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THEORETICAL BASES OF CHEMICAL TECHNOLOGY

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Flow and mixing processes in a passive mixing microfluidic chip: Parameters' estimation and colorimetric analysis

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Objectives. *The development of microfluidic systems is one of the promising areas of science and technology. In most procedures performed using microfluidic systems, effective mixing in microfluidic channels of microreactors (chips) is of particular importance, because it has an effect on the sensitivity and speed of analytical procedures. The aim of this study is to describe and evaluate the major parameters of the flow and mixing processes in a passive microfluidic micromixer, and to develop an information-measuring system to monitor the dynamics of flow (mixing) of liquids.*
Methods. *This article provides an overview of the concept of microfluidic mixing chips (micromixers) and their classification, and analyzes the kinds of points of mixing and microfluidic channels for mixing. The article presents the description and calculations of the hydrodynamic similarity criteria (Reynolds, Dean and Peclet numbers), which are the critical parameters for creating and optimizing micromixers (for example, straight and curved channels in the flow rate range between 100 and 1000 µl/min). We have developed an information-measuring system to monitor the dynamics of flow (mixing) of liquids in a microfluidic channel, which consists of a microscope with a digital eyepiece (LOMO MIB, Russia), an Atlas syringe pump (Syrris Ltd., UK) and a passive mixing microfluidic chip of interest (made of clear glass). This system was designed to quickly illustrate the principles of mixing in microfluidic channels of different configurations.*
Results. *The developed system has allowed carrying out a colorimetric analysis of the modes and dynamics of mixing two liquids (5% aqueous solution of azorubine dye and water) at the T-shaped mixing point, at the straight and curved (double-bend shaped) sections of the microfluidic channel of the passive-type micromixer with flow rates varying from 100 to 400 µl/min.*
Conclusions. *According to the obtained calculations, the share of the advective mixing processes (formation of vortex flows and increase in the contact area of the mixed substances) in flowing*

liquids is significantly higher in curved microchannels. The developed information-measuring system to monitor the dynamics of flow (mixing) of liquids in a microfluidic channel is a convenient tool for optimizing the mixing modes in the channels of micromixers, and for designing new configurations of channels in microchips. It would allow intensifying processes and increasing the performance of microfluidic systems.

Keywords: *microfluidics, microfluidic chip, passive micromixer, criteria of hydrodynamic similarity, colorimetric analysis.*

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Процессы течения и перемешивания в микрофлюидном чипе пассивного смешивания: оценка параметров и цветометрический анализ

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Цели. *Разработка микрофлюидных систем является одним из перспективных направлений развития науки и техники. В большинстве процедур, проводимых с помощью микрофлюидных систем, важное значение имеет эффективное перемешивание в микрофлюидных каналах микрореакторов (чипов), которое влияет на чувствительность и быстроту аналитических процедур. Целью работы являлись описание и оценка основных параметров течения и смешивания в микрофлюидном микросмесителе пассивного смешивания и разработка информационно-измерительной системы контроля динамики протекания (перемешивания) жидкостей в нем.*
Методы. *Данная статья содержит обзор концепции микрофлюидных чипов смешивания (микросмесителей), их классификацию, обсуждены разновидности точек смешивания и микрофлюидных каналов смешивания. Приведены описание и расчеты критериев гидродинамического подобия (числа Рейнольдса, Пекле и Дина), являющихся критическими параметрами для разработки и оптимизации микросмесителей (на примере прямого и изогнутого каналов в диапазоне скоростей потоков от 100 до 1000 мкл/мин). Разработана информационно-измерительная система контроля динамики протекания (перемешивания) жидкостей в микрофлюидном канале, состоящая из микроскопа с цифровым окуляром («ЛОМО» МИБ, Россия), шприцевого насоса Atlas (Syrris Ltd., Великобритания) и исследуемого микрофлюидного чипа пассивного смешивания, изготовленного из прозрачного стекла. Данная система предназначена для того, чтобы оперативно проиллюстрировать принципы перемешивания в микрофлюидных каналах разной конфигурации.*
Результаты. *С помощью разработанной системы проведен цветометрический анализ режимов и динамики перемешивания двух жидкостей (5% водного раствора красителя азорубина и воды) в Т-образной точке смешивания, на прямом и изогнутых (в форме змеевика) участках микрофлюидного канала микросмесителя пассивного типа при варьировании скорости потоков от 100 до 400 мкл/мин.*
Заключение. *Согласно полученным расчетам, доля адвективных процессов смешивания (образование вихревых потоков и увеличение площади контакта смешиваемых веществ) в протекающих жидкостях существенно выше в изогнутых микроканалах*

микрочипов. Разработанная информационно-измерительная система контроля динамики протекания (перемешивания) жидкостей в микрофлюидном канале является удобным инструментом для работ по оптимизации режимов смешивания в каналах микросмесителей и для проектирования новых конфигураций каналов в микрочипах, что позволяет интенсифицировать процессы и увеличить производительность микрофлюидных систем.

