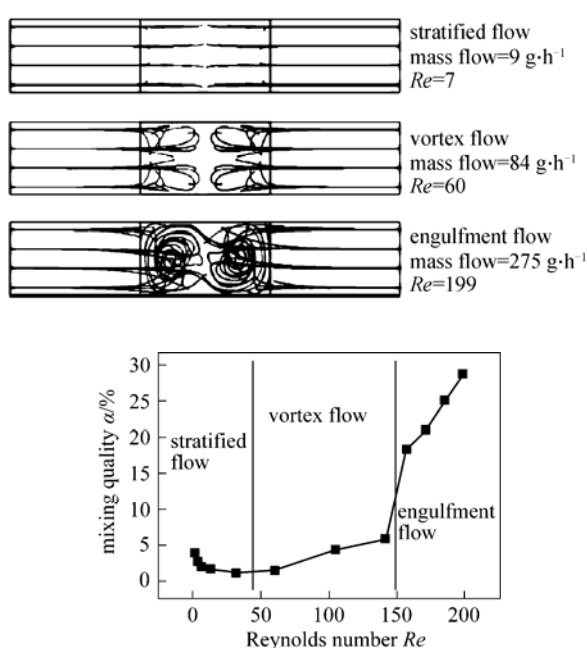


Figure 12 The three different stationary flow regimes inside a T-mixer [104]

Generally, at high flow velocity, breakup of symmetry in the flow field occurred resulting in the so-called engulfment flow, which was characterized by, some fluid from one side reaching beyond the centerline of the microchannel to engulf the fluid from the other side. As a result, a larger amount of mixing efficiency acting in cross directions, *i.e.*, perpendicular to the axial direction can be provided. Engler *et al.* [104] have found that (numerically as well as experimentally), increasing velocity inside static T-shaped micromixers with rectangular cross-sections led to increasing vortices even at low Re numbers of approximately 200 and that these affects can be used to improve mixing quality. The presence of small z velocity components in liquids flow at the inlet channels has also been investigated. The presence of such velocity results in swirling flow that enhances the mixing performance. Yu *et al.* [105] found that velocity profile act greatly on mixing efficiency and the parabola profile is the best one among plug-like, concave and parabola profiles. The effect of asymmetrical conditions in flow velocity has also been investigated [90, 106–108]. Bothe *et al.* [106] numerically reported

that, within laminar flow regimes only the engulfment flow with intertwinement of the input streams leads to efficient mixing by rolling-up the initially planar contact area (Fig. 13). As showing in Fig. 13 (a) at low velocity both inlet streams run parallel through the mixing channel and the planar contact area remains unchanged. At higher velocities the two vortex pairs get intertwined, which leads to a roll-up of regions with different concentrations [Figs. 13 (b)–(d)].

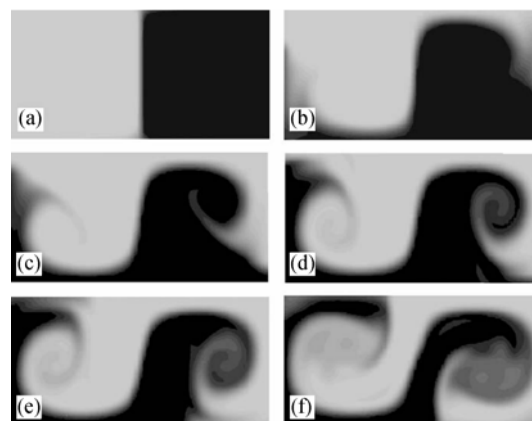


Figure 13 Tracer profiles on the cross section of the mixing channel 300 μm behind its entrance for mean velocities of (a) $0.9 \text{ m}\cdot\text{s}^{-1}$, (b) $1.05 \text{ m}\cdot\text{s}^{-1}$, (c) $1.1 \text{ m}\cdot\text{s}^{-1}$, (d) $1.15 \text{ m}\cdot\text{s}^{-1}$, (e) $1.2 \text{ m}\cdot\text{s}^{-1}$ and (f) $1.4 \text{ m}\cdot\text{s}^{-1}$ [106]

