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Introduction: mixing in microfluidics

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In this paper we briefly review the main issues associated with mixing at the microscale and introduce the papers comprising the Theme Issue.

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1. Introduction

Microfluidics is the term that is used to describe flow in devices having dimensions ranging from millimetres to micrometres and capable of handling volumes of fluid in the range of nano- to microlitres (10^{-9}–10^{-6} l). In the last few years there has been an explosion of work in this area. There are several reasons for this interest. One aspect is the confluence of technologies, for example, microfluidics and micro-electrical mechanical systems (MEMS); another is the number of fields that share an interest in this area: analytical chemistry, high-throughput synthesis, microbiological analysis systems and the many applications that come with portability and field use of the 'lab-on-a-chip' concept. The market for such devices was $400M in 2000 and it is expected to increase by a factor of five by 2005 (Stone & Kim 2001). As may be expected, there is now a considerable amount of literature on various aspects of microfluidics spread over many sub-areas: microfabrication techniques, new designs, interface with MEMS technologies, basic fluid mechanical aspects, etc.

The papers in this issue focus on one aspect of this vast landscape: mixing. The objective of this introduction is to provide a qualitative setting for the rest of the papers. For precise definitions of the terminology used here we encourage the reader to consult the paper 'Foundations of chaotic mixing' that appears in this issue (Wiggins & Ottino 2004).

The key aspect about microfluidics is smallness. And smallness brings new elements which are not only quantitative, but also qualitative. The role of interfaces becomes dominant. In solid–fluid interfaces, wettability and charge density can be exploited in various ways; in the case of liquid–liquid or liquid–gas interfaces, gradients of interfacial tension can have large effects. For example, Fair's group at Duke University (see Paik *et al*. 2003) has focused on the use of electrowetting, a phenomenon whereby an electric field can be used to alter the wetting behaviour of a droplet in contact

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with an insulated electrode. If an electric field is applied non-uniformly, then a surface energy gradient is created which can then be used to manipulate a droplet sandwiched between two plates. Electrowetting arrays allow large numbers of droplets to be independently manipulated.

Much of the basic science involved in these developments has already been established. What is important, however, is the possibility of the invention of new designs by the exploitation of boundary conditions that are simply ineffective at larger scales.

2. The role of mixing

Mixing (or lack thereof) is often crucial to the effective functioning of microfluidic devices (Knight 2002). Often the objective is rapid mixing between two initially segregated streams: rapid interspersion in a minimal amount of space. At other times, however, the objective is to prevent mixing and maintain segregation, for example, having two streams co-flowing side by side and controlling or monitoring processes occurring at the interface between the two fluids. There are excellent reviews of general aspects of microfluidics and mixing is covered to various degrees in several of them (see, for example, Stone *et al*. 2004; Stroock & Whitesides 2003). However, there appears to be no review wholly devoted to mixing: how to enhance, how to control it, or simply how to benefit from existing theory.

Consider two different examples of mixing. The *first* example is about producing mixing by molecular diffusion alone, by reducing length-scales so that molecular diffusion controls the mixing (we note here that the term *mixing* in the mathematics literature can be defined in the *absence* of molecular diffusion (see Wiggins & Ottino 2004)). The objective in this example is to capture protein folding, the process by which proteins assume their unique three-dimensional shapes. Folding takes place quickly, in time-scales of the order of 10^{-4} s. A way to follow its evolution is by controlling the environment surrounding the proteins and being able to make a quick change of solvent, thus facilitating or hindering folding. One way to change the solvent environment surrounding the protein this is by using a fluid jet that quickly becomes pinched down to a radius of tens of nanometres (Knight *et al*. 1998); in this case molecular diffusion takes place in the order of 10^{-7}–10^{-5} s, depending on the value of the coefficient of molecular diffusion.

The *second* example is more classical and involves interspersing two streams (as in the rapid mixing of macromolecular solutions for chip-based molecular diagnostics) as in the case of biochemical sensing techniques such as immunoassays and hybridization analyses, which require the rapid, homogeneous mixing of macromolecular solutions, such as DNA or globular proteins. As we shall see, mixing by molecular diffusion of macromolecular solutions may take considerable time, of the order of tens of minutes. Clearly, one has to find suitable ways to mix fluid streams in small-scale geometries in acceptable time-scales.