Ключевые слова: *микрофлюидика, микрофлюидный чип, микросмеситель пассивного смешивания, критерии гидродинамического подобия, цветометрический анализ.*

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Innovative approaches in chemical and biological analyses, in order to simplify and speed up their procedures as well as boost their performance, are in high demand. Microfluidic systems are in the focus of researchers, because such systems can be used in various fields of science and technology, including chemical and biochemical analytical procedures. The driving force behind the active development of microfluidics was the creation of microelectromechanical systems (MEMS) which received the name "System-on-a-Chip," and which allow to place several functional components on a single microdevice. It is also in line with the general tendency to miniaturize devices, to elevate their performance and sensitivity for chemical and biological studies and analytical procedures [1]. Such miniaturized total analysis systems (μTASs) are used in chemistry, biology and medicine, and they are called a lab-on-a-chip (LoC) [2, 3]. A microfluidic chip (microreactor) is a device that combines several functions, when working with a reagent-to-product or sample-to-analysis pipeline, in a single complex system whose size varies from several millimeters to several square centimeters [4].

The main difference between microfluidic systems and other currently employed analytical laboratory equipment is the use of microvolumes (microliters) in microfluidics, allowing the use of reagents and electricity, as well as the amount of the analyte or biomaterial to be significantly minimized, thus making the analysis cheaper. Microfluidic systems are the tools that we can use to develop multifunctional automated analytical and manufacturing devices in a small scale, allowing various chemical and biochemical reactions to be performed quickly, in a small volume and with the minimal human involvement. The use of small volumes of substance solutions leads to the necessity of investigating flow processes in microfluidic systems in terms of both molecular dynamics and continuum mechanics. Special microfluidic microreactors have been developed, allowing to perform several actions with liquids on a single chip, for example, mixing, separation, fragmentation, sampling, etc. [2–10]. Other microfluidic chips, which perform only a single procedure, for example, mixing (one of the most important operations, involved in almost all chemical and biochemical analytical procedures), exist as well [11–14].

Microfluidic chips for mixing, the so-called micromixers, are used to control and accelerate the process of mixing [13, 14]. There are two kinds of micromixers, active and passive. To intensify the process, active micromixers require additional equipment that acts on the liquid flow externally. For example, it can be a piezoacoustic transducer, which creates shear stress in the liquid flow by ultrasound waves, and induces fluctuations in the velocity field, thus intensifying the mixing. Another example is magnetic particles in a certain area of the microfluidic chip, which mix the liquid flows by their own active movements [14].

The design of active micromixers and their integration into microfluidic systems is quite expensive and difficult. On the contrary, passive micromixers are easier and cheaper. When creating passive micromixers, it is necessary to take into account the geometrical parameters of the micromixer channels and the flow behavior of the liquid [4]. In passive micromixers, the mixing of liquid flows is intensified by various construction features of the microfluidic channels that allow increasing the contact surface between the liquids and decreasing the diffusion distance. For example, the micromixer channels may be equipped with obstacles, or have curved configurations, allowing to abruptly change the direction of flow, make the flows collide, create vortex flows, thus making the mixing process more effective [15, 16]. Superhydrophobic surfaces may also be used in the chip channels, making the sliding of the liquids better at the sides of the channels and increasing the velocity of the flow [17].

The aim of this study was to describe and evaluate the major parameters of the flow and mixing processes in a passive microfluidic micromixer, and to develop an information-measuring system to monitor the dynamics of flow (mixing) of liquids.

Evaluation of the hydrodynamic similarity criteria of flow and mixing processes in a passive mixing microfluidic chip

The efficiency of mixing processes in a passive mixing microfluidic chip, in accordance with the abovementioned description, depends on the construction features of the channels. The key zones in the chip structure, which facilitate effective mixing, are the point of mixing and the channel of mixing. The point of mixing is a certain place in the chip where two or more channels are joined (where liquids are supplied for further mixing). The channel where the liquids are flowing together is called the channel of mixing (Fig. 1).

By changing the geometry of these chip zones, developers of microfluidic systems achieve the maximal efficiency of mixing for various solutions. The point of mixing can be T-shaped, Y-shaped or arrow-shaped (Fig. 2).

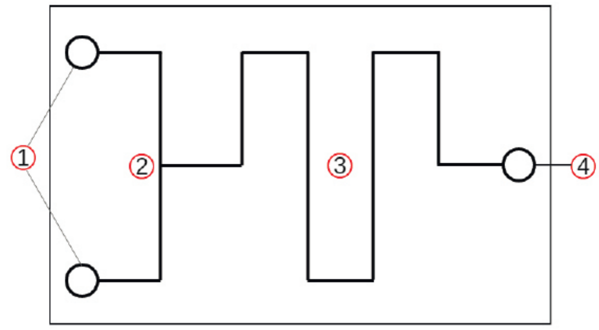
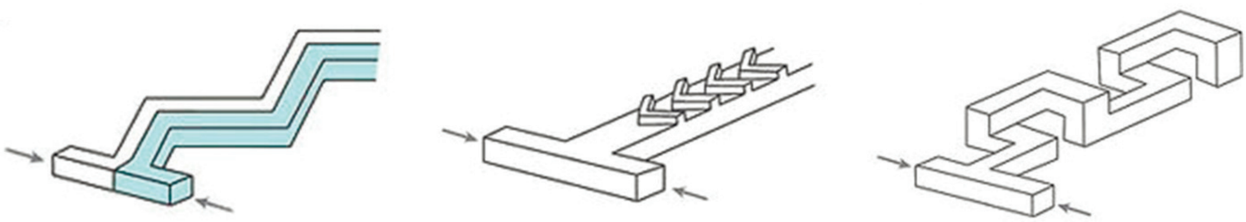


Fig. 1. Scheme of a microfluidic chip (micromixer):
1 – two points of entry of the liquids;
2 – the point of mixing;
3 – the channel of mixing;
4 – the point of exit of the resulting solution.