As a consequence, the specific contact area is enlarged, which is characteristic for the engulfment regime and an essential requirement for efficient diffusive mixing. In Figs. 13 (e) and (f), smearing of the contact area becomes visible, which results from reduced diffusion paths due to smaller segregation scales and, hence, reduced time needed for diffusive dissipation of gradients. One of the other simplest ways to induce mixing in microfluidic channels is by varying the flow rates in the inlet channels periodically with time. In this way, a pulsation of the whole stream can be achieved without using any additional geometric features, parts, or external fields. Theoretically, the decrease of flow rate induces a smaller residence time and thus a higher mixing length. Switching of the flows from a high to a low flow rate, leads to strong deformations of the interface between the two liquids. Zhao *et al.* [107] used the Villermaux-Dushman fast parallel competing reaction to study the effect of volumetric flow ratio on the micro-mixing performance. The experimental results showed that the micro-mixing performance decreased with increasing volumetric flow ratio at the same Re . In addition, time-varying pumping has several advantages such as mixing can be accomplished in less volume by sending the fluids multiple times past the features that encourage mixing, it works, at very low Re ($Re < 1$), very simple geometries, and finally it is easy to implement in mass production microfluidic devices. It has also been reported that pulsing is very effective when combined with geometries that induce secondary flow (Fig. 14) [90].

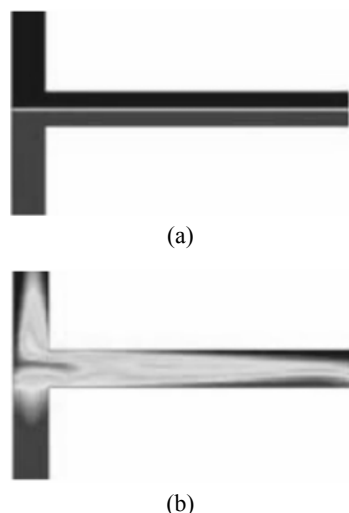


Figure 14 The effect of pulsing in mixing quality: (a) No pulsing nor ribs; (b) There is pulsing and ribs along the floor of the main channel [90]

6.2 Effect of geometrical setup

As mentioned in the above sections, viscous forces and pressure gradients with a low moment of inertia are governed the fluid flow in microfluidic channels. The result is a truly laminar, turbulence-free flow but it is not completely a creeping flow where Re is in the order of unity, secondary flow and the separation of boundary layer can be attained in this regime when there are some discontinuities in the fluid flow.

Clever geometry with presence of additional parts such as a sharp bend slanted wall, obstacles, or a junction can lead to such case (discontinuity of fluid flow). When a liquid flows past a sharp bend, the change in flow direction gives rise to a secondary flow field perpendicular to the flow of the liquid [108–112]. This lateral flow field could be used to improve mixing performance in a micromixer where mixing by turbulence is not feasible. On the other hand, the separation of boundary layers can give rise to the generation of vortices, which results in enhanced mixing performance. Vortices tend to break the stream up into layers and each layer curls in a different manner. These breaking and curling actions reduce the diffusion distance between the molecules of two liquids in a mixing process. Depending on this concept, Goullet *et al.* [109] and Johnson *et al.* [110] carried out numerical and experimental studies on mixing in a T-shaped micromixer with slanted walls (Fig. 15). They found that the slanted walls design of the mixer was able to induce a high degree of lateral transport across the channel. Since mixing within this design occurs by lateral transport, and is not limited by diffusion. Mixing efficiency of 80% has been reported at mixing length of 443 μm and velocity of $0.81 \text{ cm}\cdot\text{s}^{-1}$; whereas with the absence of slanted walls, a channel with 2300 μm is needed to achieve the same mixing efficiency at the same flow rate [28].

Wong *et al.* [111] reported a numerical investigation of obstacles at high Re . The simulated mixing channel is 300 μm in width, 100 μm in depth and 1.2–2 mm in length, and the diameter of the obstacle

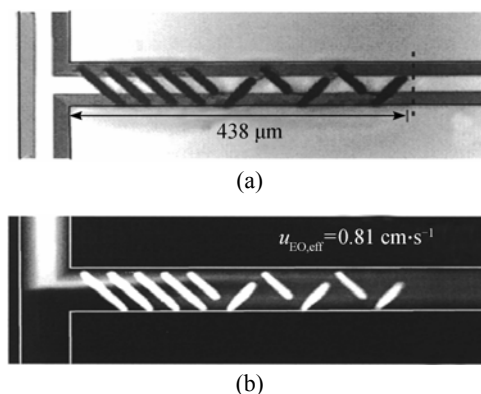


Figure 15 The effect of the presence of addition parts on mixing efficiency [110]

is 60 μm . Many arrangements of obstacles were investigated. This work found that obstacles in a microchannel at low Re cannot generate eddies or recirculation.

