Supporting Information

Sandwich mixer-reactor: Influence of the diffusion coefficient and flow rate ratios

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ESI 1: Finite-element formulation

The general equation (Eqn 3 in the manuscript) is treated by taking into account the diffusionconvection-reaction equations for the 3 considered species (A, B and C).

$$\frac{\partial c_A}{\partial t} + \nabla \bullet (-D_A \nabla c_A + V c_A) = -kc_A c_B \tag{A.1}$$

$$\frac{\partial c_B}{\partial t} + \nabla \bullet (-D_B \nabla c_B + V c_B) = -kc_A c_B$$
(A.2)

$$\frac{\partial c_c}{\partial t} + \nabla \bullet (-D_c \nabla c_c + V c_c) = k c_A c_B$$
(A.3)

The local expressions of the flux conservation (A.1-3) are derived in the global form (A.7-9) by using the Galerkin's formulation (multiplication by a projective function α and integration on the domain of study, Ω):

$$\iint_{\Omega} \alpha \left[\frac{\partial c_i}{\partial t} + \nabla \bullet \left(-D_i \nabla c_i + V c_i \right) \pm k_i c_i \right] d\Omega = 0$$
(A.4)

The convection term of (A.4) is derived by taking into account the continuity equation $\nabla \cdot V = 0$. The diffusion term is derived by decomposing the product between α and the divergence to reduce the second order derivative of c_i (divergence of the gradient) as following:

$$\alpha \nabla \bullet (-D_i \nabla c_i) = \nabla \bullet (-\alpha D_i \nabla c_i) + D_i \nabla \alpha \bullet \nabla c_i$$
(A.5)

$$\iint_{\Omega} \alpha \nabla \bullet (-D_i \nabla c_i) d\Omega = \int_{\partial \Omega} -\alpha D_i \frac{\partial c_i}{\partial n} dl + \iint_{\Omega} D_i \nabla \alpha \nabla c_i d\Omega$$
(A.6)

Integrating (A.5) on the domain Ω and using the Ostrogradsky theorem, the divergence term is rejected at the boundary (A.6), where it expresses the flux boundary condition of each

species. This boundary condition is here equal to zero: no flux at the boundaries of the domain, excepted the inlet and outlet of the channel where the equation is not solved due to the Dirichlet conditions (imposed value of the unknowns). This leads to the final formulation (A.7-9) that is introduced in the equation generator of the Flux-Expert TM software.

$$\left[\iint_{\Omega} \left[\alpha \frac{\partial c_A}{\partial t} + D_A \nabla \alpha \bullet \nabla c_A + \alpha V \bullet \nabla c_A + \alpha k c_A c_B \right] d\Omega = 0$$
(A.7)

$$\left| \iint_{\Omega} \left[\alpha \frac{\partial c_B}{\partial t} + D_B \nabla \alpha \bullet \nabla c_B + \alpha V \bullet \nabla c_B + \alpha k c_A c_B \right] d\Omega = 0$$
 (A.8)

$$\iint_{\Omega} \left[\alpha \frac{\partial c_c}{\partial t} + D_c \nabla \alpha \bullet \nabla c_c + \alpha V \bullet \nabla c_c - \alpha k c_A c_B \right] d\Omega = 0$$
(A.9)

A non-linear algorithm based on the Gauss inversion method was used for all the calculations. To prevent numerical errors, the mesh size was refined in the zones of maximum concentration gradient (junction between the incoming fluids) in order to maintain a local mesh Péclet number inferior to 100.^{S1} The error in calculations was evaluated to be 0.1% when comparing a mesh size of 5 µm with a 3 µm one. Consequently, for all the geometries tested, the mesh size was kept to 10 µm at the microchannel extremities (inlets and outlet) and was decreased to 3 µm at the fluid junction.

The transient model is there applied in a steady-state regime to a 2D cross-section of the geometry. A design with orthogonal inlets was needed for simulation with electro-osmotic flow profile due to the velocity boundary conditions applied to the walls, as well as for the calculations with lower lateral flow velocities. For these two particular situations, a transient algorithm was preferred to improve the convergence of the calculations (the convergence criteria was fixed to 0.1%).

ESI 2: Validation of the finite element convection-diffusion-reaction model

The finite element (FE) model of the convection-diffusion-reaction in a 2D channel has been frequently used in our lab. The equations of kinetics and convection-diffusion were validated by comparison with analytical models (each of them previously validated experimentally by the respective authors).

