

## Mass transfer coefficient of slug flow for organic solvent-aqueous system in a microreactor

Ana Jurinjak Tušek\*, Iva Anić\*, Želimir Kurtanjek\*, and Bruno Zelić\*\*\*,†

\*Faculty of Food Technology and Biotechnology, University of Zagreb, Pierottijeva 6, HR-10000 Zagreb, Croatia

\*\*Faculty of Chemical Engineering and Technology, University of Zagreb, Marulićev trg 19, HR-10000 Zagreb, Croatia

(Received 16 April 2013 • accepted 23 September 2014)

**Abstract**—Application of microreactor systems could be the next break-through in the intensification of chemical and biochemical processes. The common flow regime for organic solvent-aqueous phase two-phase systems is a segmented flow. Internal circulations in segments cause high mass transfer and conversion. We analyzed slug flow in seven systems of organic solvents and aqueous phase. To analyze how slug lengths in tested systems depend on linear velocity and physical and chemical properties of used organic solvents, regression models were proposed. It was shown that models based on linearization of approximation by potentials give low correlation for slug length prediction; however, application of an essential nonlinear model of multiple layer perceptron (MLP) neural network gives high correlation with  $R^2=0.9$ . General sensitivity analysis was applied for the MLP neural network model, which showed that 80% of variance in slug length for the both phases is accounted for the viscosity and density of the organic phases; 10% is accounted by surface tension of the organic phase, while molecular masses and flow rates each account for 5%. For defined geometry of microreactor, mass transfer has been determined by carrying out the neutralization experiment with NaOH where acetic acid diffuses from organic phase (hexane) into aqueous phase. Estimated mass transfer coefficients were in the range  $k_{La}=4,652-1,9807 \text{ h}^{-1}$ .

Keywords: Liquid-liquid Slug Flow, Regression Model, Mass Transfer Coefficient, Microreactors

### INTRODUCTION

Reducing the reactor scale from “macro” to “micro” opens many new experimental possibilities. This approach in process intensification is a new concept in chemical and biochemical engineering that aims to reduce capital and energy costs [1]. Due to the small dimensions of their microchannels (diameter in range from 10  $\mu\text{m}$  to 500  $\mu\text{m}$ ), microreactors have greater surface-to-volume ratio, ensure effective heat and mass transfer, low amounts of chemical are needed and reaction times are very short. According to Mills et al. [2], multiphase reactions that are catalyzed by homogeneous catalysts, heterogeneous catalysts or biocatalysts provide the basis for most commercial-scale processes for production of diverse products, ranging from petroleum-derived product to fine chemical and pharmaceuticals. Multiphase reactions are still more difficult to conduct than homogeneous reactions, because the efficiency of interactions and mass transfer between phases must be taken into account [3]. New reaction systems being widely used for multiphase (gas-liquid, liquid-liquid, gas-liquid-liquid, etc....) reactions are microreactors [4-8]. To define the optimal process conditions for reaction taking place in a multiphase microreactor, it is necessary to analyze the hydrodynamics in microchannels [9,10]. Stable flow patterns with uniform interfacial areas allow precise mass transfer tuning [11].

Introducing two immiscible liquids in the microreactor, the most usual two flow patterns that can occur are parallel flow or slug (segmented) flow [12]. Flow pattern formation depends on linear velocity [13], ratios of the phases, fluid properties, the channel geometry [11] and the microreactor construction material; all these parameters have to be considered when controlling the flow pattern. Liquid-liquid slug flow is characterized by a series of slugs of one phase separated by slugs of other phase. Each slug served as an individual processing sub volume [14]. Slug flow development and its characteristics depend on two individual transport mechanisms, convection and diffusion, and the physical force, which is the result of interfacial surface tension. Convection takes place in each slug due to internal circulations, while diffusion takes place between two slugs due to concentration gradients [14]. Convection depends on physical properties of fluids, slug geometry and flow velocities, while diffusions depend upon interfacial area available for mass transfer. The internal circulations within both slugs caused by the shear between the wall surface and slug renew the interface enhance the diffusive penetration and increase the reaction rates [15]. This fluid motion enhances mixing within the fluid segments and also improves the rate of diffusion of solute across the liquid/liquid interface by the shearing disruption of concentration gradients within the segments. In slug flow, mass transfer and chemical reaction take place at the interfacial area. According to Ghaini et al. [16], knowledge of interfacial area between two liquid phases is essential in understanding and modelling the flow and transport processes in a given liquid-liquid contactor. Dimensionless analysis is usually used to understand the driving forces of two-phase flows.

†To whom correspondence should be addressed.

E-mail: bzelic@fkit.hr

Copyright by The Korean Institute of Chemical Engineers.

According to Zhao and Middelberg [17], two-phase flows are determined by a balance of inertial, viscous and interfacial forces. The contribution of the forces can be quantified using Reynolds, capillary, Bond and Weber number [18]. The Reynolds number (Re) describes the relative importance of inertial forces to viscous forces. One of the most important parameters in microfluidics is capillary number: ratio of viscous forces to interfacial tension forces. The Bond number represents the ratio of gravity force to capillary force, while the Weber number compares the inertial and capillary forces [19,20].

The aim of this work was to define the scope of the segment flow regimes in a system of several organic solvents and aqueous phase, to explore how slug length in these systems depends on linear velocity, taken into consideration their physical and chemical properties, and at the end to propose regression models based on the experimental data. Volumetric mass transfer coefficient has been estimated in a glass microreactor by carrying out the neutralization experiments.

## MATERIALS AND METHODS

### 1. Materials

#### 1-1. Chemicals

Dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>), ethyl acetate (C<sub>4</sub>H<sub>8</sub>O<sub>2</sub>) and toluene (C<sub>7</sub>H<sub>8</sub>) were purchased from Kemika (Croatia). Ethyl acetoacetate (C<sub>6</sub>H<sub>10</sub>O<sub>3</sub>) and Coomassie Brilliant Blue G 250 were from Fluka (Switzerland), sodium hydroxide (NaOH) and acetic acid (C<sub>2</sub>H<sub>4</sub>O<sub>2</sub>) were from T.T.T. (Croatia). Diethyl ether (C<sub>2</sub>H<sub>5</sub>OC<sub>2</sub>H<sub>5</sub>) was from Chemapol (Czech Republic), hexane (CH<sub>3</sub>(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>) from Merck KGaA (Germany) and chloroform (CHCl<sub>3</sub>) from Carlo Erba (Italy).