However, the results demonstrated that obstacles could improve mixing performance at high Re . Under this condition, the asymmetric arrangement of obstacles could alter the flow directions and forces fluids to merge and create transversal mass transport. Recently, Lin *et al.* [112] studied the effect of J-shaped baffles on mixing efficiency. The simulated and experimental results showed that the T-mixer with J-shaped baffles exhibited better mixing performance, and the percentage of mixing was about 1.2 to 2.2 times higher than those without baffles (Fig. 16). These results revealed that the J-shaped baffles could result in lateral convection in the main channel, resulting in improved mixing.

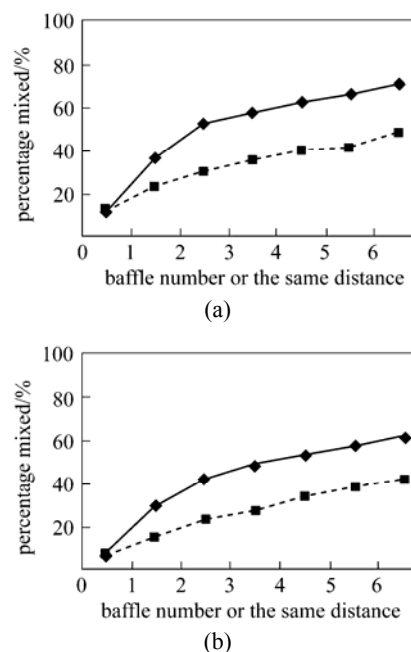


Figure 16 Mixing percentage in the tee channel with/without J-shaped baffles calculated from (a) simulated results, and (b) experimental results [112]

◆ with baffles; ■ without baffles

Engler *et al.* [113] found that for a symmetrical geometry with different inlet angles ($\neq 90^\circ$), mixing

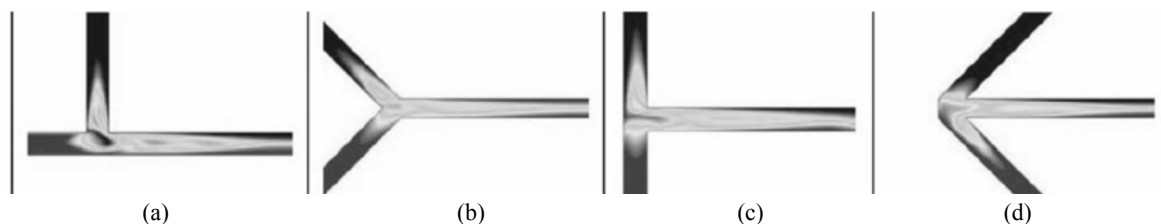


Figure 17 Comparison of the concentration plot of the “black” fluid for the four geometries [109]

(The data is for the case of 5 Hz pulsing at the same mean velocity of $1 \text{ mm} \cdot \text{s}^{-1}$ from each inlet, all of the channels are $200 \text{ } \mu\text{m}$ wide by $120 \text{ } \mu\text{m}$ deep)

quality differs not very much for various inlet angles over a wide range of Re numbers. This situation is different when only one inlet angle is varied. The authors attributed their findings to the perpendicularity or under inclined angle of one stream into the other stream make it more bent, splits, creates an enlarged mixing area, and reduces the diffusion length at the entrance of the mixing channel. Goullet *et al.* [109] considered four symmetrical intersection geometries for the inlet and outlet channels and they are: (a) Perpendicular inlet channel, (b) “Y” intersection, (c) “T” intersection, and (d) an arrowhead intersection, as shown in Fig. 17. They found that the best mixing occurs in the “T” and arrowhead intersections, *i.e.*, where the fluid path must go around a sharp bend, and the least mixing occurs in the single-perpendicular inlet intersection (where one of the inlet fluids does not have to travel around any bends at the intersection).

Wang and Lin [114] used T-sensor with three inlets for their research. They found that for the mixing controlled by diffusion, the inlet angles $>45^\circ$, mixing efficiency didn't change any more; while inlet angles $<45^\circ$, mixing efficiency decreased slowly with increasing inlet angle, since the smaller the inlet angles, the stronger the diffusion. Their results also showed that the mixing efficiency increased with decreasing width and aspect ratio of outlet [114, 115]. It has also been found that asymmetrical conditions in the geometry of T-shaped micromixer lead to an improvement in mixing quality [116]. The effect of aspect ratio has been investigated [117–119]. It has been reported that mixing length showed a weak non monotonic dependence on the aspect ratio (for constant channel width), while it decreased with increasing of aspect ratio (for constant hydraulic diameter) [117].