3. Length- and time-scales

In order to frame the discussion consider a flow in a channel of length L along the z-direction having a cross-sectional area in the (xy)-plane with a characteristic dimension h. The velocity in the z-direction is denoted $v_z(x, y)$ with mean value U. Typical numbers in microfluidic applications are $h \sim 200\,\mu\text{m}$, $\mu/\rho \sim 10^{-5}\,\text{cm}^2\,\text{s}^{-1}$,

$U \sim 1\ \mathrm{cm\,s^{-1}}$. This implies a Reynolds number $\rho Uh/\mu \approx 2$. Thus, flows in microfluidic channels are typically viscous-dominated, velocity profiles have parabolic shapes, and lubrication theory is a useful design tool. Molecular diffusion coefficients, D, range between $10^{-5}\ \mathrm{cm^2\,s^{-1}}$ at the high end (small molecule) to $10^{-7}\ \mathrm{cm^2\,s^{-1}}$ at the low end (typical of large molecule; e.g. haemoglobin in water corresponds to $0.7 \times 10^{-7}\ \mathrm{cm^2\,s^{-1}}$). Thus, the typical values of convective to diffusional time-scales, quantified in terms of the Péclet number, Uh/D, range between 10^1 and 10^5, indicating that convection is much faster than molecular diffusion. Thus, in spite of the small dimensions, molecular diffusion may not be counted on to homogenize the system to molecular scales in a reasonable amount of time. The diffusional time-scales for diffusing half of the width of the channel, $t_{\mathrm{D}} \sim h^2/D$, range from *ca.* 10 s, for a molecule with $D \sim 10^{-5}\ \mathrm{cm^2\,s^{-1}}$, to *ca.* 16 min when $D \sim 10^{-7}\ \mathrm{cm^2\,s^{-1}}$. Thus, if one has two miscible fluid streams flowing side by side, the penetration distance, $\delta_x \sim (Dt)^{1/2}$, occupies the entire width of the channel after a distance Ut_{D}. These values may range from 10 to 960 cm, depending on the values of D considered above.

Three related observations are important. First, as we have seen, to reach $\delta_x = h$ by relying solely on molecular diffusion takes a time h^2/D. So if the streams move with speed U, this process requires a distance $U(h^2/D)$ or $L\,h^{-1} \sim Pe$. Given the typical values of Pe, this may be unacceptably high.

The second observation is that, as diffusion takes place in the cross-section of the channel ((xy)-plane), particles experience a range of velocities (recall that the flow is parabolic), resulting in concentration dispersion in the z-direction and in a dispersion coefficient (Taylor dispersion) that scales as $1/D$.

The third and final observation is also a consequence of the parabolic nature of the velocity field. Near the wall the velocity field is linear with distance and thus a particle a distance d away from the wall takes a time $L\dot{\gamma}/d$ to reach L. Particles near the wall (as $d \to 0$) take a long time to exit, giving long tails in the residence time distribution (RTD). Moreover, the fluid near the wall never co-mingles with fluid elements in the centre of the channel; mixing is poor.

It is then clear that the key to effective mixing lies in our ability to mix material in the cross-section, i.e. to create a large amount of contact interface between the two fluids. Material 'sticking' to walls is bad for mixing. Two advantages come with enhanced mixing. The first is that, if particles explore all (xy)-space in a random manner, they will experience all velocities (slow near the walls, fast near the centreline) and on the whole the broadening of the RTD is reduced. The second advantage has to with transfer processes between the surface of the device and the bulk of the fluid. If mixing is effective, diffusional processes are greatly accelerated; material that is near the wall goes into the bulk and vice versa, thereby eliminating a slowdown due to diminishing concentration gradients.

