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Mathematical Model for Mixing Reactants in a Capillary Microreactor by Transverse Diffusion of Laminar Flow Profiles

Victor Okhonin, Edmund Wong, and Sergey N. Krylov*

Department of Chemistry, York University, Toronto, Ontario M3J 1P3, Canada

Transverse diffusion of laminar flow profiles (TDLFP) was recently suggested as a generic approach for mixing reactants inside a capillary microreactor. Conceptually, solutions of reactants are injected inside the capillary by high pressure as a series of consecutive plugs. Because of the laminar nature of the flow inside the capillary, the nondiffused plugs have parabolic profiles with predominantly longitudinal interfaces between the plugs. After the injection, the reactants are mixed by transverse diffusion across the longitudinal interfaces. TDLFP-based mixing is still in its infancy as only the principle was proved. Here, we develop the theory of TDLFP and introduce a dimensionless parameter, York number, which can be used in predicting the quality of TDLFP-based mixing. The theory uses a single simplifying assumption that the longitudinal diffusion is negligible; this assumption is readily satisfied. We then develop a numerical model of TDLFP and use it to simulate the concentration profiles of three reactants mixed by TDLFP in the capillary. The correlation between the York number and quality of mixing is analyzed. Two ways of improving the quality of TDLFP-based mixing are suggested and studied: (i) increasing the longitudinal interface between the plugs by a long last plug of a solvent and (ii) "shaking" the injected reactants by a series of alternating negative and positive pressure pulses. The developed theory and computational simulation of TDLFP will stimulate the practical use of capillary microreactors.

Microreactors, which facilitate the conduction of chemical processes in nanoliter and subnanoliter volumes, are highly attractive for a variety of applications including high-throughput screening,[1] multiplexed bioanalyses,[2] studies of single molecules,[3] and analyses of chemical contents of single cells.[4] The major requirements for microreactors include (i) easy and reproducible mixing, (ii) negligible evaporation, and (iii) simple interfacing with sensitive and informative analytical tools. These requirements can be met by confining the nanoliter-volume reaction mixture in a microfabricated well,[5] oil drop,[6] or capillary.[7] Each of the three formats has its specific advantages and limitations. The well- and drop- formats require precise microprinting instrumentation for the accurate mixing of reactants. The well format may require complicated technological solutions to close the wells to prevent evaporation. Both formats are not easily interfaced with separation techniques and limited to in situ optical detection. These two formats require either the use of relatively noisy fluorophore–quencher systems for monitoring noncovalent binding or rare fluorogenic substrates for studying enzymatic reactions (fluorogenic substrates do not fluoresce before becoming products).

Capillary microreactors are well-suited for the prevention of evaporation and the analysis requirements. Indeed, because of the extremely small liquid–air interface at the capillary orifice, evaporation can be neglected for as long as hours. In addition, capillary microreactors are naturally interfaced with highly efficient analytical techniques, such as capillary electrophoresis and capillary chromatography. Capillary separation can, in turn, be easily interfaced with different types of detection including optical, electrochemical, and mass-spectrometric, thus, providing ultimate analytical capabilities. The challenge that has so far precluded capillary microreactors from wide practical application was the requirement for easy and reproducible mixing of reactants. Two methods have been proposed for mixing reactants inside capillaries: electrokinetic mixing and mixing by longitudinal diffusion. Electrokinetic mixing is based on the differential velocities of reactants in an electric field applied to the ends of the capillary.[8,9] This technique also requires the knowledge of the electrophoretic mobilities of the reactants, which cannot be calculated and must be experimentally determined. Electrokinetic mixing becomes impractical when the reactants are dissolved in different buffers or when three or more reactants are to be mixed. The other method, mixing by longitudinal diffusion, is based on diffusion through transverse interfaces between separately injected plugs of reactants.[10] The characteristic length of an injected plug is 1

* To whom correspondence should be addressed. E-mail: skrylov@yorku.ca.