T- junction *Y- junction* *Arrow-shaped junction*

Fig. 2. Channel configurations at the point of mixing in passive mixing microfluidic chips.

Channels of mixing in passive micromixers can have various configurations, such as a double-bend shaped channel; a flat channel with staggered-herringbone grooves; a three-dimensional, connected out-of-plane channel (Fig. 3); and many more configurations [4].



a b c

Fig. 3. Examples of channel configurations in passive microfluidic chips:
a) Zigzag-shaped channel for chaotic mixing at high Reynolds numbers;
b) Staggered-herringbone grooves for chaotic mixing at low Reynolds numbers;
c) Three-dimensional L-shaped channel for chaotic mixing at intermediate Reynold numbers [4].

The mixing process in solutions is influenced by the parameters of the dissolved substances, such as viscosity, diffusion coefficient and the supply rate of the liquids. Other important factors, which affect the mixing process, are the material of the microfluidic chip and the characteristics of the chip itself, such as the roughness of the channel sides, length and angles of the channel.

In order to describe the mixing in microfluidic chips, it is necessary to use the following parameters of hydrodynamic similarity: the Peclet number (Pe) that characterizes the ratio of the advective processes in the flow to diffusion; the Prandtl number (Pr) that characterizes the thermodynamics of the mixed liquids; the Reynolds number (Re) that characterizes the flow mode of the liquid; the Dean number (Dn) that characterizes the occurring transversal flows at the curves and bends of the channels (Fig. 4).

We calculated these parameters in order to analyze the mixing process in channels of passive microfluidic chips with T-shaped junction in two configurations, straight and double-bend shaped.

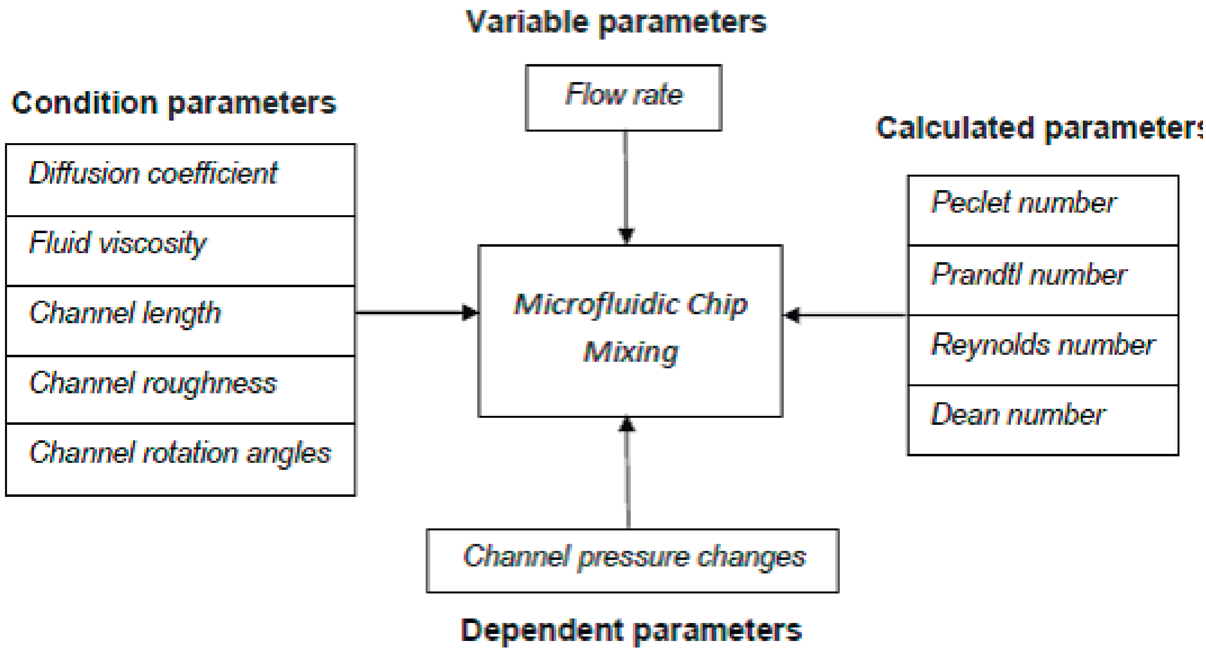


Fig. 4. Scheme of parameters for mixing of solutions in a passive microfluidic chip.

Let us consider the following setup, where we use a microfluidic chip to mix 5% aqueous solution of azorubine (carmoisine, food coloring E122; red dye supplied by *Roha Dyechem Pvt. Ltd.*, catalog number RD-09, India) and bidistilled deionized water (generated by Milli-Q Integral 5, *Merck Millipore*, France; further referred to as "Milli-Q water"), making a dilution of the starting dye solution with water to produce a homogeneous solution. The microfluidic channel has the same cross-section area of 1 mm^2 throughout the whole chip, and its length is 1080 mm. Two solutions are supplied to the micromixer channels at the rate of 400 µl/min.