4. Stretching and folding: chaotic mixing

It may be useful at this point to give a succinct review of the main elements of mixing and how it interfaces with mixing in microfluidic devices, and to present a few useful scaling-based relations. For simplicity we will consider mixing in a channel-like device: a duct flow. Duct flows are defined by the velocity field

$$v_x = \frac{\partial \psi}{\partial y}, \qquad v_y = -\frac{\partial \psi}{\partial x}, \qquad v_z = f(x, y). \tag{4.1}$$

That is, in a duct flow, a two-dimensional cross-sectional flow is augmented by a unidirectional axial flow. Note that in a duct flow the cross-sectional and axial flows are independent of both time and distance along the duct axis.

The objective of mixing is to produce the maximum amount of interfacial area between two initially segregated fluids in the minimum amount of time or using the least amount of energy. Creation of interfacial area is connected to stretching of lines in two dimensions and the surface in three dimensions. A fluid element of length $\delta(0)$ at time zero has length $\delta(t)$ at time t; the length stretch is defined as $\lambda = \delta(t)/\delta(0)$; if mixing is effective, λ increases nearly everywhere, though there can be regions of compression where $\lambda < 1$. In simple shear flow, the fastest rate of stretching, $\mathrm{d}\lambda/\mathrm{d}t$, corresponds to the instant when the element passes through the 45° orientation corresponding to the maximum direction of stretching in shear flow; for long times the stretching is linear ($\lambda \sim t$) in time as the element becomes aligned with the streamlines. In an elongational flow the rate of stretching is exponential, $\lambda \sim \mathrm{e}^t$. The distance between striations is inversely proportional to the surface area: the thinner the striations, the faster the diffusion. Note that the effects of stretching on accelerating interdiffusion enter in two different ways: a greater interfacial area means a greater area for transfer; at the same time, diminishing striation thicknesses increase the concentration gradients and increase the mass flux.

In order to conceptualize the growth of the interfacial area (or perimeter in the case of two dimensions), we can imagine small elements, areas or lines. If mixing is effective, the small elements grow in area or length (ideally, this happens everywhere in the flow; in practice, same elements may get compressed). It is apparent that the striation thickness and stretching are related in a fundamental way to dynamical systems concepts: entropy, finite-size Lyapunov exponents, and the Baker transformation. For a more complete coverage the reader should consult Ottino (1989), Aref (1991) and Wiggins & Ottino (2004).

The key to effective mixing lies in producing stretching and folding; stretching and folding may be roughly equated with chaos (see Wiggins & Ottino 2004). The simplest case corresponds to two dimensions. If the velocity field is steady, the mixing is poor and stretching for long times is linear, as in the case of a simple shear flow; i.e. the stretching *rate* of line elements decays as $1/t$ (we are restricting ourselves to bounded flows, that is were excluding elongational flows here). It is relatively straightforward to produce flow fields that can generate stretching and folding and hence chaos. In fact the most important lesson that should be learned about kinematics and mixing is encapsulated by the *link twist maps* (LTMs; see Wiggins & Ottino 2004). In rough terms, a necessary condition for chaos is the 'crossing' of streamlines (this must occur at different times). That is, two successive streamline portraits, say at t and $t + \Delta t$ for time-periodic two-dimensional flows, or at z and $z + \Delta z$ for spatially periodic flows, when superimposed, should show intersecting streamlines when projected onto the (x, y)-plane. In two-dimensional systems this can be achieved by time modulation of the flow field, for example, by motions of boundaries or time periodic changes in geometry.

Numerous experimental studies have revealed the structure of chaotic flows. Dye structures of passive tracers placed in time-periodic chaotic flows evolve in an iterative fashion; an entire structure is mapped into a new structure with persistent large-scale features, but finer and finer scale features are revealed at each period of the flow. After a few periods, strategically placed blobs of passive tracer reveal patterns that serve as templates for subsequent stretching and folding. Repeated action by the flow generates a lamellar structure consisting of stretched and folded striations, with thicknesses $s(t)$, characterized by a probability density function, $f(s,t)$, whose mean, on the average, decreases with time. The striated pattern quickly develops into a time-evolving complex morphology of poorly mixed regions of fluid (islands) and of well-mixed or chaotic regions. Islands translate, stretch and contract periodically and undergo a net rotation, preserving their identity returning to their original locations. Stretching within islands, on the average, grows linearly and much slower than in chaotic regions, in which the stretching increases exponentially with time. Moreover, since islands do not exchange matter with the rest of the fluid (in the absence of diffusion) they represent an obstacle to efficient mixing.