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mm; thus, several plugs have a cumulative length of several millimeters. Longitudinal diffusion through several millimeters may take as long as several hours. As a result, longitudinal diffusion is impractical for the typical length of plugs. This limitation is especially obvious when three or more reactants need to be mixed. As a result of the above complications, neither of the two methods provides a generic way of mixing reactions in a capillary, which is required for practical capillary microreactors.

We have recently proposed a solution to the problem with the introduction of transverse diffusion of laminar flow profiles (TDLFP) as a generic way for mixing reactants inside a capillary, which can facilitate practical capillary microreactors.[11] In the proof-of-principle work, we called such reactors nanoreactors referring to their nanoliter volume. Here, we use a wider accepted term of microreactors that refers to their linear size in the micrometer scale. The concept of TDLFP-based mixing is as follows. Solutions of reactants are injected inside the capillary by pressure as a series of consecutive plugs. The length of every plug is typically much greater than the diameter of the capillary. If the characteristic diffusion time is longer than the injection time, the laminar nature of the flow inside the capillary leads to only slightly diffused plugs with parabolic profiles and predominantly longitudinal interfaces between the plugs. Transverse diffusion causes the injected reactants to move away from the axis of the capillary and diffuse toward the walls, where the hydrodynamic velocity of the flow is lower. After the injection, the reactants are mixed by transverse diffusion as the contribution of longitudinal diffusion to mixing is negligible. Because of the narrow diameter of the capillary, mixing by transverse diffusion is fast; moreover, the time of mixing is independent of the plug length. In our previous work, we presented a simple non-numerical mathematical model of TDLFP.[11] The model was based on three simplifying assumptions: (1) longitudinal diffusion was negligible during the entire procedure of mixing, (2) transverse diffusion was negligible during the injection of plugs, and (3) transverse diffusion resulted in the elimination of concentration gradients in the transverse direction between plug injections. The assumptions were critical for finding the exact solution for a mass-transfer equation describing the mixing process. Using this model, we simulated the mixing of two reactants and proved such mixing experimentally. Although the non-numerical model was perfect for the proof-of-principle, the second assumption is too strong for the model to be generic. Indeed, for small molecules, transverse diffusion during the injection may be significant, making the model inaccurate. Moreover, the third assumption can also be not satisfied for large molecules that do not have time to diffuse between injections of plugs. The inaccurate model cannot be used for quantitative applications, which require the knowledge of precise concentration profiles of the mixed reactants.

The aim of the present work was to study the theory of TDLFP and develop a mathematical model, which would not use barely satisfied assumptions. The model developed uses only the first assumption, which is readily satisfied. The exact solution of the mass-transfer equation describing the mixing process cannot be found in this case; therefore, we used a numerical approach to solving it. The model was applied to study different scenarios of TDLFP-based mixing of three reactants. The results of this simulation suggest that three reactants can be mixed efficiently in the capillary by TDLFP.

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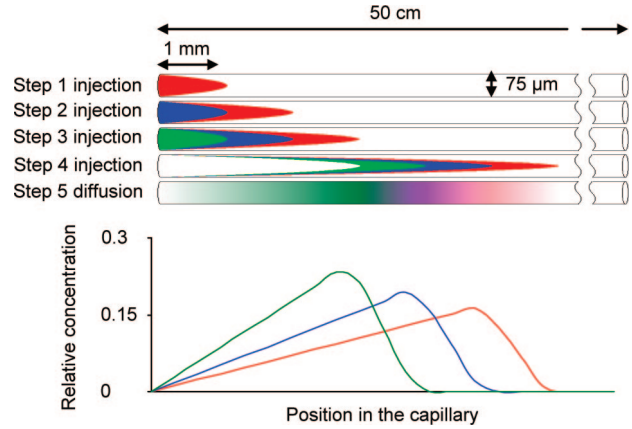

Figure 1. Schematic illustration of TDLFP-based mixing of three solutions (red, blue, and green) inside the capillary. The upper diagram illustrates four steps of injecting the solutions without diffusion and the final step of mixing by transverse diffusion. The white color inside the capillary corresponds to the pure solvent. The graph shows the simulated concentration profiles of the three substances along the capillary after mixing with a scenario depicted in the upper diagram. Concentration is relative to the preinjection concentration.

