

The study of mixing of reagents within a droplet in various designs of microfluidic chip

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Abstract. The aim of this work was to determine a design of a microfluidic droplet generator which provides the best mixing of two components within a droplet during its formation. Simulation of droplets' formation in various designs of microfluidic generators was performed. Dependences of a mixing index from a capillary number and a viscosity of continuous phase were obtained for each design. The mixing index was determined directly after the formation of the droplet. It was found that the small capillary numbers correspond to the lower mixing index due to increase of the droplets diameter. The high viscosity of the continuous phase provides vortex flows in the area of droplet formation which leads to an increase in the mixing index for asymmetric designs, but has no significant effect on the mixing in conventional symmetric flow focusing. So for the asymmetric droplet generator designs the mixing index increases up to 1.5 as compared with the conventional flow focusing designs.

1. Introduction

Microfluidic chips are used to solve various analytical tasks in biology, medicine and chemistry, as well as for the synthesis of small quantities of substances. In most of these cases laminar flows of liquids are applied, which allow accurate and reproducible conditions of analysis or synthesis. However, in some tasks the common problem is the efficient mixing of reagents, buffer and analyte, e.g. during an immunoassay, synthesis, etc. Performing mixing in microfluidic devices is not an easy task [1, 2], as in laminar flows (corresponding to low Reynolds numbers $Re < 1$) it is carried out mainly by diffusion. So diffusion time is about 100 s for the path of 100 μm of short proteins with a diffusion coefficient $10^{-10} \text{ m}^2/\text{s}$. There are various approaches to accelerate mixing in microfluidics based on different types of passive or active mixers. The first type includes microfluidic chips with a special geometry of channels [3, 4] or specific microstructures in them [5] providing a more efficient interaction of mixed fluid flows. In passive mixers it is difficult to ensure high efficiency of mixing. Active mixers are equipped with various control elements which require additional energy (usually electric [6] or mechanical [7]) for influence on the mixed flow.

Promising devices for mixing substances are droplet on-chip generators [8, 9]. In these systems necessary reactions are conducted in confined volume of droplets with diameter from about 10 to 50



micrometers. Comparing different strategies of droplet formation within microfluidic chips: T-junction, flow focusing and co-flowing, it was found that the best mixing is achieved in the T-junction [10, 11]. However, flow focusing has its own advantages. Its operating principle is based on the fact that the continuous phase flowing through two side channels meets the dispersed phase at a channels' intersection, where the dispersed phase is squeezed by the continuous phase and breaks up into droplets. It allows avoiding a contact of forming droplets with channels' walls and helps prevent potential negative effects on sample's components of the dispersed phase. Therefore, it is reasonable to modify the flow focusing design to achieve better mixing.

2. Methods

Simulation of droplets' formation and distribution of reagents was performed by means of COMSOL Multiphysics which is a software platform based on finite element method for solving physics-based problems.

During the simulation the designs shown in figure 1 were considered.