Duct flows, like steady two-dimensional flows, are poor mixers. They can be converted into efficient mixing flows (i.e. flows with an exponential stretch of material lines with time) by time modulation or by spatial changes along the duct axis (see Ottino 1989; Wiggins & Ottino 2004). One example of the spatially periodic class is the classical partitioned-pipe mixer (PPM). This flow consists of a pipe partitioned by a sequence of n orthogonally placed rectangular plates. The cross-sectional motion is induced through rotation of the pipe with respect to the assembly of plates, whereas the axial flow is caused by a pressure gradient. There is one control parameter in the system: the ratio of cross-sectional twist to mean axial flow, β (Khakhar *et al*. 1987; Kusch & Ottino 1992). The flow is regular for no cross-sectional twist ($\beta = 0$) and becomes chaotic with increasing values of β.

Consider now a few typical numbers. Consider a striation thickness reduction, or equivalently a length stretch, where the initial length-scale $s(0) \sim h$ is reduced to a size $s(t_{\mathrm{F}})$ in an amount of time t_{F}. According to the typical numbers given earlier we take the typical shear rates in our device to be $\lambda_{0,m} = \lambda_{0,1}\lambda_{1,2}\lambda_{2,3}\cdots\lambda_{m-1,m} = U/(h/2) \sim 10^2\ \mathrm{s}^{-1}$. Consider a typical striation thickness reduction $s(0)/s(t_{\mathrm{F}})$ or length stretch $\lambda \sim 10^4$, that is, a reduction from 10^2 to $10^{-2}\ \mu\mathrm{m}$, or 10 nm. At 10 nm, molecular diffusion is fast at these scales: 10^{-7} s for $D = 10^{-5}\ \mathrm{cm}^2\ \mathrm{s}^{-1}$, to 10^{-5} s for $D = 10^{-7}\ \mathrm{cm}^2\ \mathrm{s}^{-1}$.

How long does it take to accomplish this striation thickness reduction? In simple shear, we have that $s(0)/s(t_{\mathrm{F}}) \sim \dot{\gamma}t_{\mathrm{F}}$. Therefore, the time needed to accomplish this reduction is $10^4/10^2\ \mathrm{s}^{-1} = 10^2$ s. An elongational flow, on the other hand, can accomplish the same reduction with a much lower value of elongational rate compared with $\dot{\gamma}$. In this case $s(0)/s(t_{\mathrm{F}}) = \exp(\alpha t_{\mathrm{F}})$. Thus $\alpha = \ln(10^4)/100\ \mathrm{s} = 4 \times 10^{-2}\ \mathrm{s}^{-1}$. Elongational flows are not practical; however, a succession of simple shear flows with a periodic reorientation of the line elements accomplishes the same objective.

5. Reorientation

Consider now a length stretch of 10 per cycle. Clearly, we need four cycles of 25 s. For each cycle we have

$$\dot{\gamma} = \left[\frac{s(0)}{s(t_{\mathrm{F}})}\right]\frac{4}{(t_{\mathrm{F}})} = 25\ \mathrm{s}^{-1}.$$

Many chaotic flows may be imagined as a sequence of shear-like flows with time-periodic random reorientations of material elements relative to the flow streamlines. In all cases, the effect of the reorientation is an exponential stretching of material elements; in the example above, the stretching goes as $s(0)/s(t_{\mathrm{F}}) \sim 10^n$, where n is the number of reorientations. The interval between two successive reorientations is an important parameter of such systems. In general there is an optimum interval such that the total length stretch is maximum for a fixed time of mixing: in the limit of very small periods, material elements are stretched and compressed at random, and hence the average length stretch is small (and there is an unnecessarily large amount of energy expenditure); in the limit of very large time periods, the flow approaches a steady shear flow and again the length stretch is small. The maximum in the average stretching efficiency for simple shear flows and vortical flows corresponds when the strain per period is between 4 and 5 (Ottino 1989). Similar results are obtained when there is a distribution of shear rates.