RESULTS AND DISCUSSION

Preamble. The purpose of TDLFP is to facilitate the mixing of the reactants injected into the capillary as separate plugs without using additional devices. To assist the reader with understanding the principle of TDLFP, we simulated TDLFP-based mixing of three solutions using the analytical model similar to that described in ref 11 with two assumptions: (i) longitudinal diffusion is negligible at all times and (ii) transverse diffusion is negligible during plug injections and starts after injecting the last plug only. The second assumption is very strong but acceptable for the illustration of mixing principles. Figure 1 schematically illustrates the steps of mixing using the above two assumptions and the resulting concentration profiles of the three mixed reactants simulated with the analytical model. The injected plugs form a needlelike structure deeply penetrating into the preceding solution. The longitudinal component of the interface between the plugs is much longer than the transverse one. Transverse diffusion, therefore, contributes to mixing much more efficiently than the longitudinal one. In other words, to mix reactants by diffusion, the distance that the molecules need to diffuse in the transverse direction is much shorter than that in the longitudinal direction. Mixing by transverse diffusion is, therefore, much faster than mixing by longitudinal diffusion.

In order for TDLFP to be used in quantitative studies, such as kinetic measurements, the postmixing concentration profiles have to be accurately calculated. The analytical model with the assumption of no transverse diffusion during the injections cannot be used for accurate calculations of the concentration profiles as the assumption is not generally satisfied. Therefore, a mathematical model has to be developed without making such an assumption. The next section considers the general principles of mathematical modeling of TDLFP that uses only the assumption of no longitudinal diffusion at any time.

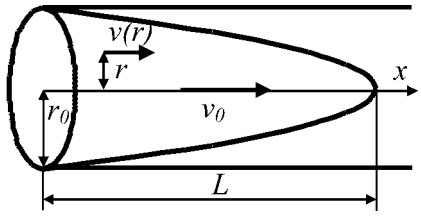

Figure 2. Characteristic parameters essential for modeling TDLFP.

Table 1. York Numbers for Different Diffusion Coefficients of Reactants and Capillary Radii and an Identical Injection Time of 5 s

	capillary radius (μm)		
diffusion coefficient (cm^2/s)	25	37.5	50
10^{-4}	80	40	20
10^{-5}	8	4	2
10^{-6}	0.8	0.4	0.2
10^{-7}	0.08	0.04	0.02
10^{-8}	8×10^{-3}	4×10^{-3}	2×10^{-3}
10^{-9}	8×10^{-4}	4×10^{-4}	2×10^{-4}

Mathematical Modeling of TDLFP. The general model of mass transfer aims at calculating the concentration of every reactant mixed by TDLFP as a function of the position in the capillary and time passed from the beginning of mixing. If the reactant is injected into the capillary by differential pressure, the mass transfer is described by the following equation:

$$\frac{\partial n}{\partial t} = -v(r)\frac{\partial n}{\partial x} + \mu\left(\frac{\partial^2 n}{\partial x^2} + \frac{1}{r}\frac{\partial}{\partial r}r\frac{\partial n}{\partial r}\right), \quad v(r) = v_0\left[1 - \left(\frac{r}{r_0}\right)^2\right], \quad \mu\frac{\partial n}{\partial r}\bigg|_{r=r_0} = 0 \quad (1)$$

Here, n is the concentration of the reactant, μ is the diffusion coefficient, r is the distance from the axis of the capillary in the transverse direction, x is the distance from the injection inlet of the capillary in the longitudinal direction, t is the time from the beginning of the injection, r_0 is the radius of the capillary, $v(r)$ is the injection velocity of the solution, and v_0 is the injection velocity on the axis of the capillary ($r = 0$). Figure 2 illustrates the major parameters used in our consideration.