1) Validation of the numerical kinetic model

The FE equations for the kinetics of a single or consecutive reaction were compared to an analytical model. This model has been described for a consecutive reaction to predict tagging extents at the end of a microchannel in an electrospray microchip, and was validated experimentally. ^{52, S3}

The addition between BQ tags and a peptide containing one cysteine, the rate law follows a first order kinetics for each reactant:

$$v = -\frac{d[BQ]}{dt} = -\frac{d[P]}{dt} = \frac{d[PQ_1]}{dt} = k[P][BQ]$$

where v is the rate of the reaction, k is the rate constant and [BQ], [P] and [PQ₁] represent respectively the concentration of BQ tags, of a peptide P containing one cysteine residue and of the tagged product PQ₁ at the time *t*.

The kinetic model can be applied to consecutive reactions within the electrospray micromixer when the peptide possesses several cysteine units. In the case of a three-cysteine-containing peptide, the first step has an apparent rate constant that can be considered given as $k_1 = 3k$, since the rate law can be here formulated as illustrated below.

$$P \xrightarrow{BQ} PQ_1 \xrightarrow{BQ} PQ_2 \xrightarrow{BQ} PQ_3$$

In the present work, the same consecutive reaction was simulated in 1D or 2D microchannel by finite element. To validate the FE kinetic equations, the results for a 1 D reaction where all the reactants (i.e. P and BQ) are ideally mixed were compared to the results from the analytical model. As illustrated in Figure S1, the reaction extents are similar for both model.

Let compare the relative abundance of the reactant and products for an initial $[BQ]_0 = 20 \text{ mM}$. The relative error is 1.60 %, 0.09 % and 1.45 % for PQ₁, PQ₂ and PQ₃, respectively. Consequently, the mean relative error for these values between the analytical and the FE model is 1.04 %



Figure S1: Relative abundance of the species involved in the consecutive reaction as a function of the initial concentration of the BQ reactant.

This validation concerns the consecutive reaction but is also valuable for a single reaction as the one presented in the present publication. In the fact, the same equations were used with the PQ_2 , PQ_3 , k_2 , k_3 variables not defined.

2) Validation of the numerical convection-diffusion model

The numerical convection-diffusion in a two-lamellae mixer was validated with the analytical model described by Z. Wu *et al.*^{S4} The simplified 2D analytical model of convective-diffusive transport in parallel lamination micromixers is depicted in Figure S2. The geometry is a long channel of width W, two inlets and one outlet. One inlet stream is the solute with a concentration $c = c_0$ and a diffusion coefficient D. The other inlet stream is the solvent with a concentration c = 0. The two streams present the same viscosity and fluid density. As in the present work the calculations were performed for two inlet streams of equal width, the dimensionless interface width *r* is equal to 0.5.



Figure S2: Models for convective-diffusive mixing ratio in the channels. (Top) The physical model. (Bottom) The dimensionless model.

Neglecting the diffusion in the flow direction (Pe > 100), the analytical solution is as follows:

$$c^{*}(x^{*}, y^{*}) = \frac{2}{\pi} \sum_{n=1}^{\infty} \frac{\sin n\alpha\pi}{n} \cos(n\pi y^{*}) \exp(-\frac{n^{2}\pi^{2}}{\text{Pe}}x^{*}) + \alpha$$

n = 1, 2, 3, ...

with $c^* = c/c_0$, $y^* = y / W$ and $x^* = x / W$, Pe = UW / D. Analytical calculations were

performed with Maple 10.0.

The analytical results were compared with the 2D finite element model used in this study setting k = 0 and with an EOF flow profile. The solute was injected in one half of the microchannel inlet. The isovalues of the solute distribution along the microchannel is illustrated by their isovalues in Figure S3.



Figures S3: Isovalues of the solute distribution along the microchannel for $D = 1.10^{-10}$ m².m⁻¹ and $D = 1.10^{-9}$ m².m⁻¹.

Figure S4 is the comparison of the analytical and numerical models in the same condition, for $D = 1.10^{-10} \text{ m}^2.\text{m}^{-1}$ and $D = 1.10^{-9} \text{ m}^2.\text{m}^{-1}$. The two models follow the same trend for the positions x* = 10, 20 and 40 along the microchannel, with a difference of 1.3% (averaged error value) that validate the numerical model used in this study.



Figures S4: Dimensionless concentration distribution for two stream mixing in the channels for x*=10, 20 and 40, A) $D = 1.10^{-10} \text{ m}^2.\text{m}^{-1}$ and B) $D = 1.10^{-9} \text{ m}^2.\text{m}^{-1}$.

ESI 3: Evaluation of chemical/diffusional regime

In this study, the position of the reactants A and B is optimised according to their diffusion coefficient (with $D_B > D_A$) in the *sandwich* geometry: ABA or BAB.