#### 1-2. Experimental Set-up

Experiments were performed in a microreactor system (Miconit Microfluidics B.V., Netherlands) consisting of microchip placed into a stainless steel holder that provides leak-free connection. The microchip with borosilicate tubular glass microchannels (length : width : height=332 mm : 150 μm : 150 μm with internal volume of 6 mm<sup>3</sup>) was equipped with two “Y”-shaped inlets and one outlet. Specific surface roughness of the microchannel of the used microreactor was 1 μm. Two syringe pumps (PHD 4400 Syringe Pump Series, Harvard Apparatus, USA) equipped with high-pressure stainless steel syringes (8 cm<sup>3</sup>, Harvard Apparatus, USA) were used for solution supply. The microreactor chip was connected to pumps with fused silica connection (375 μm O.D., 150 μm I.D., Miconit Microfluidics B.V., Netherlands). Fluid flow in microreactor was observed using a microscope (Motic B1-220A, binocular Weltzar, Germany) at magnification of 40x (eyepiece magnification=10x; objective magnification=4x).

### 2. Methods

#### 2-1. Slug Lengths Measurement in Microreactor

Flow profiles for seven systems organic solvents (chloroform, dichloromethane, diethyl ether, ethyl acetate, ethyl acetoacetate, hexane and toluene) - water were analyzed in the microreactor. The two phases were separately introduced into the microreactor. Aqueous phase was stained blue using Coomassie Brilliant Blue G 250 dye, while organic phase was kept colorless. All experiments were performed at equal ratio of flow rates. Flow profiles were observed with a microscope and photos of flow profiles were taken

for all investigated flow rates (in range of total flow rate from q=2 mm<sup>3</sup> min<sup>-1</sup> to approximately q=200 mm<sup>3</sup> min<sup>-1</sup>; maximal tested flow rate varied depending on used organic solvent). The photos of the flow profiles were taken at the middle of the microreactor microchannel after the slow stabilization (after four residence times). Photos of flow profiles were used for determination of segment length for both organic and aqueous phase using software package Paint (Microsoft Corporation, USA). Segment lengths were obtained by measuring the distance between first and the last pixel. All experiments were performed in triplicate and average values are presented. In the 95% confidence range the results showed no significant difference.

#### 2-2. Nonlinear Regression Models

To predict the slug lengths of both organic and aqueous phase non-linear regression models were proposed. Slug length  $l_{o(a)}$  (μm) was modelled as a function of superficial flow velocity,  $v$  (m s<sup>-1</sup>); organic solvent molar mass,  $M_o$  (g mol<sup>-1</sup>); organic solvent density,  $\rho$  (kg m<sup>-3</sup>); organic solvent viscosity,  $\mu$  (Pa s) and organic solvent surface tension,  $\gamma$  (N m<sup>-1</sup>) (Eqs. (1)-(2)). Physical and chemical properties of used organic solvents are given in Table 1.

$$l_{o(a)} = f(v, M_o, \rho, \mu, \gamma) \quad (1)$$

$$l_{o(a)} = b_0 \cdot v^{b_1} \cdot M_o^{b_2} \cdot \rho^{b_3} \cdot \mu^{b_4} \cdot \gamma^{b_5} \quad (2)$$

Taking into account physical and chemical properties of used organic solvents, characteristic dimensionless numbers were included into the model (Eqs. (3)-(4)).

$$l_o = \left( \frac{v_o \cdot d \cdot \rho_o}{\mu_o} \right)^{b_1} \cdot \left( \frac{v_a \cdot \mu_a}{\gamma_o} \right)^{b_2} \cdot M_{r_o}^{b_3} \quad (3)$$

$$l_o = Re_o^{b_1} \cdot Ca^{b_2} \cdot M_{r_o}^{b_3} \quad (4)$$

Possible effect of molar mass on system behavior is included in the model in dimensionless form as a ratio molar mass of tested organic solvents/molar mass of hexane as referent solvent (Eq. (5)).

$$\frac{l_o}{l_{hex}} = Re_o^{b_1} \cdot Ca^{b_2} \cdot \left( \frac{M_{r_o}}{M_{r_{hex}}} \right)^{b_3} \quad (5)$$

Parameters of nonlinear regression model were estimated using the Levenberg-Marquardt algorithm implemented in Statistica 10.0 (StatSoft, USA). The algorithm ensures numerical solutions in function parameter space using least squares method. Calculation was

**Table 1. Physical and chemical properties of seven organic solvent-aqueous phase systems**

Organic solvent (T=25 °C)	$M_r$ (g mol <sup>-1</sup> )	$\rho$ (kg m <sup>-3</sup> )	$\mu \cdot 10^{-4}$ (Pa s)	$\gamma$ (mN m <sup>-1</sup> )
Chloroform	119.38	1479.90	5.42	26.67
Dichloromethane	84.93	1324.00	4.30	26.52
Diethyl ether	74.12	713.40	2.23	16.61
Ethyl acetate	88.10	9101.00	4.30	23.50
Ethyl acetoacetate	130.14	1021.00	17.00	30.27
Hexane	86.18	654.80	2.94	18.43
Toluene	92.14	862.27	5.80	28.82
Water (T=25 °C)	18.02	997.00	8.92	71.99

performed in 50 iterations with convergence of  $10^{-6}$  and confidence interval of 95%.

Alternatively, an essentially nonlinear neural multiple layer perceptron (MLP) network was applied. MLP neural network consisted of five inputs, six hidden neurons and two outputs. Tangh(x) function was selected as neuron activity function. The model structure is given by the following expression (Eq. (6)):

$$\begin{pmatrix} l_a \\ l_o \end{pmatrix} = \text{ANN} \left( 5 \times 6 \times 2 \begin{pmatrix} q \\ \gamma \\ \mu \\ \rho \\ M_r \end{pmatrix} \right) \quad (6)$$

The artificial neural network (ANN) training was performed with separation of the data into training and validation sets as 70:30 ratio. Back error propagation algorithm available in Statistica 10.0 (StatSoft, USA) was applied for the model training.

Statistical significance of the organic phase properties and flow rate on slug length prediction was evaluated by the general sensitivities as the ratio of variances of individual parameter relative to the total variance given by Eq. (7).

$$S(\beta) = \frac{\sigma^2(\beta)}{\sigma_{tot}^2} \quad (7)$$

### 2-3. Linear Regression Models

By expressing logarithm forms of Eq. (2) and Eq. (5), linear regression models for prediction of slug lengths of the organic and aqueous phases were obtained (Eq. (8)-(9)):

$$l_{o(a)} = \ln \beta_0 + \beta_1 \cdot \ln v + \beta_2 \cdot \ln M_r + \beta_3 \cdot \ln \rho + \beta_4 \cdot \ln \mu + \beta_5 \cdot \ln \gamma \quad (8)$$

$$\frac{l_o}{l_{hex}} = \beta_0 + \beta_1 \cdot \ln Re_o + \beta_2 \cdot \ln Ca + \beta_3 \cdot \ln \left( \frac{M_r}{M_{r_{hex}}} \right) \quad (9)$$

Parameters of linear regression models were also estimated using Statistica 10.0 (StatSoft, USA).