We assume that the characteristic length of the injected plugs, L, is related to the injection time, T, by the equation $L = Tv_0$, and the length of the injected plugs, L, is much greater than the diameter of the capillary, $L/r_0 \gg 1$. In this case, the time required for transverse diffusion, t_r, is much shorter than the time required for longitudinal diffusion, t_x:

$$t_r = r_0^2/\mu, \quad t_x = L^2/\mu, \quad t_x/t_r = L^2/r_0^2 \gg 1 \quad (2)$$

This allows us to neglect mixing by longitudinal diffusion and simplify the top equation in system 1 to have the following system:

$$\frac{\partial n}{\partial t} = -v(r)\frac{\partial n}{\partial x} + \mu\frac{1}{r}\frac{\partial}{\partial r}r\frac{\partial n}{\partial r}, \quad v(r) = v_0\left[1 - \left(\frac{r}{r_0}\right)^2\right], \quad \mu\frac{\partial n}{\partial r}\bigg|_{r=r_0} = 0 \quad (3)$$

The simplified equation was first introduced by Taylor, who used the same assumptions.[12] In order to transform the equation into a dimensionless form, we introduce the following variables:

$$\rho = r/r_0, \quad \chi = x/L, \quad \tau = tv_0/L \quad (4)$$

If mixing involves a few steps of injections with the same pressures and velocities but different injection times, then L is defined to be the length of the shortest plug. Applying these variables to system 3 we obtain

$$\frac{\partial n}{\partial \tau} = -(1-\rho^2)\frac{\partial n}{\partial \chi} + \mathrm{Yo}\frac{1}{\rho}\frac{\partial}{\partial \rho}\rho\frac{\partial n}{\partial \rho}, \quad \frac{\partial n}{\partial \rho}\bigg|_{\rho=1} = 0 \quad (5)$$

where

$$\mathrm{Yo} = \mu L/(v_0 r_0^2) = \mu T/r_0^2 \quad (6)$$

We denote Yo to be the York number (while it seems appropriate to name this variable after Taylor, this cannot be done as another variable, the Taylor number, bears his name). The York number is a single parameter in a dimensionless equation (eq 5). Therefore, if two mixing procedures share similar initial and boundary conditions and both have an identical York number, they will proceed via similar kinetics and generate similar final distributions of the mixed reactants. The York number may be presented via the dimensionless Schmidt number ($\mathrm{Sc} = \eta/\mu$), dimensionless Reynolds's number ($\mathrm{Re} = r_0 v_0/\eta$, where η is the kinematical viscosity of the fluid), and dimensionless ratio of L/r_0:

$$\mathrm{Yo} = L/(r_0 \cdot \mathrm{Sc} \cdot \mathrm{Re}) \quad (7)$$

It is also possible to present the York number through the Péclet number ($\mathrm{Pe} = r_0 v_0/\mu$) and the dimensionless ratio of L/r_0:

$$\mathrm{Yo} = L/(r_0 \cdot \mathrm{Pe}) \quad (8)$$

It is instructive to consider York numbers that correspond to the typical range of diffusion coefficients of the reactant and capillary radii (Table 1).

The York number is a dimensionless value that characterizes the extent of transverse diffusion over the distance traveled by the plug during the injection. Note, that York numbers decrease with decreasing diffusion coefficients and increasing capillary radii. Indeed, transverse diffusion during the injection influences the quality of mixing. We will study the relationship between the York number and quality of mixing by TDLFP in the later part of the paper.

Numerical Modeling of TDLFP-Assisted Mixing. Although system 5 provides the general basis for modeling plug formation, finding its exact solution is difficult. The exact solution can be found if either of the two terms on the right-hand side of the top equation in system 5 is negligible with respect to the other one. In particular, the exact solution can be found if Yo is much smaller than 1. However, this condition cannot be satisfied for small molecules for which diffusion coefficients are typically greater than

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10^{-6} cm^2/s, as shown in Table 1. The York number is much less than 1 only for bulky biopolymers. Therefore, if the mixing process involves small molecules, the exact solution of system 5 cannot be found and a numerical approach to solving the system has to be used. We prefer using the "explicit" numerical solution of system 5. Alternatively the Monte Carlo method could be used for modeling the diffusion processes without "explicitly" solving system 5.[13] The Monte Carlo method, however, requires longer calculation times to achieve the same accuracy as the explicit solution.