The Reynolds number can be calculated by the following formula (1) [18]:

$$\mathrm{Re} = \frac{\rho v d}{\eta}, \qquad (1)$$

where ρ – density of the medium, kg/m^3;

v – characteristic velocity, m/s;

d – hydraulic diameter, m;

η – dynamic viscosity of the medium, kg/(m·s)

As a result, the Re number (in a straight channel) at the flow rate of 400 µl/min equals to 6.6.

In this mass transfer process, when mixing a dye solution with water, it is more important and descriptive to analyze the ratio of advective processes to diffusion, i.e. the ratio of the mass transfer caused by the movement of the medium to the mass transfer caused by the chaotic thermal movement of molecules. It can be characterized by the Peclet number according to the formula (2) [18]:

$$\mathrm{Pe} = \mathrm{Re} \times \mathrm{Pr} \qquad (2)$$

The Prandtl number (Pr) equals to 7.02 for the flow of azorubine aqueous solution at 20 °C [19].

Therefore, for the liquid flow with Re = 6.6 (the flow rate is 400 µl/min) in a straight channel, the Peclet number equals to 46.33.

When flowing in a double-bend shaped channel, the liquid changes its direction at the bends of the channel. As we can see from the scheme of this channel (Fig. 5), the flow changes its direction twice. As a result of the centrifugal force action, the layers of the liquid begin to flow irregularly, the flow separates into layers, thus intensifying the mixing.

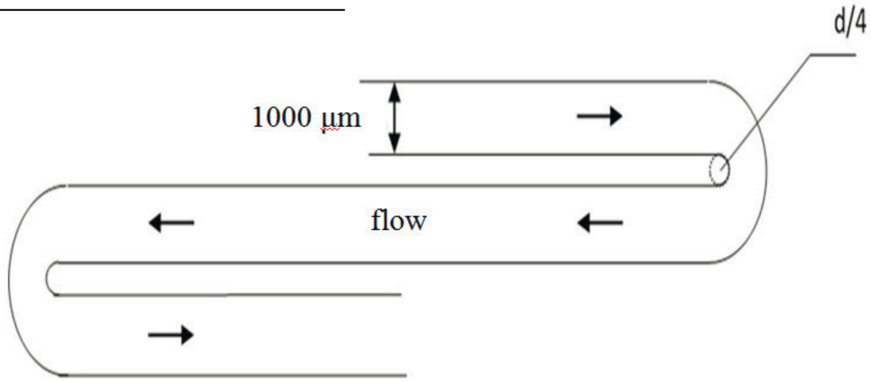


Fig. 5. Scheme of a part of a double-bend shaped channel.

By using similarity coefficients, flow in channels with turns can be characterized by the Dean number [18]:

$$Dn = \frac{\nu}{\upsilon} \times \sqrt{\frac{L^3}{2 \times r}}, \quad (3)$$

where υ – kinematic viscosity, m^2/s;
ν – flow velocity/rate, m/s;
L – characteristic length, m;
r – radius of curvature, m.

The Dean number can also be calculated using the Reynolds number [18]:

$$Dn = \text{Re} \times \sqrt{\frac{L}{r}} \quad (4)$$

Then the Pe number for this type of mixing channel can be expressed by the following formula:

$$\text{Pe} = (\text{Re}_1 \times \text{Re}_2) \times \text{Pr}, \quad (5)$$

$$\text{Re}_2 = 2 \times \left(\frac{Dn}{\sqrt{\frac{L}{r}}} \right), \quad (6)$$

where Re_2 characterizes the movement of the liquid at the bends of the double-bend shaped channel (the multiplier 2 is the number of bends in the double-bend shaped channel); Re_1 – the Reynolds number for the straight part of the channel.

The resulting number (Re_1+ Re_2) for this channel will be equal to 35.5. Therefore, the Pe number for the double-bend shaped channel will be equal to 250.6. The results of these calculations are shown in Table.

Similarity criteria for the straight channel and the double-bend shaped channel

Similarity criteria	Straight channel	Double-bend shaped channel
Re (Reynolds number)	6.6	35.5
Pe (Peclet number)	46.33	250.6

The calculations described above confirm that the share of advective mixing processes is much higher in the double-bend shaped channel than in the straight channel. It indicates that more bends in microfluidic channels are required for fast and effective mixing of liquids. Similarly, we calculated Peclet and Dean numbers for the straight channel and the double-bend shaped channel at various flow rates. The resulting dependencies of these similarity criteria on flow rates are shown in Fig. 6.

According to these graphs, for the double-bend shaped channel, the increase in the Pe number (that characterizes the ratio of the advective processes in the flow to diffusion) is directly proportional to the Re number, i.e. there is a significant dependency on the flow rate. More vortex flows at the bends of the mixing channel lead to larger contact areas of the liquids and more effective mixing.