### 2-4. Mass Transfer Coefficient Estimation

For the defined geometry of microreactor in slug flow profile, volumetric coefficient of mass transfer was determined by neutralization reaction of acetic acid with sodium hydroxide in the hexane aqueous two-phase system [13]. Acetic acid solution in hexane ( $c=0.6 \text{ mol dm}^{-3}$ ) and aqueous sodium hydroxide solution ( $c=0.65 \text{ mol dm}^{-3}$ ) were introduced into the microreactor at equal flow rates. Phenol red indicator was added into aqueous sodium hydroxide solution (in alkaline stained purple). Hexane was chosen because of its frequent use as a solvent in the biotransformations performed in microreactors [8,21]. Experiments were carried out at following total flow rates:  $0.5 \text{ mm}^3 \text{ min}^{-1}$ ,  $1 \text{ mm}^3 \text{ min}^{-1}$ ,  $2 \text{ mm}^3 \text{ min}^{-1}$ ,  $3 \text{ mm}^3 \text{ min}^{-1}$ ,  $4 \text{ mm}^3 \text{ min}^{-1}$  and  $5 \text{ mm}^3 \text{ min}^{-1}$ . The neutralization reaction occurs in the aqueous phase, because acetic acid diffuses from the organic to aqueous phase. Position of complete neutralization of the slug flow in a microreactor (change of color of the aqueous phase from purple to yellow) was observed with a microscope. The coefficients of mass transfer at specific flow rates were calculated by using the mean distance required for complete neutraliza-

tion of acetic acid. According to Burns and Ramshaw [13], acetic acid transfer rate is defined with Eq. (10):

$$\frac{dc}{dt} = -k_L a \cdot \Delta c \quad (10)$$

where  $c$  represents acetic acid concentration in organic phase,  $\Delta c$  concentration gradient between segments of organic and aqueous phase,  $k$  mass transfer coefficient and  $a$  surface area where mass transfer takes place. An assumption that acetic acid is consumed instantly when diffuses into aqueous phase is included into calculation. Concentration gradient between segments can be approximated with acetic acid concentration in organic phase (Eq. (11)).

$$\frac{dc_o}{dt} = -k_L a \cdot \Delta c_o \quad (11)$$

By solving the balance expressed with Eq. (11) time necessary for defined percent of acetic acid neutralization is obtained (Eq. (12)).

$$t = -\frac{1}{k_L a} \cdot \ln(1 - \alpha) \quad (12)$$

When calculating surface area for mass transfer in slug flow, two cases are possible: (i) segments of one phase are surrounded with layer of other phase, e.g., total surface area of all slugs is available for mass transfer, or (ii) segments are in contact with microchannel surface and only their ends are available for mass transfer. For the tested system acetic acid dissolved in hexane and aqueous solution of sodium hydroxide, the surface area for mass transfer was calculated assuming that only lateral surfaces are involved in mass transfer (Eq. (13))

$$a = \frac{2 \cdot w^2}{l \cdot w^2} = \frac{2}{l} \quad (13)$$

where  $w$  represents microchannel width and  $l$  segment length.

## RESULTS AND DISCUSSION

### 1. Segment Length Measurement

Introducing two immiscible liquids into the microreactor, slug flow can be developed [22]. Slug or segmented flow is composed of alternating segments of two phases. The length of the slugs depends on microchannel geometry, construction material and physical and chemical characteristics of used liquids. We used seven organic solvents for analysis: (chloroform, dichloromethane, diethyl ether, ethyl acetate, ethyl acetoacetate, hexane, and toluene) immiscible with water. Flow profiles were analyzed for the flow rates in the range from  $q=2 \text{ mm}^3 \text{ min}^{-1}$  to  $q=200 \text{ mm}^3 \text{ min}^{-1}$ . Maximum tested flow rate depends on used organic solvent.

The experimental results show that when two immiscible liquids are introduced in "Y" shaped microchannel, with specific surface roughness of  $1 \mu\text{m}$  (Micronit Microfluidics B.V., Netherlands), at equal flow rates at  $25^\circ\text{C}$  slug flow was developed at all analyzed flow rates. Fig. 1 presents flow profiles for all seven systems at three flow rates ( $q=5 \text{ mm}^3 \text{ min}^{-1}$ ,  $20 \text{ mm}^3 \text{ min}^{-1}$ ,  $50 \text{ mm}^3 \text{ min}^{-1}$ ). In all photographs the organic phase is colorless while aqueous phase was stained blue. Just by observing these pictures it can be noticed that development of flow profiles with different organic solvent