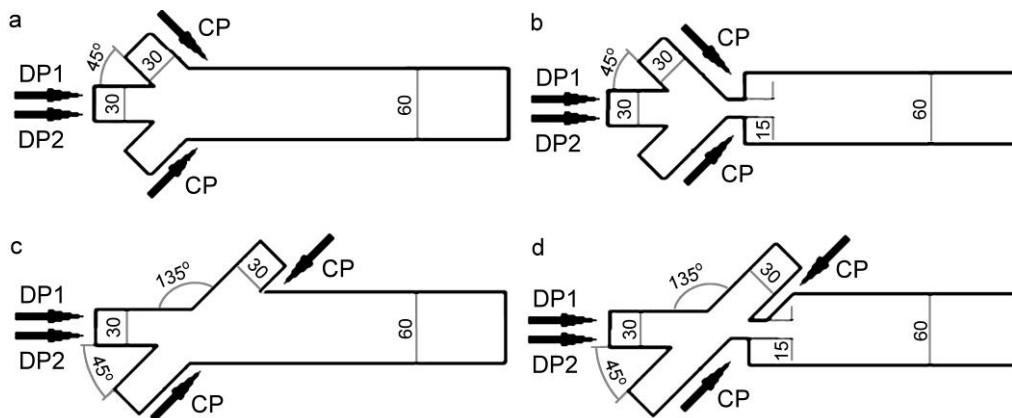


Figure 1. Simulation area for different droplet generator designs: a) conventional flow focusing; b) conventional flow focusing with pinched region; c) asymmetric; d) asymmetric with pinched region. All sizes are in micrometers. DP1 is the disperse phase with reagent, DP2 is the buffer disperse phase, CP is the continuous phase

The Navier-Stokes equations were solved to calculate the velocity profile of the fluid:

$$\rho \left(\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} \right) = -\nabla p + \mu \nabla^2 \mathbf{u} + \mathbf{F}_s \quad (1)$$

$$\nabla \cdot \mathbf{u} = 0$$

where $\mathbf{u}$ is the flow velocity vector (m/s), ρ is the fluid density (kg/m³), μ is the fluid viscosity (Pa·s), p is the pressure (Pa), $\mathbf{F}_s$ is the surface tension force (H/m³).

The Fick's second law with the added convective term was used for modeling the distribution of concentration:

$$\frac{\partial c}{\partial t} + \mathbf{u} \cdot \nabla c = D \nabla^2 c \quad (2)$$

where D is the diffusion coefficient of reagent (m²/s), c is the concentration of reagent (mol/m³).

Displacement of the interface between two immiscible fluids was described by a phase field in which the spatial distribution of the two phases was defined by a phase field variable φ which takes values from -1 to 1. Changing of this variable in time was determined by minimization of the system's free energy [12]:

$$\frac{\partial \varphi}{\partial t} + \mathbf{u} \cdot \nabla \varphi = \nabla \cdot \gamma \nabla \left(\frac{\partial f_{\text{tot}}}{\partial \varphi} - \nabla \cdot \frac{\partial f_{\text{tot}}}{\partial \nabla \varphi} \right) \quad (3)$$

where f_{tot} is the total free energy density of the system (J/m^3), γ is the relaxation parameter ($\text{m}^3\cdot\text{s/kg}$).

Calculation of the mixing index that characterizes the ratio of the variance of reagent to the maximum possible variance was performed using the following expression [13]:

$$I = \left[1 - \left(\frac{\iint (c - \bar{c})^2 dA}{A \cdot \bar{c} (c_{\text{max}} - \bar{c})} \right)^{1/2} \right] \cdot 100\% \quad (4)$$

where A is the area of cross-section of the droplet (m^2), c is the concentration of reagent (mol/m^3), $\bar{c}$ and c_{max} is the average and the maximum concentration of the reagent within the droplet respectively (mol/m^3). Index equals 1 for the complete mixing and 0 when the mixing absent. Mixing index was determined directly after the formation of the droplet.

The dependence of the mixing index on the viscosity of the continuous phase and the capillary number Ca was investigated during the work:

$$Ca = \frac{U \mu_c}{\sigma} \quad (5)$$

where U is the average flow velocity after channel's crossing (m/s), μ_c is the viscosity of the continuous phase ($\text{Pa}\cdot\text{s}$), σ is the surface tension between the dispersed and continuous phases (N/m).