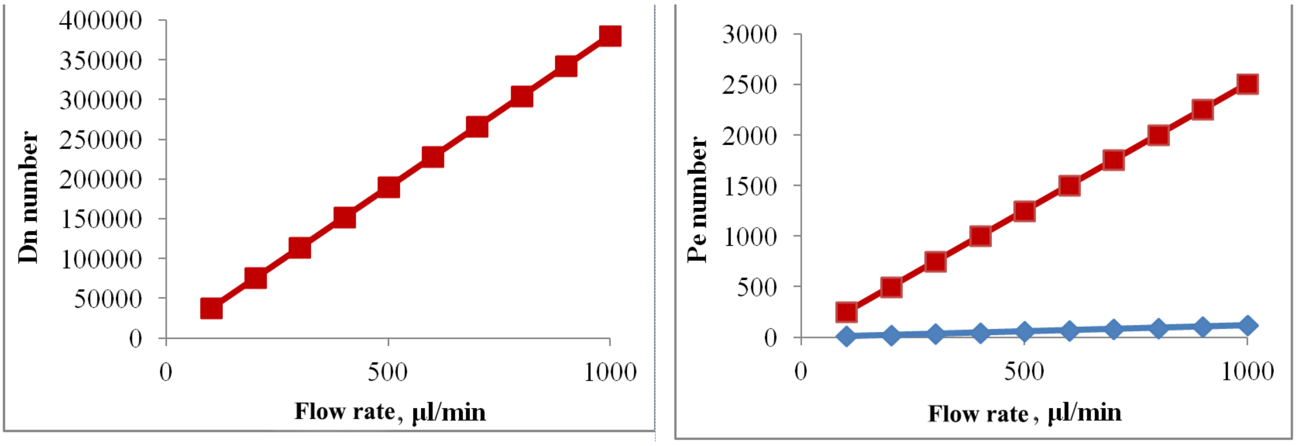


Fig. 6. Dependency of Dn and Pe numbers on flow rates for the mixing of azorubine aqueous solution with Milli-Q water. *Left*, double-bend shaped channel; *Right*, straight channel (diamonds, blue line) and double-bend shaped channel (squares, red line).

Colorimetric analysis of liquid flow in microchannels

In order to analyze the flow and mixing processes in passive microfluidic chips, we have developed an information-measuring system (IMS) to monitor the dynamics of liquid flow. The IMS (Fig. 7) consists of a microscope with a digital eyepiece (to take photographs and record videos when connected to a computer; *LOMO MIB*, Russia); an Atlas syringe pump (to supply liquids at a certain rate into the microfluidic chip; *Syrris Ltd.*, United Kingdom); and a passive mixing microfluidic chip of interest (a double-bend shaped channel, made of clear glass).

In preliminary experiments, we obtained a series of microscopic photographs that showed the mixing process of 5% aqueous solution of azorubine (red dye) with Milli-Q water. We used an algorithm designed with AutoHotKey script language for colorimetric analysis. The results obtained in the RGB color space were transformed into the CIE Lab color coordinate system. The red chromaticity was calculated by division of the "a" coordinate (green–red) by the "L" coordinate (brightness) [19].

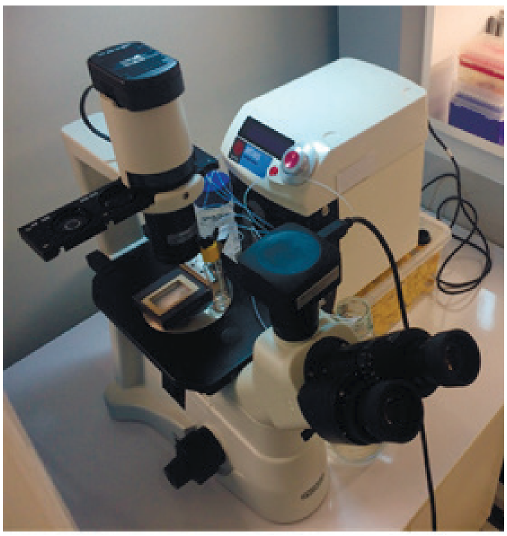


Fig. 7. View of the information-measuring system (IMS) for monitoring of the dynamics of liquid flow in a microfluidic chip.