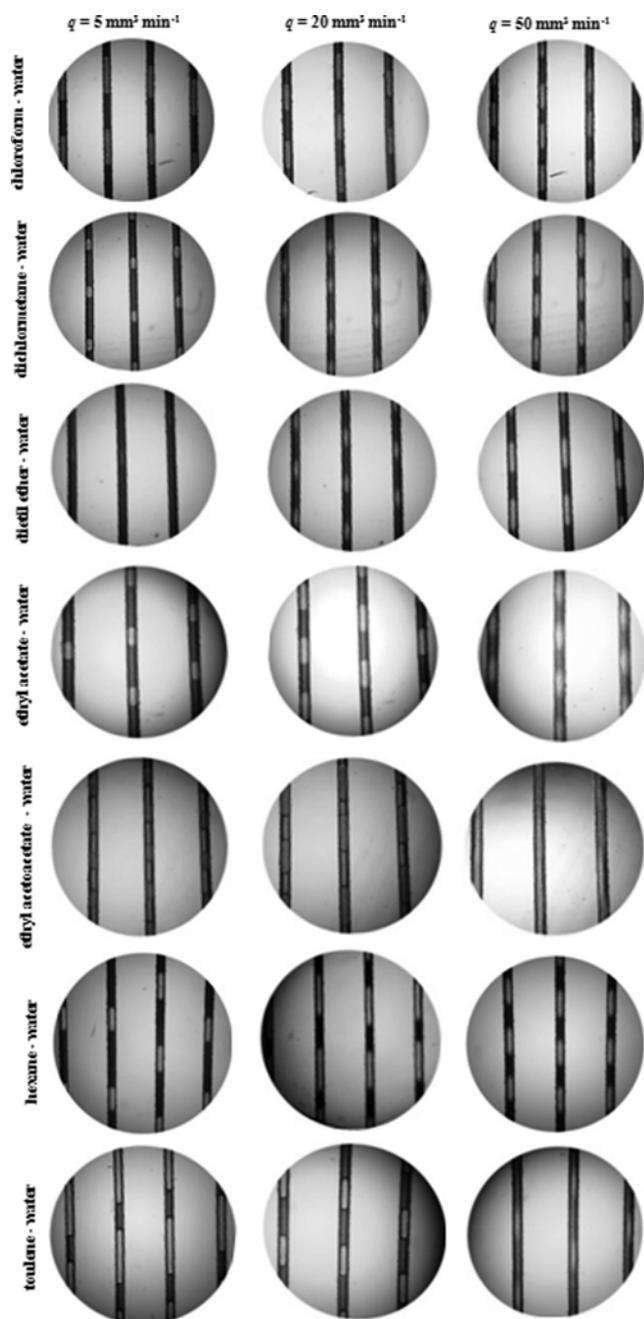


Fig. 1. Flow profiles at different flow rates for seven organic solvent-water two-phase systems.

differs; slugs differ in length and geometry. To get the better insight in change of slug dimension at different flow rates, slug lengths of organic and aqueous phases were measured for all analyzed organic solvent-aqueous phase systems (Fig. 2), from photographs taken during observation of the flow in microreactor using a microscope.

By observing the graphs it can be seen that five systems (chloroform, dichloromethane, diethyl ether, ethyl acetate and hexane) have one thing in common: at low values of flow rate the segments of aqueous phase are longer than segments of organic phase; increasing the flow rates, the length of slugs of aqueous phase decreases. For each of the systems there is flow rate at which slug lengths “change

places.” In case of chloroform-water two-phase system diffusion of color from aqueous phase to organic phase was noticed at lowest tested flow rate ( $q=1 \text{ mm}^3 \text{ min}^{-1}$ ). Slugs of organic phase are evenly distributed between segments of aqueous phase, and are considerably smaller than slugs of aqueous phase at low flow rates. Increasing the flow rate, length of slugs of organic phase is growing and at  $q=15 \text{ mm}^3 \text{ min}^{-1}$  slugs of organic phase are becoming slightly longer than slugs of aqueous phase. Furthermore, the flow rate increment has no effect: slugs of both phases have approximately the same length. Analyzing the slug lengths of organic and aqueous phase in dichloromethane-water two-phase system, it was noticed that at low values of flow rate there is a clear interfacial border between slugs. Also, there is a thin film of aqueous phase around organic phase slugs. When working with diethyl ether as organic phase, at flow rates lower than  $q=5 \text{ mm}^3 \text{ min}^{-1}$  dye diffuses from aqueous phase to organic phase and it is impossible to define the slug borders. Slugs of both phases can be distinguished in a range of flow rate from  $q=5 \text{ mm}^3 \text{ min}^{-1}$  to  $q=120 \text{ mm}^3 \text{ min}^{-1}$ . At total flow rate from  $q=1 \text{ mm}^3 \text{ min}^{-1}$  to  $q=10 \text{ mm}^3 \text{ min}^{-1}$  in two-phase system hexane-water, organic phase slugs are significantly smaller than segments of aqueous phase. At  $q=15 \text{ mm}^3 \text{ min}^{-1}$  slug lengths “change places”; organic phase slugs become greater than aqueous phase slugs. Increasing the total flow rate over  $q=100 \text{ mm}^3 \text{ min}^{-1}$  length of slugs of both organic and aqueous phase is approximately the same. Two-phase system ethyl acetoacetate-water differs from all previously described. In all other tested systems the organic phase formed concave slugs and aqueous phase convex slugs, but in case of acetoacetate-water two-phase system, the organic phase formed convex slugs, whereas aqueous phase formed concave slugs. An interesting phenomenon was also noticed in the toluene-aqueous phase two-phase system: at low values of flow rate (lower than  $q=15 \text{ mm}^3 \text{ min}^{-1}$ ) organic phase forms slugs longer than aqueous phase slugs; at higher values of flow rate both phase segments have similar length.

## 2. Non-linear Regression Models

To analyze how length of slugs in seven tested systems (chloroform - water, dichloromethane- water, diethyl ether - water, ethyl acetate - water, ethyl acetoacetate - water, hexane - water and toluene - water) depends on linear velocity and physical and chemical properties of used organic solvents regression model are proposed. According to Eq. (1) the length of slugs dependent on linear velocity and physical and chemical properties of used organic solvents is highly non-linear.

When Eq. (2) is expressed in linear form using logarithmic transformations, a disruption of order of magnitude of simulated data occurs. For easier and better comparison of the experimental data and model predictions, it is more suitable to use the non-linear models.

Non-linear regression models were proposed for prediction of length of slugs of both organic and aqueous phase. Results of dispersion of segments length of organic and aqueous phase comparing to model predictions are presented in Fig. 3.

Parameters of both models, according to Eq. (2), were estimated using Levenberg-Marquardt algorithm implemented in Statistica 10.0 with confidence interval of 95% (Table 2).

From Fig. 3(a) (dispersion of slug lengths of organic phase) the biggest dispersion of slug lengths is for two-phase systems with di-