To facilitate solving system 5 numerically we presented the equations in the following form:

$$\frac{\partial n}{\partial \tau} = -(1-u)\frac{\partial n}{\partial \chi} + 4\mathrm{Yo}\frac{\partial}{\partial u}u\frac{\partial n}{\partial u}, \quad \left.\frac{\partial n}{\partial u}\right|_{u=0} = 0, \quad \left.\frac{\partial n}{\partial u}\right|_{u=1} = 0 \tag{9}$$

where we introduced a new variable, $u = \rho^2$. When numerically modeling system 9, we chose an algorithm that gave no distortion of concentration profiles in the absence of diffusion. Every iteration in the computation procedure consisted of two subiterations. In the first subiteration, the process of longitudinal plug shift was modeled assuming no transverse diffusion. In contrast, in the second subiteration, transverse diffusion was modeled without a longitudinal shift of the plug. The first subiteration was designed so that after a large number of iterations, the error in the modeling of longitudinal shifts was averaged out. In the second subiteration, a numerically stable scheme of computation was used. Computational modeling was performed for a uniform three-dimensional grid with axes T, Y, and U, incremental steps Δt, Δy, and Δu, and lengths from zero to T, Y, and U, respectively. The resulting computational scheme is presented below:

$$n^{T+(1/2)}_{Y+Dy_{T,U},U} = n^{T}_{Y,U}, \quad \frac{\left(n^{T+1}_{Y,0} - n^{T+(1/2)}_{Y,0}\right)}{\Delta t} = \left(\frac{2\mathrm{Yo}}{\Delta u^2}\right)\left(n^{T+1}_{Y,1} - n^{T+1}_{Y,0}\right),$$

$$\frac{n^{T+1}_{Y,U} - n^{T+(1/2)}_{Y,U}}{\Delta t} = \left(\frac{4\mathrm{Yo}}{\Delta u^2}\right),$$

$$\left[\left(U+\frac{1}{2}\right)n^{T+1}_{Y,U+1} + \left(U-\frac{1}{2}\right)n^{T+1}_{Y,U-1} - (2U+1)n^{T+1}_{Y,U}\right], \quad 0 < U < \tilde{U},$$

$$\frac{\left(n^{T+1}_{Y,\tilde{U}} - n^{T+(1/2)}_{Y,\tilde{U}}\right)}{\Delta t} = \left(\frac{4\mathrm{Yo}}{\Delta u^2}\right)\left(\tilde{U}-\frac{1}{2}\right)\left(n^{T+1}_{Y,\tilde{U}-1} - n^{T+1}_{Y,\tilde{U}}\right) \tag{10}$$

where shifts along the capillary axis, $Dy_{T,U}$, were calculated using the following algorithm:

$$Dy_{T,U} = \mathrm{round}\left\{\left[(1-U\Delta u)T\Delta t - \sum_{T=0}^{T=T-1} Dy_{T,U}\right]\Big/\Delta y\right\} \tag{11}$$

In system 11, we used a function of rounding to the nearest natural number, round. Variables in system 9 are related to discrete variables in systems 10 and 11 in the following way:

$$\tau = T\Delta t, \quad \chi = Y\Delta y, \quad u = U\Delta u \tag{12}$$

In addition, the following equality is fulfilled

$$\tilde{U}\Delta u = 1 \tag{13}$$

Using the above computational approach, we modeled the TDLFP-facilitated mixing of three reactants under different mixing geometries.