The second Damköhler number (Da) establishes the relationship between the mixing rate and reaction rate that defines three main regions:

- For $Da \ll 1$: The reaction is purely limited by the kinetics
- For 0.1 < Da < 10: The reaction is governed both by the kinetics and the diffusion
- For Da >>1: The reaction is purely limited by the diffusion

Figure S5 represents the reaction extent as a function of the kinetics and Da, for three mean residence time. The simulations could not have been run for higher values of k due to a non-convergence of the calculations. Another way to increase the extent with reasonable value of k is to increase both c and D (same Da number) or to increase the residence time.





Figure S6 represents the gain obtained with the optimised positioning of the reactants within *sandwich* mixer as a function of the kinetics and Damköler number. In this graph, it appears clearly that this study does not make sense at high kinetics as the gain is going down due to a reaction extent close to completion in one or both design that is here compared.



Influence of the concentration ratio

The study deals with convection-diffusion and reaction between two species along a microchannel defined as sandwich mixer-reactor. As illustrated by the Damkhöler number, kinetic and diffusion are related and determines whether a reaction is governed by the diffusion and/or the kinetics.

This section evaluates the position of the reactants according to their concentration ratio $(C_B \ge C_A)$. Figure S7 is the gain between *ABA* and *BAB* geometries that is determined for concentration ratios ranging from 1 to 1000, for k = 20 and 200 M⁻¹·s⁻¹, at the end of a microchannel of 2000 µm length. The maximal gain obtained is 12% and 11% for k = 20 (with $C_B / C_A = 200$) and 200 M⁻¹·s⁻¹ (with $C_B / C_A = 20$), respectively. The reaction extent

for the two sandwich configurations shows a decrease of the gain when ξ is higher than 60%. Afterwards, the reaction is tending to completion that limits the gain.



Figure S7: Gain between the sandwich ABA and BAB as a function of the concentration ratio of the reactants A and B, for k = 20 and $200 \text{ M}^{-1} \cdot \text{s}^{-1}$ and $L = 2000 \text{ }\mu\text{m}$.

Figure S8 represents the evolution of the gain as a function of the non-dimensional time t_R / t_D . As t_D is not changed, it allows visualizing the fluctuation of the gain along the microchannel.

The change of species concentration modifies the reaction kinetics as the reaction rate in a first order reaction is correlated to kc_Ac_B . By increasing the concentration of B, the reaction kinetics is then increased allowing tending more quickly to reaction completion.

The small gain between *ABA* and *BAB* is probably due to the positioning of the concentration gradient across the parabolic velocity profile. We determined the contribution of the concentration gradient on the diffusion (for the ABA design). In one case the simulations were performed with $c_A = c_B$ and $k = 200 \text{ M}^{-1} \cdot \text{s}^{-1}$ ($\xi = 5.71\%$). In the other case we fixed $c_B = 10 \cdot c_A$ and $k = 20 \text{ M}^{-1} \cdot \text{s}^{-1}$ ($\xi = 6.01\%$). So, in both case, kc_Ac_B is the same. According to the

simulations, the concentration gradient increases of 5% the reaction extent by modifying slightly the diffusion. This effect explained the difference observed between the two geometrie.



Figure S8: Gain between the sandwich ABA and BAB as a function of the non-dimensional time, for k = 20 (Top) and 200 M⁻¹·s⁻¹ (Bottom) and $L = 2000 \,\mu\text{m}$. The C_B/C_A ratios of 2, 10, 20, 100, 200 and 1000 are presented.

ESI 4: Extent to well-known inlet geometries

Because geometries with orthogonal inlets are often used in the litterature, ^{S5, S6} the performance of the two designs herein presented was compared to an equivalent Y-mixer and cross-mixer. The reaction extent is simulated for identical residence time, chemical reaction constant, reactant concentration and diffusion coefficients. The present study is performed at relatively high Peclet number (Pe = 1500), so the following comparisons are valuable as the longitudinal diffusion is negligible. The results are presented in the following Table. The geometries were compared for an advanced reaction extent ξ ($k = 5000 \text{ M}^{-1}\text{s}^{-1}$) and a low reaction extent ξ_{Ref} ($k = 200 \text{ M}^{-1}\text{s}^{-1}$). The relative error between the two double-inlet design and the two triple-inlet designs is slightly higher at low reaction extents. Nevertheless, in all the conditions the relative error is inferior or equal to 0.6 % meaning that the conclusions from this study are also valuable for the more "commonly" used designs such as the Y-mixer, T-mixer or the cross-mixer.

	Advanced reaction extent		Low reaction extent (Reference case)	
Geometries	ξ (%)	Relative error	ξ_{Ref} (%)	Relative error
	45.21	0.03%	2.6236	0.24%
>	45.2		2.629	
—	53.61	0.13%	5.707	0.60%
	53.67		5.741	

Table S1: Comparison of the inlet design influence for a side-branch mixer, a Y-mixer, a sandwich mixer and a cross mixer.