The discussion so far has been in terms of average striation thickness; in practice there is a distribution (Muzzio *et al.* 1991). Computational studies indicate that within chaotic regions the distribution of stretches becomes self-similar, achieving a scaling limit, and approaches a lognormal distribution at large n. A rough argument is as follows. Let $\lambda_{n,n+1}$ denote the length stretch experienced by a fluid element between periods n and $n+1$. The total stretching after m periods of the flow, $\lambda_{0,m}$, can be written as the product of the stretchings from each individual period:

$$\lambda_{0,m} = \lambda_{0,1}\lambda_{1,2}\cdots\lambda_{m-1,m}. \tag{5.1}$$

The stretchings between successive periods (i.e. $\lambda_{1,2}$ and $\lambda_{2,3}$) are strongly correlated. However, the correlation in stretching between non-consecutive periods (e.g. $\lambda_{0,1}$ and $\lambda_{4,5}$) grows weaker as the separation between periods increases due to chaos (the presence of islands in the flow complicates the picture). Thus, $\lambda_{0,m}$ is essentially the product of random numbers and

$$\log\lambda_{0,m} = \log\lambda_{0,1} + \log\lambda_{1,2} + \cdots + \log\lambda_{m-1,m} \tag{5.2}$$

is a sum of random numbers. According to the central limit theorem, any collection of sums of random numbers will converge to a Gaussian. Therefore, the distribution of $\lambda_{0,m}$ is lognormal.

6. Diffusion and scaling

With the above caveats, we consider now the role of molecular diffusion. Consider molecular diffusion across a thinning striation with striation thickness $s(t)$ as it is followed in a Lagrangian sense along a mixer (the arguments are similar to those in Ottino (1994); we correct a couple of typographical errors in the original paper). The initial thickness, $s(0) \sim h$, is thinned down according to a stretching function $\alpha(t)$ according to $\mathrm{d}\ln(s(t))/\mathrm{d}t = -\alpha(t)$. The stretching function is bounded by the shear rate; in chaotic flow the time average of α is positive; in two-dimensional flows or duct flows it decays as $1/t$. As a rule of thumb, the value of α is typically an order of magnitude smaller than the typical shear rate, U/h.

In the frame of the striations the diffusion process is described by

$$\frac{\partial c}{\partial\tau} = \frac{\partial^2 c}{\partial\xi^2}, \tag{6.1}$$

where c is the concentration, ξ is a striation-thickness-based space, and τ is the so-called warped time, defined as

$$\xi = \frac{x}{s(t)} \tag{6.2}$$

and

$$\tau = \int_0^t \frac{D}{(s(t'))^2}\,\mathrm{d}t'. \tag{6.3}$$

The penetration distance in the (ξ, τ)-space is given by $\delta\xi \sim \tau^{1/2}$ and therefore in terms of x, t variables we have

$$\frac{\delta_x}{s(0)\mathrm{e}^{-\alpha t}} = \left[\frac{D}{(s(0))^2 2\alpha}(\mathrm{e}^{2\alpha t} - 1)\right]^{1/2}. \tag{6.4}$$

Thus, for long times, the penetration distance stabilizes to $\delta_x \sim (D/\alpha)^{1/2}$. This time may not be reached in practice, however, as striations fuse together due to molecular diffusion. One can argue that the mixing is complete when $\delta_x = s_{\mathrm{F}}$, the penetration distance growth catches up with the thinning striations after a time t_{F}.

This happens when

$$1 = \left[\frac{D}{(s(0))^2 2\alpha}(\mathrm{e}^{2\alpha t} - 1)\right]^{1/2}. \tag{6.5}$$

The value of α can be estimated as the inverse of shear rate, i.e. $\alpha \sim U/h$. Therefore $Pe \sim \alpha h^2/D$. Therefore, if $\exp(2\alpha t_{\mathrm{F}}) \gg 1$, the necessary length for mixing scales as

$$\frac{L}{h} \sim \ln Pe. \tag{6.6}$$

Clearly, this is much more efficient than the $L/h \sim Pe$ relationship uncovered earlier.