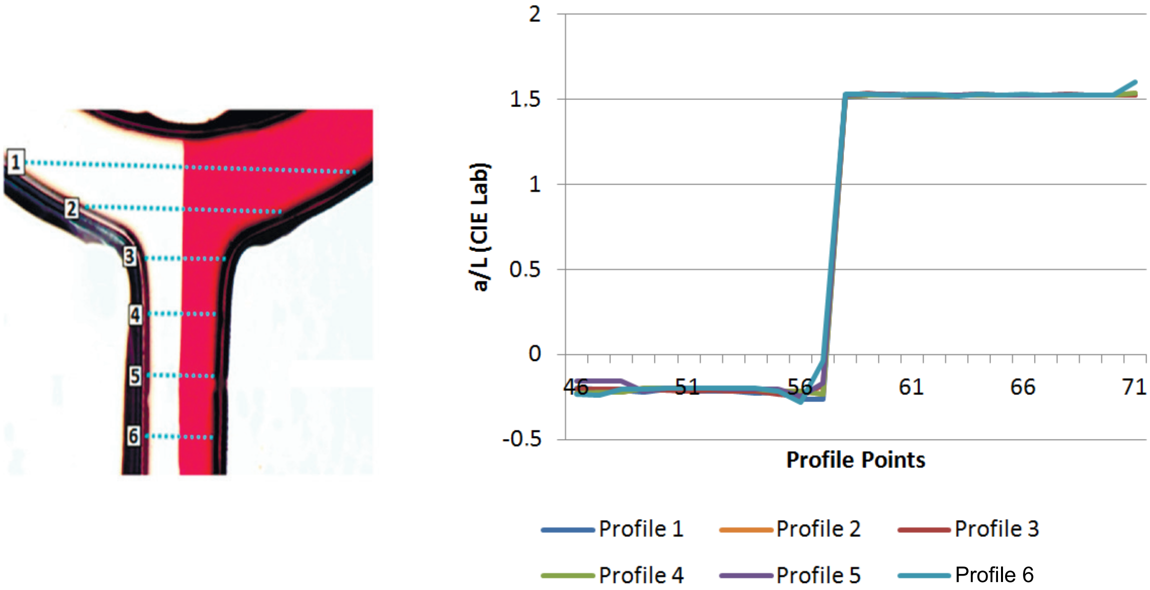
Using this IMS, we performed a colorimetric flow analysis (at the flow rate of 400 µl/min) at the T-shaped mixing point of the microfluidic chip for 5% aqueous solution of azorubine (bright red) and Milli-Q water (Fig. 8).

As we can see, the intensity of red chromaticity is always constant and there is a clear boundary between the flows. We can assume that the concentration also does not change, meaning that there is no convection mass transfer at the mixing point. Previously, a similar curve for distribution of concentrations was obtained by mathematical modeling [20, 21].

When we decrease the rate of one of the flows to 100 µl/min, we observe channel blocking (Fig. 9) caused by excess density of one of the flows; it is not optimal because mixing does not occur in this case.

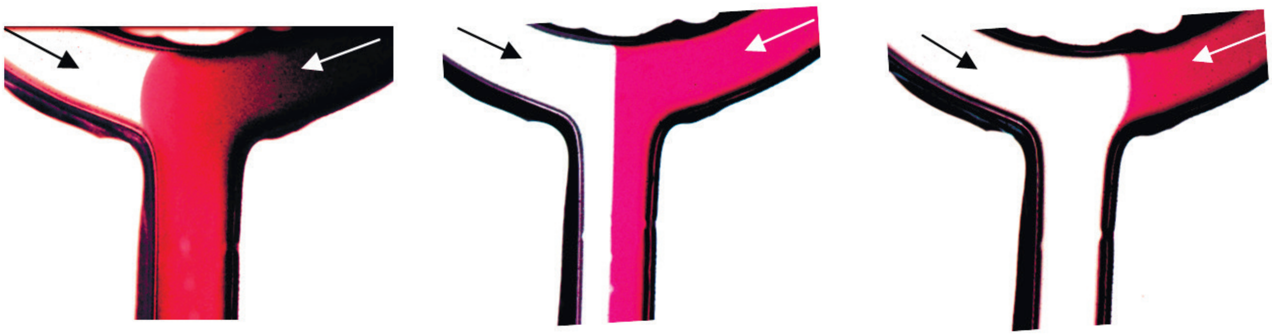
The colorimetric profile of dye distribution for flow in a straight channel is shown in Fig. 10.

The resulting curve for distribution of chromaticity intensity clearly has fluctuations of values at the sides, and shows formation of heterogeneity in azorubine concentration due to the interaction between dye molecules and sides of the channel. The profile of flow rates is parabolic, because the flow in the channel consists of a fast center and slow sides. The resulting curve for distribution of chromaticity intensity in the channel (Fig. 10) looks like the curve obtained in [20] by mathematical flow modeling for a straight channel, using methods of molecular dynamics (Fig. 11). It has been suggested that heterogeneity in flow rates may cause heterogeneity in concentration of the dissolved substance in the cross-section of the channel [20].



a b

Fig. 8. a) Microscopic photograph (4× magnified) of the T-shaped mixing point, with flows of 5% aqueous solution of azorubine and Milli-Q water. Dotted lines show colorimetric profiles – lines where chromaticity changes; b) Chromaticity curves.



a) Left channel blocking. Flow rates: solvent (left) – 100 μl/min, dye (right) – 400 μl/min

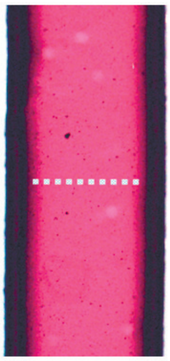
b) Uniform flow. Flow rates: solvent (left) – 100 μl/min, dye (right) – 100 μl/min

c) Right channel blocking. Flow rates: solvent (left) – 400 μl/min, dye (right) – 100 μl/min

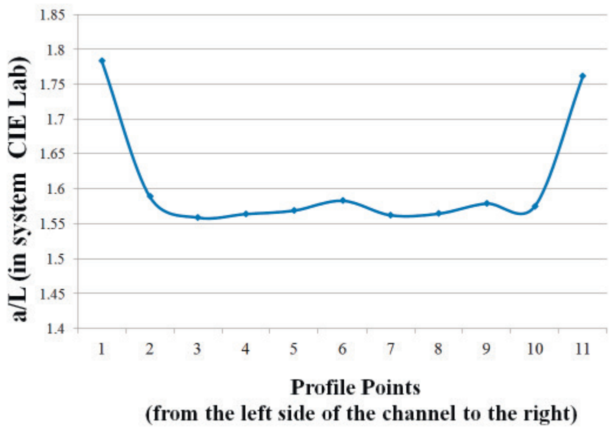
Fig. 9. Microscopic photographs (4× magnified) for various flow modes of 5% aqueous solution of azorubine and Milli-Q water at the T-shaped mixing point of the microfluidic chip. Arrows show directions of flow.