Gobby and Angeli [118] reported that, as aspect ratio increases the effect of the horizontal wall shear decreases, which leads to symmetrical velocity profiles achieved closer to the enters of center channel and hence better mixing. A few investigations have been done on the effect of mixing channel length on mixing quality [104, 120]. Engler *et al.* [104] have found that, reducing channel length lead to increasing energy dissipation and therefore decreasing the mixing time. So mixers with small channel dimensions seem to have a better mixing performance. Bothe [120] reported that, to exploit the stirring effect of the secondary flow, the length of mixing channel should be at least about ten times larger than its hydraulic diameter. Mengeaud *et al.* [121] fabricated zig-zag microchannel with a width of $100 \text{ } \mu\text{m}$, a depth of $48 \text{ } \mu\text{m}$ and a length of 2 mm . A critical Re of ~ 80 was reported. Below a

critical Re , the flow profile remains parabolic and the mixing, only ensured by molecular diffusion, is strongly dependent on the effective length and width of the channel.

Mansur *et al.* [122] numerically reported that, splitting the inlet streams into n substreams lead to increase the contact surface between the two fluids causing diffusion to occur faster. As can be seen in Figs. 18 and 19, it is clearly demonstrates that the number of effective contact areas between the two sample fluids increases from 1 to 3 for the T-shape mixer and double-T-shaped micromixer. As a result, it is obvious that the contact area of the sample flow plays an important role in the mixing performance such that the double-T-shaped micromixer provides the best mixing efficiency more than the T-shaped micromixer.

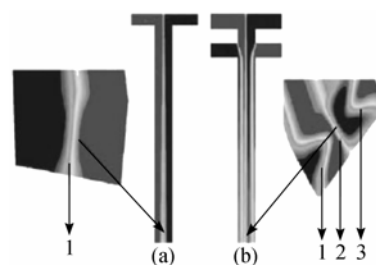


Figure 18 Number of effective contact areas between the two sample fluids: (a) T-shaped microfluidic mixer, and (b) double-T-shaped microfluidic mixer [122]

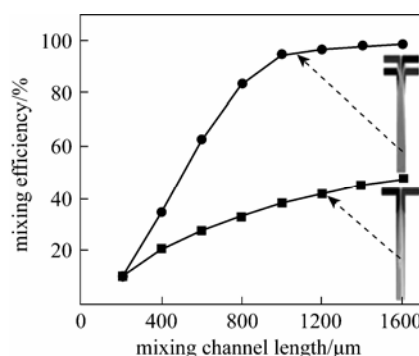


Figure 19 Mixing efficiency over the length of mixing channel [122]

■ T-shaped mixer; ● double-T-shaped mixer

6.3 Effect of external energy

As it is mentioned in the above sections, mixing can also be accomplished by the action of fluctuating

electric fields that causes the two fluids to stretch and fold rapidly thus increasing mixing efficiency. Chen *et al.* [123] presented preliminary experiments and detailed stability analyses using depth-averaged linearized equations for the study of convective instability in the T-shaped intersection of two microchannel flow streams. In those experiments, they visualized coherent wavelike disturbances that were convected downstream with the electro-osmotic flow. They also showed that the flow became absolutely unstable at applied fields in excess of the critical applied field required for onset of instability.

Moctar *et al.* [124] found experimentally that the application of an electric field creates a strong force perpendicular to the interface, causing the two fluids to intermingle and therefore enhancing mixing between the two fluids (Fig. 20). As can be seen in Fig. 20, it is clearly that the fluids in case (b) are somewhat mixed with a remaining dark green layer in the upper part of the channel, and well mixed in case (c) when electric field of intensity of 4×10^5 and 6×10^5 $\text{V} \cdot \text{m}^{-1}$ is applied respectively. Mixing thus improves with increasing potential difference, and therefore with increasing electric field strength.