The flow velocity was calculated from the volumetric flow rate for channel depth of $30\ \mu\text{m}$. Flow rate of the continuous phase was varied from $10\ \mu\text{l/min}$ to $1\ \mu\text{l/min}$ and flow rate of dispersed phase was varied from $1\ \mu\text{l/min}$ to $0.1\ \mu\text{l/min}$ to provide a range of capillary number's values from 0.06 to 0.006 at constant viscosity of continuous phase $\mu_c = 0.03\ \text{Pa}\cdot\text{s}$. Diffusion coefficient also was varied to achieve constant Peclet number. It took values from 10^{-10} to $10^{-11}\ \text{m}^2/\text{s}$ corresponded to short proteins. The ratio between continuous and dispersed phases 10:1 was chosen to achieve dripping regime of droplets generator and prevent their contact with the channel's walls to minimize walls' influence. The water with $\rho_d = 1000\ \text{kg/m}^3$ and dynamic viscosity $\mu_d = 0.001\ \text{Pa}\cdot\text{s}$ was considered as the dispersed phase. The oil with density $\rho_c = 880\ \text{kg/m}^3$ was considered as the continuous phase. When the oil viscosity μ_c was varied from 0.03 to 0.003 $\text{Pa}\cdot\text{s}$ the flow rate also was changed to achieve constant $Ca = 0.006$. The surface tension σ at the oil-water boundary was equal $0.051\ \text{N/m}$.

3. Results and discussion

During analysis two-dimensional formulation of the problem was used. Since the inertial force was negligible in considered model (Reynolds number equal 0.01–0.1) the process of droplet formation was controlled by the ratio of viscous and surface tension forces that is expressed by the capillary number. Surface tension tries to minimize two-phase interface and interferes with droplet formation. On the other hand viscous stress from the continuous phase elongates disperse phase and breaks up droplets. Thus, droplet diameter L was inversely proportional to the Ca as shown in figure 2a. While droplet size was reducing, the mixing index was increasing (figure 2b) as shorter diffusion length provides enhancing mixing. With increasing of the Ca 10 times the I increased 1.1–1.4 times and the droplet diameter decreased 1.5–1.75 times depended on design. Improvement of mixing ability in droplet generators with pinched region also related to decreasing of droplet diameter. So adding a pinched region improved the mixing for the conventional flow-focusing 1.5 times and for the asymmetric 1.25 times with decreasing of droplet diameter 2.25 and 2.75 times respectively.