It is known that, when both flow rates decrease, the flow is stabilized, the mixing mode is disrupted, the flow becomes laminar, and separates into layers without mixing [22]. For colorimetric analysis of mixing modes, we supplied 5% aqueous solution of azorubine and Milli-Q water to a double-bend shaped micromixer at the following flow rates: 100, 200, 300, 400 μl/min. We obtained microscopic photographs and curves for distribution of intensity of chromaticity (Fig. 12).

As we can see from these graphs of colorimetric profiles, the decrease in flow rate causes stratification of the flow. At flow rate of 400 μl/min, the colored solution fills the whole cross-section of the bent channel quite uniformly, indicating the effective mixing of the two flows. The reddish flow at 300 μl/min indicates that a gradient of dye concentration occurs, and the dye concentrates in the right part of channel. At 200 μl/min, we observe the unstable, yet appearing plateau of dye concentration. The curve of chromaticity intensity at



Microscopic photograph (4×magnified)



Distribution curve for intensity of chromaticity in the channel

Fig. 10. Colorimetric profile of flow in a straight channel for 5% aqueous solution of azorubine.

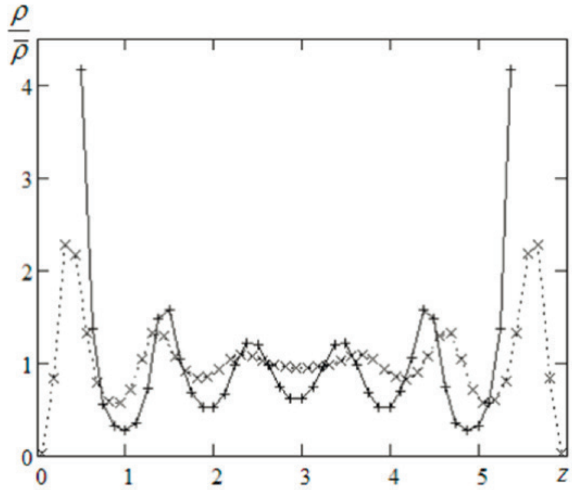
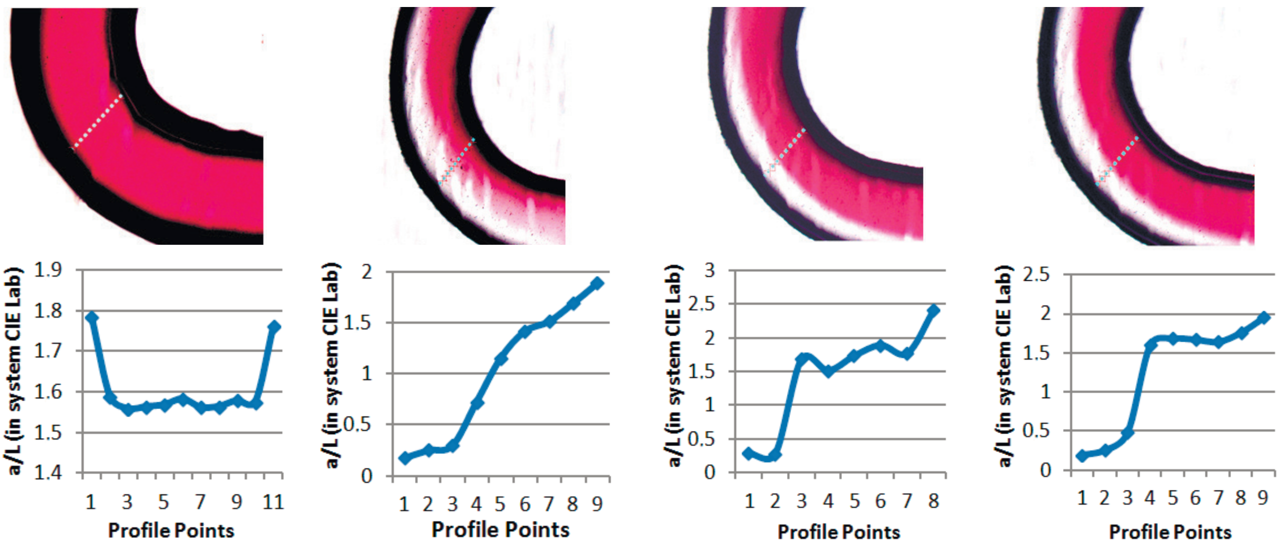


Fig. 11. Profile of flow density in the cross-section of a straight channel for molecules whose interaction is described: by the potential of hard spheres (+); by the Lennard-Jones potential (×) [20].



a) Flow rate: 400 µl/min b) Flow rate: 300 µl/min c) Flow rate: 200 µl/min d) Flow rate: 100 µl/min

Fig. 12. Microscopic photographs and curves of distribution of chromaticity intensity for mixing in a bent channel of a micromixer, while decreasing rate in both flows – azorubine solution and Milli-Q water (see from left to right – from a to d).