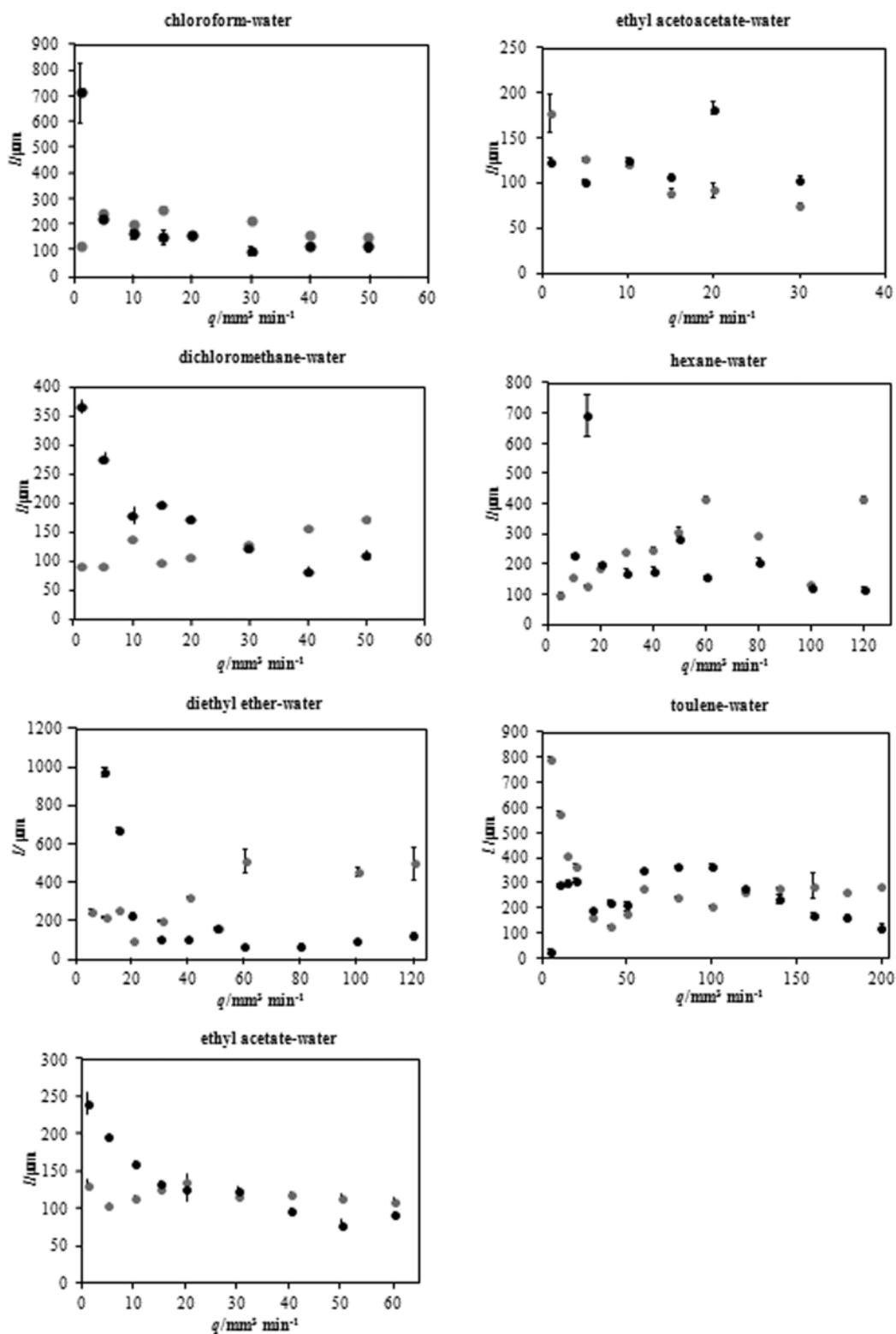


Fig. 2. Slug lengths for seven organic solvent-water systems at flow rates analyzed in the range  $q=1\text{-}200 \text{ mm}^3 \text{ min}^{-1}$ ; (○) organic phase, (●) aqueous phase.

ethyl ether and toluene as an organic phase can be noticed. In a case of these two organic phases, slug lengths change mostly with changing the flow rate. This phenomenon can be explained by analyzing the physical properties of used organic solvents (Table 1); it

can be seen that diethyl ether has the lowest value of surface tension of all used organic solvents. The lowest data dispersion was noticed in case of dichloromethane as organic phase. For all estimated non-linear regression model parameters used for predic-

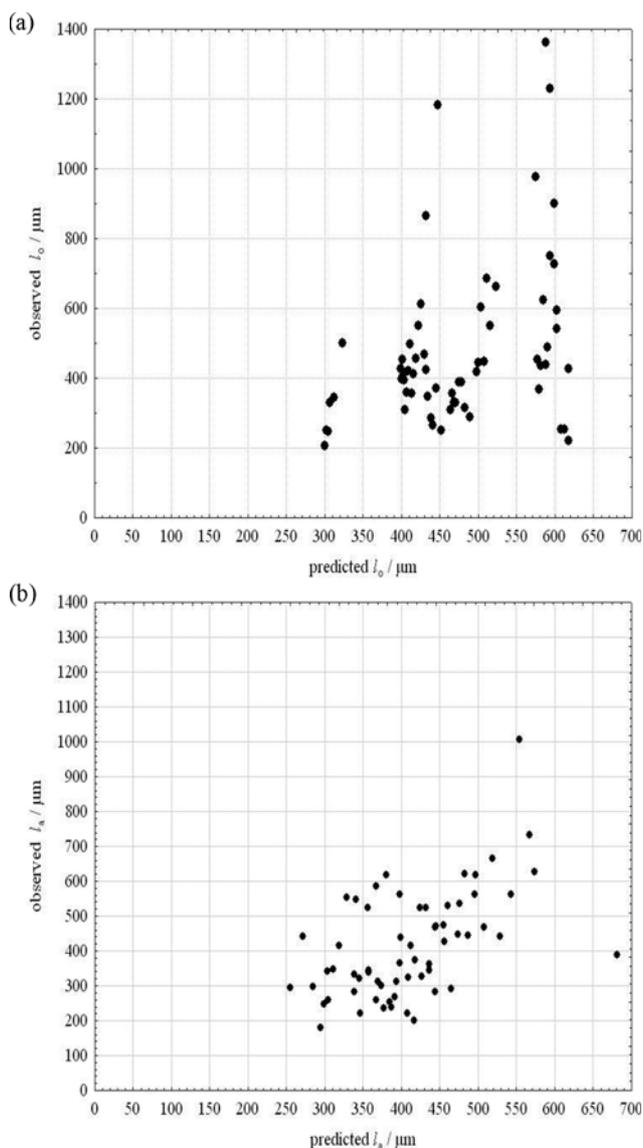


Fig. 3. Dispersion of slug lengths of (a) organic phase and (b) aqueous phase comparing to non-linear regression model predictions ( $R^2$  (organic phase)=0.368,  $R^2$  (aqueous phase)=0.531).