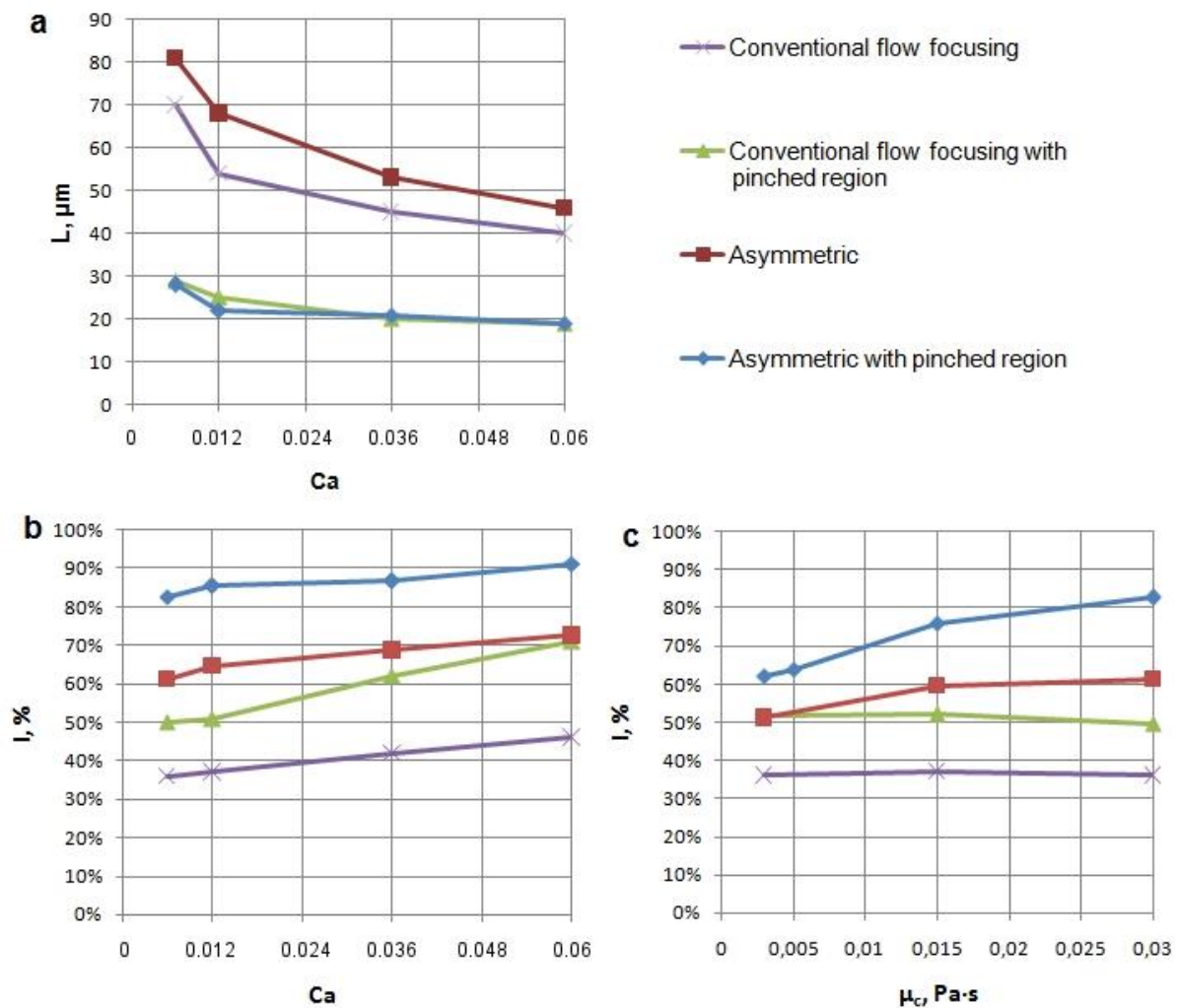


Figure 2. Simulation results: a) dependences of the droplet diameter on the capillary number Ca ; b) dependences of the mixing index on the capillary number Ca with $\mu_c = 0.03$ Pa·s; c) dependences of the mixing index on the viscosity of continuous phase with $Ca = 0.006$

Asymmetric design and asymmetric design with pinched region provided on average up to 1.5 times higher mixing index compared with conventional flow-focusing and conventional flow-focusing with pinched region respectively. The superiority of asymmetric designs related to vortex flows and their asymmetric character in the area of droplet formation. This was evidenced by the results for varying μ_c at constant Ca (figure 2c). Decreasing in μ_c led to decreasing mixing index by 20% for the asymmetric design with pinched region and by 10% for the asymmetric without it, but had no significant effect on the mixing in conventional flow focusing. Viscosity of fluid relates to momentum transport between its laminae and is proportional to shear stress, so high viscosity and velocity ratios between continuous and disperse phases induced vortex flows in water which decreased with μ_c reduction (figure 3a, b). In symmetric design there are two vortices occupying left and right sides of forming droplet, such as there is no transfer of reagent from one part of a droplet to another (figure 3c). In asymmetric design most of the two-phase interface is exposed to the flow from the right side channel and any counter vortex isn't created. Thereby, this single vortex flow enhances mixing.