Modeling of TDLFP-Assisted Mixing of Three Substances. Using the numerical model, we first studied the influence of the York number on the quality of TDLFP-facilitated mixing of three substances. Figure 3 shows the final distributions of the three reactants over the capillary length for the following scenario of mixing. The order of the reactants was red, blue, and green. For each diagram, the York numbers of the three reactants were assumed identical and the injected volumes were also identical. A solvent plug of a volume 4 times the cumulative volume of the three solutions was injected after the green reactant. This final injection played an important role in improving the uniformity of the mixed reactants, leading to better mixing. The time between injections of individual plugs was assumed to be long enough for the transverse diffusion to create complete uniformity of all reactants throughout the capillary cross-section.

Results show that the mixing can be efficient only with a sufficiently low York number (Figure 3A). The quality of mixing decreases with an increasing York number. This decrease becomes very significantly when the value of the York number exceeds 1 (Figure 3C). The low quality of mixing is attributed to fast transverse diffusion during the injection, preventing the formation of the needlelike structure of the injected plug and decreasing the efficiency of the interpenetration of the mixed solutions.

One way to improve the quality of mixing is to decrease the York number by decreasing the injection time. Decreasing the injection time, while keeping the injected volume constant, can be difficult due to the hydrodynamic inertia. It is possible, however, with available instrumentation to generate short pulses (less than 1 s) at a suitably high pressure (more than 3 psi) to inject long enough (more than 1 mm) plugs of solutions very fast. Hence, York numbers can be significantly decreased even for reactants with large diffusion coefficients. Another way to improve the quality of mixing is to increase the volume of the solvent plug in the final step (Figure 4A). Although increasing the length of the solvent plug will simultaneously decrease concentration of reactants due to dilution, which may cause lower kinetic rates in concentration-dependent reactions, the dilution factor can be calculated by the model. This advantage allows for the a priori finding of the initial preinjection concentration at which the desirable kinetics can be achieved. One of the drawbacks of increasing the volume of the pure solvent plug, however, is that the solution plugs travel further from the inlet of the capillary, increasing the overall volume of the mixture. This decreases the separation efficiency if separation follows the reaction. Moreover, if the injected pure solvent is different from the separation buffer, the separation conditions may be altered significantly.

To overcome these problems, we have proposed a "shaking" method, in which a series of negative and positive pressure pulses are applied to the capillary inlet after the final solvent plug. The negative pressure reverses the parabolic profiles and improves the quality of mixing. The alternating backward and forward movements show improvement repeatedly and are somewhat

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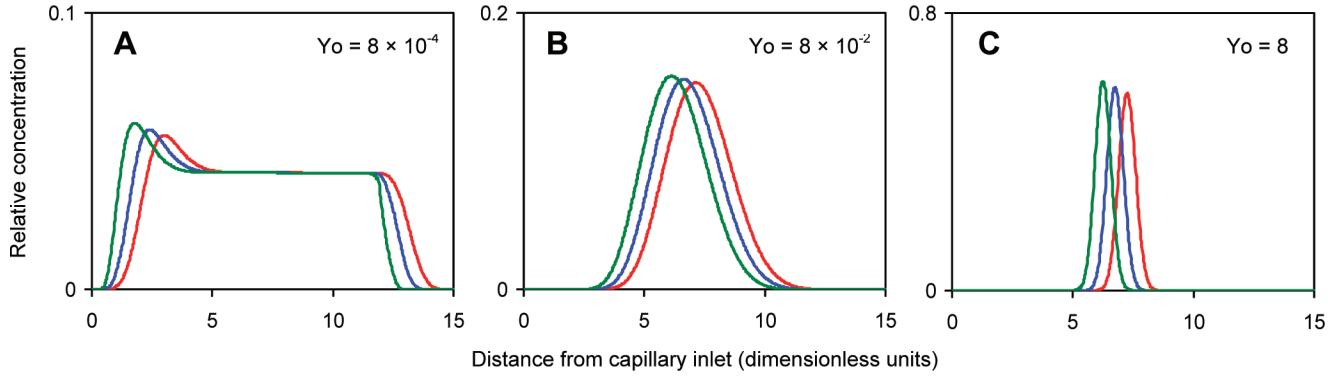

Figure 3. The influence of the York number on the quality of TDLFP-facilitated mixing. The graphs show the concentration profiles of red, blue, and green components after simulated mixing in the capillary, obtained for different values of the York number, Yo, of the reactants. In each diagram, the York numbers of the three components are identical. In this simulation, identical volumes of the red, blue, and green components are injected consecutively into the capillary. A plug of solvent was then injected with a volume 4 times the cumulative volume of the three injected components. The dimensionless distance from the capillary inlet can be converted to a real value using eq 4.