tion of slug lengths of organic phase (Table 2)  $p$ -values are greater than 0.05, indicating that there are no significant model parameters. Dispersion of slug lengths of aqueous phase in two-phase sys-

tem organic solvent-aqueous phase is quite uniform (Fig. 3(b)), with only two outliers (slugs in two-phase system diethyl ether-aqueous phase and toluene-aqueous phase). Slug lengths of aqueous phase vary in range from 200  $\mu\text{m}$  to 700  $\mu\text{m}$ . From  $p$ -values of estimated parameters of non-linear model for prediction of slug lengths of aqueous phases, it can be seen that parameter  $b_1$  is significant for the model. This parameter comes with superficial flow velocity in the model. Other parameters have no significant influence. By increasing the number of parameters included in the regression model, better agreement between model and experimental data can be achieved. On the other hand, the model becomes more complex. For fast analysis of experimental data it is usually more convenient to use simple models with small number of parameters. To simplify, the prediction of both organic phase and aqueous phase slug lengths prediction by non-linear regression model that includes dimensionless numbers was also proposed (Eqs. (3)-(5)). Physical properties of used organic solvents were included in two dimensionless numbers: Reynolds number and capillary number. To exclude the possible influence on system behavior, molar mass was included in the model in dimensionless form as a ratio of tested organic solvent molar mass and molar mass of hexane. Slug length of analyzed organic solvent was also expressed in dimensionless form by dividing it with an average value of hexane slug length. By introducing dimensionless form, the number of model parameters is reduced from six to four. Dependence of measured and calculated values of ratio of organic phase slug lengths and average value of hexane slug length (Fig. 4) shows a similar trend as a dispersion of slug lengths of organic phase (Fig. 3(a)). Slug length of diethyl ether and toluene varies mostly. Estimated model parameters values are presented in Table 3. Statistical analysis showed that there is no significant parameter; for all three parameters,  $p$ -values are higher than 0.05. Based on these results it can be concluded that introducing the dimensionless numbers into the model, the influence of physical and chemical properties of used organic solvent on slug lengths of organic and aqueous phase is not evident.

### 3. Linear Regression Models

To test the relationship between physical properties (viscosity, density and surface tension) and chemical properties (molar mass), and slug lengths of both organic and aqueous phases in two-phase systems at defined flow rate (or superficial flow velocity) linear regression models are proposed. Logarithmic linearization is used (Eq. (6)). Parameters of models (prediction of organic phase slug lengths and aqueous phase slug lengths) were estimated using variance minimization (Table 4).

Table 2. Non-linear regression models coefficients for prediction of organic and aqueous phase slug lengths

Parameter	Organic phase		Aqueous phase	
	Value	$P$ -value	Value	$P$ -value
$\beta_0$	105.622 $\pm$ 411.194	0.798	59.995 $\pm$ 147.838	0.686
$\beta_1$	-0.022 $\pm$ 0.061	0.724	-0.158 $\pm$ 0.036	0
$\beta_2$	0.849 $\pm$ 0.910	0.355	-0.115 $\pm$ 0.607	0.851
$\beta_3$	-0.125 $\pm$ 0.418	0.766	0.043 $\pm$ 0.253	0.864
$\beta_4$	-0.557 $\pm$ 0.494	0.264	-0.392 $\pm$ 0.298	0.193
$\beta_5$	-0.003 $\pm$ 0.928	0.998	0.455 $\pm$ 0.547	0.409

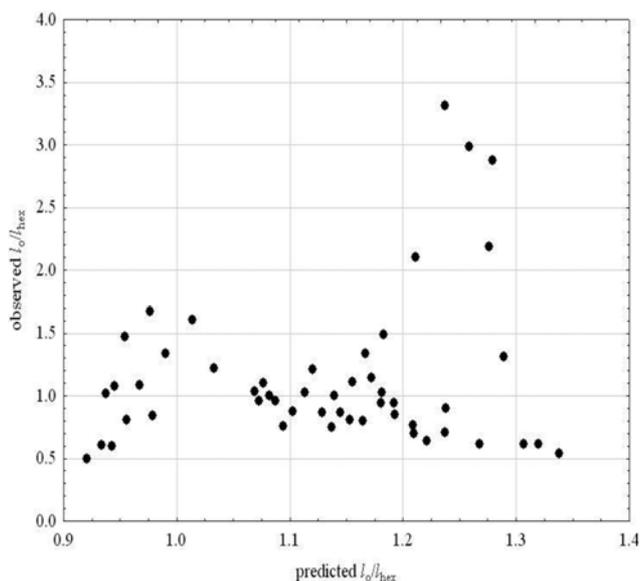


Fig. 4. Dispersion of relative slug lengths of organic phase comparing to non-linear regression model prediction including dimensionless numbers ( $R^2=0.193$ ).

Table 3. Non-linear regression models coefficients including dimensionless numbers

Parameter	Value	P-value
$\beta_1$	$-0.008 \pm 0.052$	0.877
$\beta_2$	$-0.025 \pm 0.016$	0.110
$\beta_3$	$-0.659 \pm 0.055$	0.197

Table 4. Linear regression models coefficients for prediction of organic and aqueous phase slug lengths

Parameter	Organic phase		Aqueous phase	
	Value	P-value	Value	P-value
$\beta_0$	$5.870 \pm 1.482$	0	$4.319 \pm 1.186$	0
$\beta_1$	$-0.025 \pm 0.021$	0.216	$-0.082 \pm 0.016$	0
$\beta_2$	$2.275 \pm 0.727$	0.003	$0.572 \pm 0.582$	0.329
$\beta_3$	$-0.857 \pm 0.316$	0.008	$-0.497 \pm 0.253$	0.054
$\beta_4$	$-1.133 \pm 0.316$	0	$-0.654 \pm 0.253$	0.012
$\beta_5$	$1.366 \pm 0.614$	0.030	$1.337 \pm 0.412$	0.009

By analyzing the estimated parameters for slug length of organic phase, it was observed that the most significant parameter is  $\beta_3$  with  $p$ -value of 0.0002. This parameter represents the intercept on the axis y. Also, the physical and chemical properties of used organic solvent are significant for the model; this effect was not noticed with non-linear form of model. In case of model for prediction of aqueous phase segments length, the most significant was parameter  $\beta_1$  ( $p$ -value 0.000004) coming with superficial flow velocity; parameters  $\beta_2$  (coming with molar mass) and  $\beta_3$  (coming with density) showed no significance. It is interesting to compare the significance of parameters coming with superficial flow velocity for prediction of organic phase slug length and aqueous phase slug length.