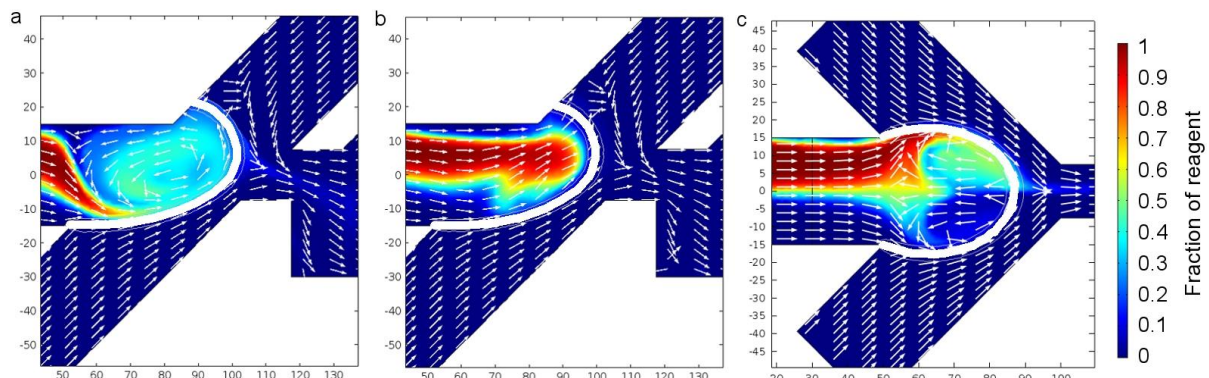


Figure 3. Fraction of reagent in designs with pinched region with the same capillary number $Ca = 0.006$ and different viscosity of the continuous phase μ_c : a) asymmetric with $\mu_c = 0.03$ Pa·s; b) asymmetric with $\mu_c = 0.003$ Pa·s; c) symmetric with $\mu_c = 0.03$ Pa·s. Arrows show the direction of the flow. Solid white contour correspond to the interface between dispersed and continuous phases

In three dimensional case special phenomena might appear, because extra constrains are added at a top and a bottom. Checking the possibility of vortex formation in 3D model the appropriate simulation was conducted at $Ca = 0.006$ and $\mu_c = 0.03$ Pa·s. As shown in figure 4 the flow at the center of the channels had the same character as during 2D simulation.

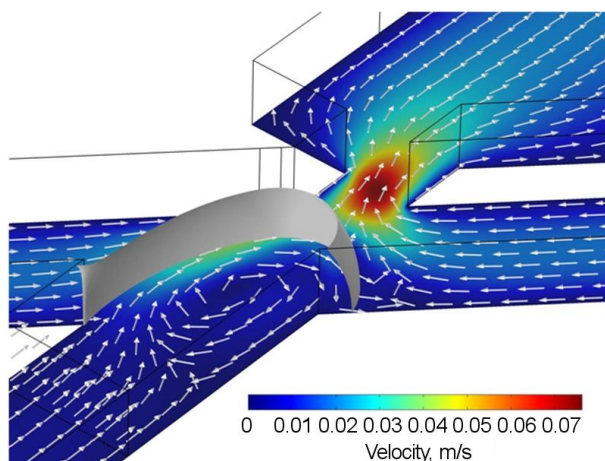


Figure 4. Flow velocity in the center of the channel. Arrows show the direction of the flow. The two-phase interface is marked by gray

4. Conclusions

Dependences of the mixing index on the capillary number Ca and viscosity of the continuous phase μ_c were obtained for four different designs. So for conventional flow-focusing design mixing index was 46%, for conventional flow-focusing with pinched region and asymmetric it was 71% and for asymmetric with pinched region it was 91% when $Ca = 0.06$ and $\mu_c = 0.03$ Pa·s. It was found that with decreasing of the capillary number 10 times the mixing index decreased 1.1-1.4 times associated with increase in droplet diameter. Decreasing of continuous phase viscosity led to decreasing of vortex flows and the mixing index for both types of asymmetric designs, but didn't affect on conventional variants, because vortex flows were symmetric in them and didn't give a contribution in mixing.

Thus, the best mixing efficiency was achieved in case of the asymmetric designs. Such designs increased mixing index up to 1.5 compared with conventional flow-focusing. Two-dimensional formulation of the problem and finite element method impose restrictions on the data obtained, but, as three-dimensional simulation showed, they provide an opportunity to get relevant estimates and make principal conclusions. So, we can conclude that proposed in the paper asymmetric design of droplet

generator with pinched region allows achieving higher efficiency of mixing in conjunction with the benefits of flow-focusing design.

Acknowledgments

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