7. Papers in this Theme Issue

A classification of possible micromixing devices quickly reveals the need for a multi-dimensional matrix and we will not attempt such a categorization here. (Moreover, it is likely that the classification may need to be revised in light of a yet-to-be-invented device.) Suffice it to say that the type of device dictates the precise level of detail of the mixing theory needed: a two-dimensional device requires different levels of theoretical tools than a fully three-dimensional device, and mixing with chemical reactions brings yet other elements to the picture (Ottino *et al.* 1979). However, as we argue in Wiggins & Ottino (2004), a two-dimensional description is a very useful starting point, for example, it is a picture which is key for the understanding of duct flows.

A possible classification may or or may not involve a reliance on inertia. As we have seen the answer is typically not, although there are instances where this can be exploited (Shelby *et al.* 2003), and Stremler *et al.* (2004) focus on this case. It also matters if the system is single phase or multiphase, and in the case of manipulation of droplets (Bringer *et al.* 2004), etc. Possibly the most useful classification from the point of operability is in terms of the number of *independent control parameters*. In the simplest possible case the only control parameter is the flow rate Q. If mixing relies on inertia, setting Q sets the level of mixing: Q sets *Re*, and *Re* sets secondary flows, for example, in the case of a twisted channel (Jones *et al.* 1989). On the other hand, if *Re* is small, this means that the *performance of the device is independent* of Q; the typical case here is a static mixer; the end result (though not the throughput) is the same no matter what the value of Q (Stroock *et al.* 2004). Mixing depends on the geometry of the device. However, once the device is built, the mixing is set. Thus, a control parameter in a duct-like flow must be a parameter other than Q. The herringbone mixer of Stroock *et al.* (2002) has no independent control parameter. The mixers by Tabeling *et al.* (2004) and Bottausci *et al.* (2004) have two control parameters: an amplitude and a frequency of pressure gradients producing cross-flows (the system of Bottausci *et al.* in fact has three pairs). Examples of other control parameters include speed of moving parts (impellers and so on), frequency of time-dependent electric fields. All these devices allow for optimization without changing the device itself.

Wiggins & Ottino (2004) review elements of the necessary theory and definition of terminology in a mathematically rigorous way. They present a basic representation of mixing applicable to two-dimensional blinking flows, and with proper caveats, to duct flows. This does not mean that all necessary theory has already been developed, and it is clear that further mathematical developments are needed; in fact we outline a few steps that should be taken to complete the description. It is fair to say, however, that the field would benefit by closer convergence of applications and theory.

Ordering papers is always somewhat artificial. Stroock *et al.* (2004) analyse the mixing in the three-dimensional staggered herringbone mixer, which they have introduced in an earlier publication. The cross-section is modelled in terms of a Stokes flow, with the flow mimicked in terms of a lid-driven cavity flow. The model reproduces well the advection patterns in previous experimental work (Stroock *et al.* 2002). Poincaré maps, simulation of the mixing between two initially segregated streams and resident time distributions and a range of optimal geometries are identified.

Tabeling *et al.* (2004) consider mixing in a cross-channel intersection—a mean stream is perturbed by an oscillatory flow driven by an external source. Experiments and computations are presented. Depending on the parameters, stretching and folding is possible. Depending on the amplitude and frequency of oscillatory flow, one obtains a rich array of wavy and chaotic-like regimes.

Bottausci *et al.* (2004) go one step further and present a design with even more built-in flexibility from an operational viewpoint. Mixing occurs in a rectangular channel, and three cross-stream secondary channels provide the possibilityof time-dependent actuation of the primary flow stream. Besides the frequency and amplitudes of the cross-channel flow, the spacing between the channels is also important. Bottausci *et al.* present three-dimensional computations, experiments and theory, and examine issues such as optimization and the Taylor dispersion characteristics of the device.

The two examples in Stremler *et al.* (2004) move us outside the duct flow paradigm. The first example is a pulsed source-sink chamber: mixing of two fluids in a thin chamber having a depth that is much smaller than either the width or length. This particular system can be viewed as a Hele-Shaw potential flow (a flow where viscosity plays no role) and significant modelling is possible. The second device is a serpentine channel inspired in the design of Liu *et al.* (2000) and is the only device mentioned in the issue which relies on inertial effects. For $Re \sim 1$, mixing is poor, but for $Re \sim O(10)$ mixing is excellent.