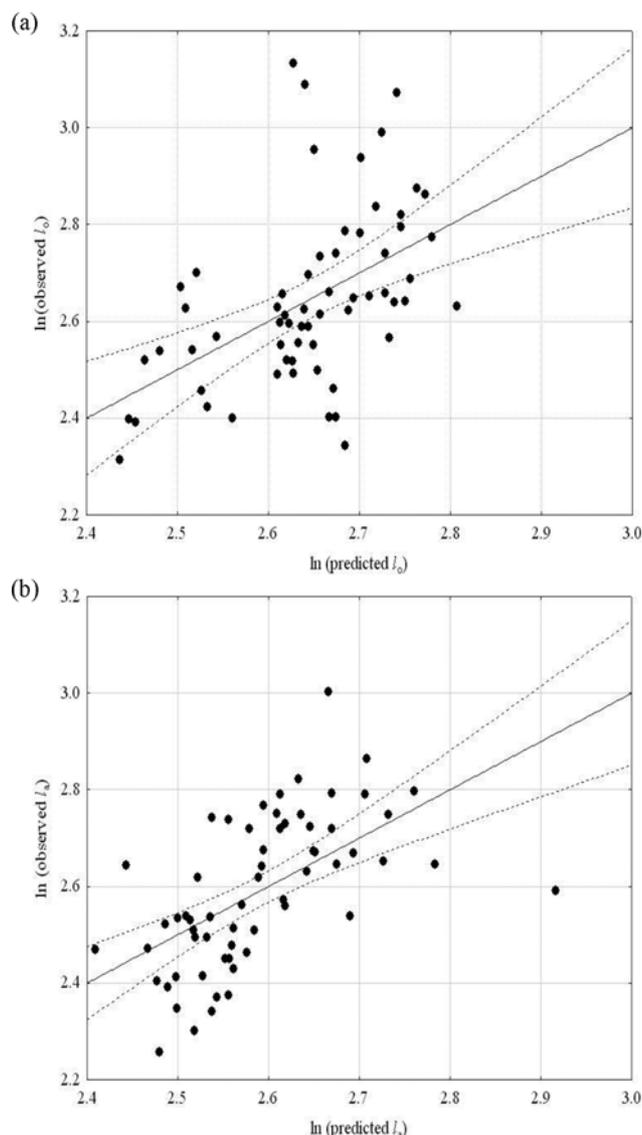


Fig. 5. Dispersion of slug lengths of (a) organic phase, (b) aqueous phase comparing to linear regression model predictions ( $R^2$  (organic phase)=0.247,  $R^2$  (aqueous phase)=0.343).

In case of a model for organic phase, this parameter shows no significance, while in case of aqueous phase it is the most important parameter. Graphs of dispersion of experimental and calculated slug lengths of both phases show that models describe measured data approximately (Fig. 5); there are some experimental data out of 95% confidence interval.

#### 4. Neural Network Model

Results of prediction of MLP ANN (5 x 6 x 2) are shown in Fig. 6. Model predictions of slug lengths of both phases versus experimentally determined lengths for the complete experimental data set are depicted. The model has five input nodes corresponding to the parameters of the organic phases and flow rate, and simultaneous two output variables corresponding to slug lengths of each of the phases (Eq. (6)). Function  $\tanh(x)$  was applied for neuron activity model. The criterion of minimum variance in prediction of the both lengths was selected. Backward error propagation algorithm

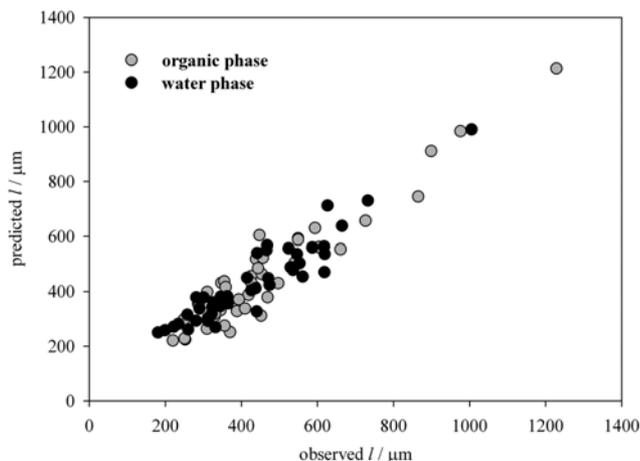


Fig. 6. Nonlinear MLP model with five inputs, six hidden nodes, and two outputs.

was applied for the model training. To validate the model the data set was split into two subsets with the training and testing data sets in the ratio 70 : 30. Selected is as the best “simplest” network with minimal number of hidden neurons, six neurons compared to five inputs, which gave high predictivity with  $R^2=0.9014$  and with the significance level ( $p$ -value) for the validation with untrained data of  $p=0.87$ .

Statistically, the importance of individual parameters of the organic phases and flow rate is evaluated based on simulation of the selected model. Obtained are the following relative sensitivity coefficients (Eq. (7)): viscosity (40%), density (38%), surface tension (10%), molecular mass (7%), and flow rate (5%), shown on Fig. 7. Relative unimportance of the flow rate is probably due to the selected experimental conditions for equal flow rates for each of the component.

##### 5. Mass Transfer Coefficients for Two-phase Liquid-liquid System

Two-phase system hexane-aqueous phase was used for measure-

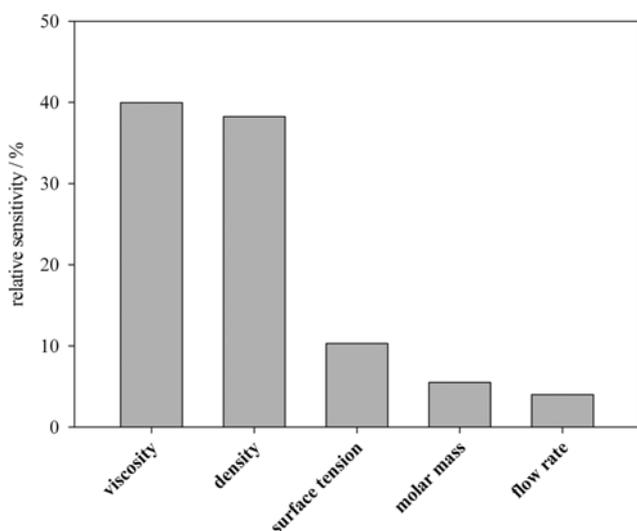


Fig. 7. General relative sensitivities  $S$  (%) of organic phase (viscosity, density, surface tension, molar mass) parameters and flow rate on prediction of the slug lengths.

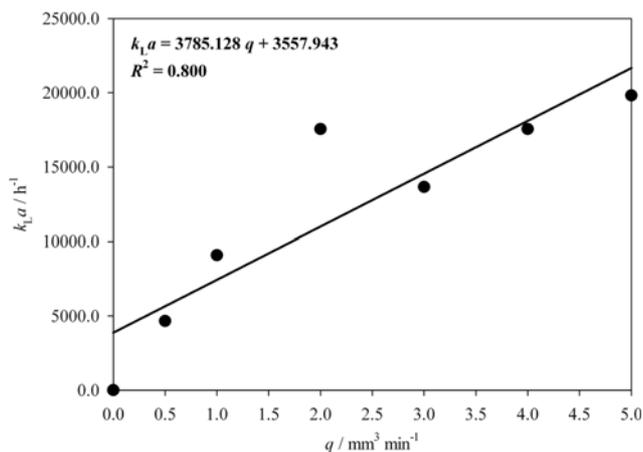


Fig. 8. Dependence of mass transfer coefficient on flow rate.

ment of mass transfer coefficient. According to Burns and Ramshaw [13] the method is based on simple neutralization. Aqueous sodium hydroxide solution with phenol red indicator (in alkaline stained purple) was introduced at one inflow and acetic acid solution in hexane at the other. The spot of total neutralization was determined, observing the process in microreactor under the microscope (indicator changes its color from purple to yellow). Experiments were performed at previously mentioned flow rates.