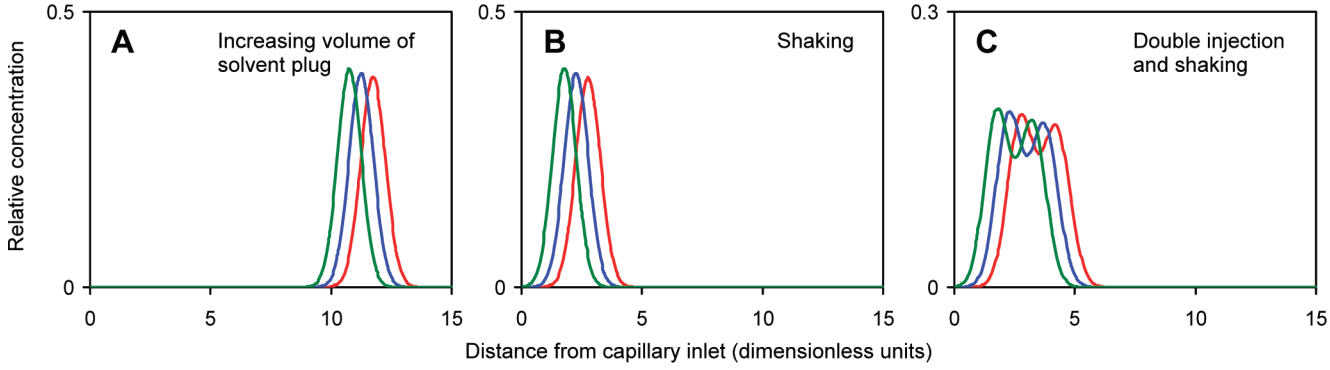

Figure 4. Improvement of the quality of mixing by (A) increasing the volume of the last solvent plug; (B) using the "shaking" approach; and (C) using double injection combined with the "shaking" approach. The graphs show the concentration profiles of the three components after simulated mixing in the capillary. The York number of the three components is 8 in all cases. In part A, a longer solvent plug, with a volume 7 times the cumulative volume of the three solutions, is injected. In part B, after the injection of a solvent plug with a volume of 4 times the cumulative volume of the three solutions, a reverse pressure pulse with the same amplitude and time is applied to the capillary inlet. In part C, the injection of the three reactants is repeated with half-concentrations, followed by the injection of a solvent plug and "shaking".

analogous to mechanical shaking. The simulation showed that the quality of mixing for the "shaking" approach was comparable to the one with increased volume of the last solvent plug (parts A and B of Figure 4). In Figure 4A, the last plug was $^{7}/_{4}$ longer than that in Figure 4B. While the effects of the longer last plug and shaking are similar, shaking has advantages of lesser dilution of reactants and shorter plugs. To further improve the quality of mixing, we combined the "shaking" approach with double injection, in which each reactant is injected twice separately with half of the concentration. For instance, after consecutive injection of the three reactants into the capillary with half-concentrations, each reactant is injected again in the same order and concentration. Our simulation showed that combining the "shaking" approach with double injection significantly improved the quality of mixing without injecting a relatively long solvent plug (parts A and C of Figure 4), even in the case of a large York number.

CONCLUSION

We have developed the detailed mathematical model of TDLFP which simulates the mixing of substances in a capillary. The numerical simulation with this model does not use a barely satisfied assumption of no transverse diffusion during the injection, thus, allowing for the simulation of mixing and for the accurate prediction of the quality of mixing. The developed model provides the basis for the practical use of capillary microreactors in important applications, such as high-throughput screening of drug candidates and enzyme inhibitors.

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