Modulation of surface stresses can also used to manipulate free surface flows. Techniques based on electrical or thermally generated stresses have been used to transport, split or mix narrow continuous films and discrete droplets along the surface of a solid substrate. Under these conditions, the flow field is directly coupled to the shape of the liquid surface, leading to some interesting mixing regimes. Darhuber *et al*. (2004) investigate convective and diffusive mixing in narrow rivulets propelled by thermocapillary forces on chemically micropatterned surfaces. Theoretical, numerical and experimental studies are used to extract optimal operating conditions for a working device based on thermocapillary actuation. Micromixing analogues of purely diffusive dynamics, Rhines–Young shear-augmented diffusion and Taylor–Aris dispersion are identified for appropriate parameter ranges.

The next two papers exploit moving parts. Mensing *et al*. (2004) present an inexpensive and easy to fabricate active magnetic mixer using a liquid-phase photopolymerization technique. The device functions on top of a common magnetic stir-plate device can mix up to a rate of $10\,\mathrm{ml\,min^{-1}}$. Campbell & Grybowski (2004) go one step further on the concept of impeller-driven mixing: letting the mixer assemble itself. In this device, an external rotating magnetic field causes uniformly suspended iron elements to dynamically self-assemble inside a microfluidic channel. The self-assembly is due to two opposing effects. Particles spin due to the application of a rotating magnetic field. The magnetic field makes the particles move towards each other; however, when the particles get close, hydrodynamic forces become repulsive. This results in a competition between the attractive and repulsive effects and the particles arrange in patterns which can be used to efficiently mix the fluids driven through the microfluidic system. Campbell & Grybowski speculate on the possible role of self-assembly in microfluidic devices.

Bringer *et al*. (2004) cleverly induce mixing within droplets, thus making a droplet act like a tiny chemical reactor. The mixing is produced by inducing a three-dimensional time-periodic flow within the drop as it sneaks though a sequence of straight and curvy channels. Many experimental aspects are considered: channel widths, flow velocities and diffusion. It is argued that the twists and turns generate chaotic advection within the droplet and it is very likely that this is the case. The flow within droplets has been studied by a handful of investigators (Bajer & Moffatt 1990; Stone *et al*. 1991); the flow is topologically equivalent to that within the 'fundamental mixing tank' studied experimentally by Fountain *et al*. (1998). The angle of the impeller would vary depending on the curvature of the channel. In this analogy, when the drop goes though a straight channel the flow is axisymmetric and mixing is regular. However, if the channel is curved, the symmetry is broken and mixing becomes chaotic.

All previous papers focus on the mixing aspect of the microfluidic device. Ugaz *et al*. (2004) is the only paper in this issue that focuses on lab-on-a-chip applications. They review recent efforts in the area of microfabricated electrophoresis devices to conduct size-selective fractionation of DNA fragments capable of being used in field locations in variety of medical and sensing applications. They suggest that high-resolution separations over the distance of a few cm or less are indeed possible using inexpensive portable genomic equipment.

8. Remaining issues: the interplay between science and technology

Clearly, there are several subjects connected with mixing which remain untouched by the papers in this issue and it is impossible for us to make thoughtful comments about all of them. Many people, for example, have focused on the role on slip boundary conditions. However, in the context of mixing, except in special circumstances, no slip is an excellent approximation (Stone *et al*. 2004). Other problems have received relatively little attention. One worth mentioning, since it connects with fabrication issues and the presence of corners, is the presence of Moffatt eddies (Moffatt 1964). Flows in these regions are, generally speaking, $O(10^2)$ times weaker than the primary flows and for all practical purposes do not contribute to mixing. Material within Moffatt eddies is, for all practical purposes, stagnant. More generally, we should mention also Stokes separated flows as they occur in cavities (see Horner *et al*. 2002), as they may be exploited in microfluidic applications (Shelby *et al*. 2003).