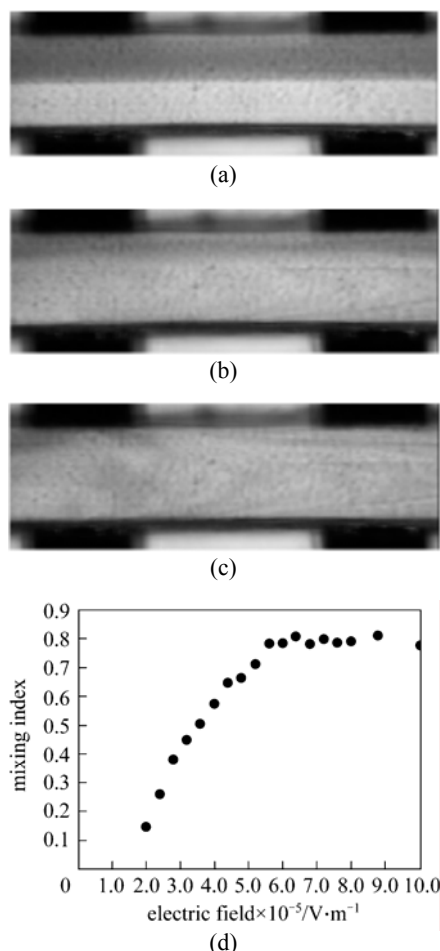


Figure 20 The effect of applied electrical field on performance of T-micromixer: (a) initial condition; (b) after the application of an electric field of intensity $E = 4 \times 10^5$ $\text{V} \cdot \text{m}^{-1}$; (c) same as (b) with an electric field intensity of $E = 6 \times 10^5$ $\text{V} \cdot \text{m}^{-1}$ and (d) variation of the mixing index with the intensity of the DC electric field [124]

Recently, Fu and Tsai [125] proposed a method in which interlaced injection samples, controlled electric field strengths, and periodically time-pulsed switching techniques are used together in order to increase the contact area and contact time of the samples and to produce perturbations of the fluid field (Fig. 21). They reported that, the pullback effect enhances the mixing ratio, and that the interactive frequency and main electric field dominate the mixing phenomenon for specified ranges of pullback electric field intensity.

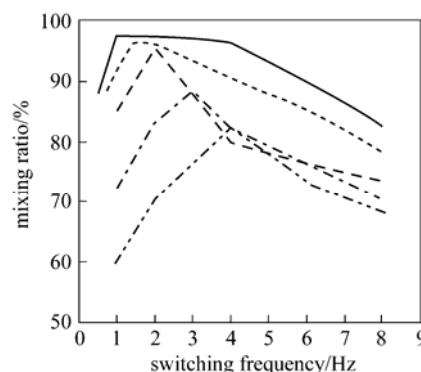


Figure 21 Mixing ratio for different driving electric fields and switching frequencies at cross section located 1000 mm downstream from the secondary T-junction [125]
electric field/ $\text{V} \cdot \text{cm}^{-1}$: — 50; - - - 75; - · - · 100; - · - · 125; - · - · 150

For the proposed active-double-T-shaped micromixer, the mixing ratio can be as high as 95% within a mixing length of 1000 mm downstream from the secondary T-junction when $50 \text{ V} \cdot \text{cm}^{-1}$ driving electric field strength and a 2 Hz periodic switching frequency are applied.

7 FUTURE TOPICS

The development of microfluidic systems has been progressing rapidly in recent years. Nevertheless, microfluidics is still considered a very young field of research and it would take some time before more products like these appear in the commercial markets. Micromixers are the essential components in integrated microfluidic systems involved in the sample preparation stage of a chemical analysis prior to certain chemical or biological reactions taking place. The mixing principles applied can be divided in two classes relying either on the pumping energy or provision of other external energy to achieve mixing, termed passive and active mixing, respectively. As far as passive mixing is concerned, devices and techniques such as T-type flow-, multi-laminating-, split-and-recombine-, chaotic-, recirculation flow-mixers and others are discussed. Active mixing can be accomplished by time-pulsing flow owing to a periodical change of pumping energy or electrical fields, acoustic fluid shaking, ultrasound, electrowetting-based droplet shaking, microstirrers, and others. Although it is very difficult to attain turbulent flow in microchannels, but rapid mixing is still possible by the generation of secondary flow, swirling flow and vortices

in the microchannels. The presence of addition parts such as a sharp bend, slanted wall, or a junction, as well as asymmetrical flow conditions at the inlets of microchannels results in enhancing mixing performance.

Generally, a closer look at the flow phenomena in microfluidic systems is still missing; mixing within microfluidic system is still an actual object of research and investigation. As far as we can judge from the present review, distinguish between the flows phenomena in macro- and microfluidic system has not yet been addressed in a sufficient way, more work is needed in this field.

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