100 μl/min shows that the flow is stabilized as two laminar flows; the dye concentration in the right flow is uniform, which can be seen in the graph as a clear plateau between profile points 4 and 8.

We have also analyzed the mode of flow at 100 μl/min of dye solution in the bends of the channel filled with Milli-Q water (Fig. 13).

We can see that the dye fills up the central area first, i.e. the core of the flow. The change in the flow trajectory is caused by the appearing centrifugal force that acts on the flow, since its velocity is much higher than that of the side layers. By comparing the colorimetric profiles 1 and 2, we can see that the flow is shifted after the bend of the channel. At high flow rates, the destabilizing effect is higher, and active mixing occurs.

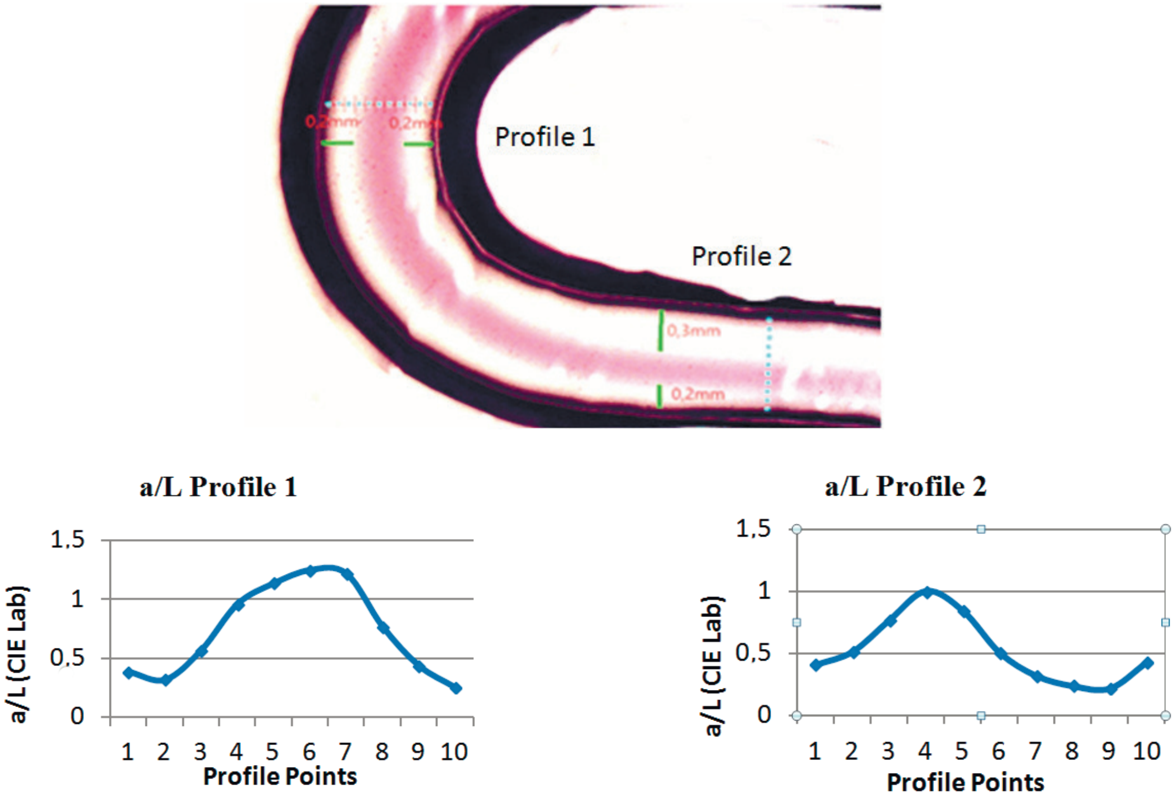


Fig. 13. Analysis of dye flow in a channel already filled with water.

Conclusions

We can conclude that the criteria of hydrodynamic similarity, which are Reynolds, Peclet and Dean numbers, are crucial for development and optimization of microfluidic mixers. These parameters are markers for prompt evaluation and correction of flow modes in various micromixers in order to ensure effective mixing.

We have developed an information-measuring system to monitor the dynamics of flow (mixing) in a microfluidic channel. It allows the principles of mixing in microfluidic channels of different configurations to be quickly illustrated, and modes and dynamics of mixing in various parts of the channels of various microfluidic chips to be evaluated. Using the IMS, we have shown that the flow rate of 400 μl/min is enough for effective mixing in the micromixer used in this study. It is a confirmation of the fact, previously described in research papers, that fast and effective mixing can be achieved in microfluidic micromixers at low Reynolds numbers. The developed IMS is a convenient tool for optimization of mixing modes in channels of micromixers and for development of novel channel configurations in microchips, which allow intensifying processes and boosting the performance of microfluidic systems.

Conflict of interests. *The authors of this article are employed by OOO "NPF "MATERIA MEDICA HOLDING", a company sponsoring this study.*

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