Taking into account the time needed for neutralization (neutralization took place in time range from 0.4 s to 1.8 s, depending on flow rate), mass transfer coefficients ( $k_L a$ ) were calculated according to Eq. (12) (Fig. 8). Mass transfer area,  $a$ , for tested system (hexane-aqueous phase) was calculated using the assumption that only lateral surface of slugs takes place in mass transfer (Eq. (13)).

Obtained values of volumetric mass transfer coefficients for two-phase system hexane-aqueous phase for defined microreactor geometry were in the range from  $k_L a=4,652-19,807 \text{ h}^{-1}$ . For microreactor systems characteristic values of mass transfer coefficients are in the range from  $k_L a=18,000-54,000 \text{ h}^{-1}$ , while for macroreactor systems the mass transfer coefficients are in the range from  $k_L a=36-288 \text{ h}^{-1}$  [23]. Based on obtained results for volumetric mass transfer coefficient, it can be concluded that the reaction rate for tested two-phase systems is two orders of magnitude higher than for macroreactor systems. This result is consistent with the literature because it shows the efficiency of microreactors for mass transfer.

## CONCLUSION

Although quite simple and statistically not precise enough, regression models describe qualitatively the organic solvent-aqueous phase two-phase system with low accuracy. Applying a true nonlinear model with neural networks, statistical predictions of the slug lengths are of high significance ( $R^2=0.9$ ). The global sensitivity analysis based on the neural network predictions shows that viscosity and density of the organic phases account for 80% of the length predictions. Regression models can be used for approximate prediction of slug lengths of both phases in two-phase systems, taking into account physical and chemical properties of used organic solvent. Also, the developed model can be easily used for prediction

of surface area between two-phase when biotransformations are performed on contact area between organic and aqueous phase. Experimental measurement based on neutralization in defined microreactor geometry and mass transfer calculation showed the efficiency of microreactors for mass transfer between two phases.

#### ACKNOWLEDGEMENT

This research was financially supported through the National Foundation for Science, Higher Education and Technological Development of the Republic of Croatia.

#### LIST OF SYMBOLS

a	: mass transfer area [m <sup>2</sup> ]
b	: parameter of non-linear regression model
c	: concentration [mol dm <sup>-3</sup> ]
Ca	: capillary number [-]
k <sub>L</sub> a	: mass transfer coefficient [h <sup>-1</sup> ]
l	: slug length [μm]
M <sub>r</sub>	: molar mass [g mol <sup>-1</sup> ]
q	: flow rate [μL min <sup>-1</sup> ]
Re	: Reynolds number [-]
S	: parameter sensitivity
t	: time [s]
v	: superficial flow velocity [m s <sup>-1</sup> ]
w	: microchannel width [μm]
x	: proportion of acetic acid consumed [-]
β	: parameter of linear regression model
γ	: surface tension [N m <sup>-1</sup> ]
μ	: viscosity [Pa s]
ρ	: density [kg m <sup>-3</sup> ]
σ <sup>2</sup>	: variance
a	: aqueous phase
o	: organic phase

#### REFERENCES

1. A. Pohar and I. Plazl, *Chem. Biochem. Eng. Q.*, **23**, 537 (2009).
2. P. L. Mills, D. J. Quiram and J. F. Ryley, *Chem. Eng. Sci.*, **62**, 6992 (2007).
3. J. Kobayashi, M. Yuichiro and S. Kobayashi, *Chem. Asian J.*, **1-2**, 22 (2006).
4. G. Dumann, U. Quittmann, L. Gröschel, D. W. Agar, O. Wörz and K. Morgenschweis, *Catal. Today*, **79-80**, 433 (2003).
5. R. Halder, A. Lawal and R. Damavarapu, *Catal. Today*, **125**, 74 (2007).
6. Y. Voloshin, R. Halder and A. Lawal, *Catal. Today*, **125**, 40 (2007).
7. R. A. Maurya, C. P. Park and D.-P. Kim, *Beilstein J. Org. Chem.*, **7**, 1158 (2011).
8. A. Šalić, A. Tušek, Ž. Kurtanjek and B. Zelić, *Biotechnol. Bioproc. Eng.*, **16**, 495 (2011).
9. A. L. Dessimoz, L. Cavin, A. Renken and L. Kiwi-Minsker, *Chem. Eng. Sci.*, **63**, 4035 (2008).
10. S. Waelchli and P. R. von Rohr, *Int. J. Multiphase Flow*, **32**, 791 (2006).
11. M. N. Kashid and D. W. Agar, *Chem. Eng. J.*, **131**, 1 (2007).
12. G. N. Doku, W. Verboom, D. N. Reinhoudt and A. van den Berg, *Tetrahedron*, **61**, 2733 (2005).
13. J. R. Burns and C. Ramshaw, *Lab Chip*, **1**, 10 (2001).
14. M. N. Kashid, F. Platte, D. W. Agar and S. Turek, *J. Comput. Appl. Math.*, **203**, 487 (2007).
15. M. N. Kashid, A. Renken and L. Kiwi-Minsker, *Chem. Eng. Res. Des.*, **88**, 362 (2010).
16. A. Ghaini, A. M. N. Kashid and D. W. Agar, *Chem. Eng. Process.*, **49**, 358 (2010).
17. C.-X. Zhao and A. P. J. Middelberg, *Chem. Eng. Sci.*, **66**, 1394 (2011).
18. A. L. Dessimoz, P. Raspail, C. Berguerand and L. Kiwi-Minsker, *Chem. Eng. J.*, **160**, 882 (2010).
19. M. K. Akbar, D. A. Plummer and S. M. Ghiaasiaan, *Int. J. Multiphase Flow*, **29**, 855 (2003).
20. M. C. Ruzicka, *Chem. Eng. Res. Des.*, **86**, 835 (2008).
21. A. Tušek, A. Šalić, Ž. Kurtanjek and B. Zelić, *Eng. Life Sci.*, **12**, 49 (2012).
22. R. Gupta, D. F. Fletcher and B. S. Haynes, *Chem. Eng. Sci.*, **64**, 2941 (2009).
23. M. W. Losey, M. A. Schmidt and K. F. Jensen, *Ind. Eng. Chem. Res.*, **40**, 2555 (2001).