Finally, another problem that should be taken into account has to do with the near-inevitable presence of unmixed regions in the cross-sectional section of the system. It is theoretically possible to design a system with no islands (Wiggins & Ottino 2004); however, one has to be prepared for this eventuality. This is particularly important in systems where there is no external control parameter—designs whose performance depends solely on the geometry of the device. For example, the mixing elements may consist of right-handed (R) and left-handed (L) helices or, in the herringbone mixer, it could whether the channel zigzags to the right or to the left. Thus, in all spatially periodic mixers we have a sequence of R-L-R-L-R, and so on, each 'L' followed by an 'R'. This can clearly work, but, it should be remembered that, if there are unmixed regions and tubes, having more elements will not make them go away. In this case, breaking the sequence, for example, R-L-R-R-L-R, may improve the mixing. This is the basic idea behind a systematic destruction of symmetries to improve mixing (Franjione & Ottino 1992).

What is possible today? It is now possible to compute, using standard fluid-dynamics codes, precise maps of striation-thickness distributions over the cross-section of static mixers and to capture unmixed islands (Galaktionov *et al*. 2003; van der Hoeven *et al*. 2001; Zalc *et al*. 2003). And this is not only at low but also at finite Reynolds numbers. A quick examination of these devices, developed in the context of polymer processing, reveals that some of the designs (for example, geometries to produce multiple layers) are essentially identical to some microfluidic devices proposed in the literature.

However, before resorting to detailed computations it is worth mentioning a couple of issues, which may often be crucial. Implicitly, in everything mentioned above, inlet conditions are assumed implicitly to be *steady*. However, this may not be the case. One reason is the surprisingly long start times due to compressibility (Stone *et al*. 2004). Another may be due to the metering devices themselves. This is particularly important in the case of systems involving chemical reactions. This is a case where, no matter how good the cross-sectional mixing, the mixing will be poor. This is because the narrow RTD, due to good cross-sectional mixing, precludes what in classical mixing terminology is called 'backmixing'; the material entering at t will not be intermingled with material entering at $t + T$. There are remedies though. However, these may require the used of additional devices, some of which may be difficult to build using microfluidic techniques (Nauman *et al*. 2002).

Microfluidics is a beautiful interplay between basic knowledge and technology. Basic knowledge suggests concepts for possible designs that, if realized, may led to systems of technological importance and in turn produce new developments in science—many microfluidic devices are in fact scientific instruments. However, the fact that something can be imagined does not mean that it can be built and, even if it could, manufacturing dictates that this should be done inexpensively. The goal is to find ideas that are realizable. Surface patterning, a wall with small grooves oriented at oblique angles with respect to the axis of the main flow (e.g. Stroock *et al.* 2002), suggests several other possible designs (see Wiggins & Ottino 2004), and some of these may be possible with conventional planar fabrication techniques. Surface charge, having bands of positive and negative charge density in order to generate electro-osmotic flows (EOFs), suggests other designs and there are undoubtedly many other possibilities (Oddy *et al.* 2001). However, there may be technological issues to do with the reliability of possible mechanisms. In fact, this is what at the moment seems to limit devices based on EOF effects. Finally, some designs may be attractive but not technologically feasible. For example, planar fabrication techniques cannot produce the geometric patterns in static mixer design. Other techniques may be possible, for example, Bertsch *et al.* (2001) built replicas of large-scale industrial mixers using a micro-stereolithography process. Currently the dimensions of the objects are large for microfluidic applications (O(mm)). Limitations are due to available materials. Bertsch *et al.* use an acrylate-based resin, which has the same mechanical characteristics as the acrylate-based plastics used in the rapid prototyping field. However, it is only a matter of time before new materials emerge.

It may be argued that the science base for microfluidics is already largely developed and what remains is technological development. There is no question that this is a technological area dominated by ingenuity; exploitation of clever mechanisms and sophisticated and inventive device developments may be expected in the near future. What may not be apparent is that the room for creativity is enormously broad; design is an inherently divergent activity. The scientific building blocks may now be established but the possible combinations are enormous. And with new designs there is a need to devise new techniques to analyse the systems and so on. It is, however, clear that designs are often led by fabrication techniques and that this group may be fairly removed from developments taking place in the physics, mathematics and fluid mechanics literature, where most of the frontier developments about analysis take place. It is our belief that an examination of this literature may lead to new insights and, quite possibly, the avoidance of re-discovery.

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