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Editorial

Microfluidic mixing and separation

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It is with great pleasure we reflect on the strong interest and large number of high-quality papers in this focus issue on microfluidic mixing and separation. These two interlinked research fields have witnessed rapid development and significant advances in the past decade.

A wide range of mixing and separation methods are presented, including the use of gas bubbles, ultrasonics, dielectrophoresis and hydrodynamics. The use of micro-scale devices for separation of particles and cells has a number of important applications, particularly for medical research. We are delighted to present a number of innovative pieces of research in this area. Some (but not all) of these interesting and original pieces of work, which present many aspects of microfluidic mixing and separation, are highlighted below.

Many of the papers are on active mixing, for example that of Workamp, Saggiomo and Dijksman, whoshow an efficient use of a mixing chamber with 30–40% of glass microbeads and a small magnetic stirrer, allowing for efficient mixing at a low pressure drop. Brandhoff *et al* present an ultrasonic streaming mixer for an integrated magnetic bead ELISA, proving both efficient mixing of the beads and cleansing of proteins absorbed from chamber walls. Wan, Xia and Kumar study the mixing performance of a miniaturized Wankel pump, integrating three valves to allow for mixing. Sugano *et al* demonstrate how a three-inlet configuration and high-frequency switching of pumping between the inlets results in pulsed mixing in a short distance.

With regards to passive mixing, Wijethunga and Moon demonstrate the downscaling of an aqueous two-phase system (ATPS) to digital microfluidics. A novel passive micromixer by Hai Le The *et al* with trapezoidal-zigzag channels provides a single-step process and yet high efficiency comparable to more complicated passive 3D micromixers. A novel approach for a digitally programmable generation with mixing of liquid slugs in segmented flow microfluidics iss presented by Chen *et al*.

In relation to active separation, Zhou and Wang demonstrate an enhanced pinched flow fractionation by introducing acoustically generated bubbles. Dielectrophoretic active separation is a more established method, which Yan *et al* combine with a hydrophoretic channel to improve its efficiency.

For passive hydrodynamic separation, a scale invariant focusing mechanism in a spiral channel is suggested by Tallapragada *et al* as a result of studies of large diameter particles. There are already good reasons for sorting such large particles, e.g. the separation of pancreas islets, however, if the mechanism also holds true for dimensions suitable for the separation of sub-micron particles, this would be of great interest. Alvankarian and Majlis present a mechanically tuneable crossflow filter. SadAbadi, Packirisamy and Wuthrich show the use of mixing in an integrated microreactor to integrate gold nanoparticles into a biosensing surface in a microfluidic system. In addition, Godino *et al* apply inertia-based separation for the purification of microalgae from bacterial contamination.

Deterministic separation in an array of micro pillars is another well-studied field of passive separation. In Du and Drazer's paper, a reconfigurable array in macro-size is used to ease the modelling and interpretation of this type of separation. Their results disagree with the commonly used model developed by Inglis *et al*. Measures are taken to make the particles behave as they do microfluidic arrays, but further validation in miniaturized models is needed. It will be interesting to follow this development in modelling.

Whether the novel 3D circular microfluidic centrifuge that is controlled by the centred inlet flow and the secondary rotational flow of two outlets is an active or passive device is to be discussed. However, Jeon *et al* show good separation of mixed particles by using their different centrifuge times, with the potential to also do so for smaller particles or

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macromolecules. The high dilution of the resulting fraction may be a limiting issue for some applications.

A microfluidic system for negative selection and enrichment of circulating tumour cells (CTC) by Luo *et al* shows promise for the unbiased handling of different cancer cells, and particularly for those not expressing EpCAM. Unfortunately, CTC selection is an extremely difficult task and today's recovery of the CTC is too low. This is because the depletion of the other large cells which express CD45 is far from complete and they are a million times more abundant. Still, with further improvements this chip may provide an important alternative to the EpCAM-based positive selection methods.

When cells are captured on a filtering microstrainer, it may be difficult to release them. Liu *et al* simply break apart the small size-controlling filter piece of parylene through sacrificial etching of an undelaying Mg film. Mg is for many systems biocompatible and can be etched in saline aqueous buffers.

It is good to see further influence from fluid mechanical modelling into microfluidic mixing and separation. Computation fluid dynamics (CFD) simulation is used by Sarkar *et al* to study the effects of wall protrusions on microfluidic mixing. Djukic, Topalovic and Filipovic use numerical simulation to simulate the individual motion of cells through a microfluidic chip. This may be used in many applications, e.g. the microfluidic handling of CTCs.

Good time-resolved measurements by Carrier *et al* on droplet formation show that microscale particle imaging velocimetry (μPIV) is an indispensable tool for better understanding of microfluidics.

A systematic study by Wang *et al* on the tuning of magnetofluidic spreading in microchannels may improve its use in mixing or separation.

In addition to these original papers, six Topical Reviews together provide in-depth overviews of the ongoing research in microfluidic separation and sorting. These are Balasuriya 'Dynamical systems techniques for enhancing microfluidic mixing', Cong *et al* 'Recent progress in preparation and application of microfluidic chip electrophoresis', 'Separation and sorting of cells in microsystems using physical principles' by Lee *et al*, the two reviews by Tripathi *et al* 'Passive blood plasma separation at the microscale: a review of design principles and microdevices', and 'Performance study of microfluidic devices for blood plasma separation—a designer's perspective', and 'Mixing in microfluidic devices and enhancement methods' by Ward and Fan.

Our conclusion is that although the field of microfluidic mixing and separation is well established, the ample work and novel approaches presented here show that there is still much to learn and considerable opportunities for improvement. The field needs stronger support from tools such as CFD simulation and μPIV when evaluating a new design. It is clear that the area of mixing is further developed than that of separation, and we look forward to more work also on active components in microfluidic separation and sorting.

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Page 2
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