ESI 5: Determination of the Péclet limit

The reaction extent normalized by the reaction rate and mean residence time (ξ/kt_R) was simulated for different values of diffusion coefficient *D*. For each value of *D*, the residence time is adapted in order to keep constant the term *Dt* (constancy of the diffusion length \sqrt{Dt}). The adaptation of the residence time is done by measuring the reaction extent at different microchannel lengths. As $t_R/t_D = Dt_R/\delta^2$, this ratio is also constant in all the points in Figure S9 ($t_R/t_D \approx 0.05$).

According to the plateau of Fig S9, the results of Figure 4-B, 6-B and 7 can be extrapolated for another value of (D, t, δ) couple giving for the same values of t_R/t_D , with the condition that respectively: **Pe** > **50** for $k = 20 \text{ M}^{-1} \cdot \text{s}^{-1}$, **Pe** > **300** for $k = 200 \text{ M}^{-1} \cdot \text{s}^{-1}$, **Pe** > **6000** for $k = 2000 \text{ M}^{-1} \cdot \text{s}^{-1}$. Consequently, the results presented in Figure 4-B, 6-B and 7 for $k = 2000 \text{ M}^{-1} \cdot \text{s}^{-1}$ cannot be extrapolated as the Pe number in this study is 1500 (not included in the plateau in Figure S9).



Figure S9: Reaction extent normalized by the reaction rate and residence time as a function of the Peclet number value. The simulations were performed with $D_A = D_B$ and for k = 20 (green), 200 (blue) and 2000 (red) M⁻¹·s⁻¹.

ESI 6: Details on the determination of the $\overline{V_c}$ value

The flat flow profile corresponding to the mean flow velocity ($\overline{V} = 1.5 \text{ mm} \cdot \text{s}^{-1}$) is represented by the horizontal dotted line in Figure S10. The intersection between this line and the parabolic flow velocity profile delimitate three areas: the two zones next to the walls where $t_R > \overline{t}_R$, and the one at the centre of the microchannel where $t_R < \overline{t}_R$. Figure 2 in the manuscript shows that for high D_B/D_A , the reaction extent is higher than a bulk reaction for the same mean residence time \overline{t}_R . Our hypothesis is that this overpassing of the bulk reaction extent is due to the location of C (and so the location of the reaction) close to the walls where $t_R > \overline{t}_R$.

To validate this hypothesis, the mean flow velocity $\overline{V_c}$ of the C species was determined according to the position of the maximal production of C across the microchannel. This position was then reported on the parabolic flow profile curve in order to define this velocity. The simulation in bulk was run with this corrected value as presented in Figure 2 of the manuscript. With this corrected mean residence time corresponding to $\overline{V_c}$, the reaction extent in PDF condition tends asymptotically to the bulk reaction extent, confirming this hypothesis.



Figure S10: Flux density distribution of the product C (filled areas) along the microchannel cross-section at a distance L (i.e. microchannel outlet), L/2 and L/4. The pressure-driven flow profile in the microchannel is represented by the dark line and the corresponding mean flat flow profile (in the case of a EOF profile or ideal mixing) by the dotted line.

ESI 7: <u>Contribution of the parabolic flow profile in the performance of the</u> Sandwich ABA ($k = 200 \text{ M}^{-1} \cdot \text{s}^{-1}$, $L = 2000 \text{ \mu m}$)

To quantify the contribution of the parabolic flow profile in the gain value observed, the reaction extent was compared to simulations performed with a flat electro-osmotic driven flow (EOF) profile within the *Sandwich* geometries.

Figure S11 quantifies the contribution of the velocity flow profile in the reaction extent as a function of D_B/D_A ratio. In optimal conditions, the parabolic profile allows an increase of the reaction extent from 0 to 22 % for high D_B/D_A . For $D_B/D_A < 2$, the simulation in EOF conditions gives better results than the one with a parabolic profile. On the contrary, when the position of the reactants is not optimised according to their diffusion coefficients, the loss induced by the parabolic flow profile compared to a flat flow profile reaches 20 % for high D_B/D_A ratio.



Figure S11: Evaluation of the gain due to the flow profile in the optimal (*ABA*) and non-optimal (*BAB*) sandwich mixer.

ESI 8: Evolution of the gain between ABA and BAB as a function the non-

dimensional time



Figure S12: Gain of the optimised sandwich mixer as a function of the nondimensional time for DB/DA from 1 to 100, for $k = 20, 200, \text{ and } 2000 \text{ M}^{-1} \cdot \text{s}^{-1}, L = 20000 \text{ }\mu\text{m}.$

ESI 9: Relation between the flow rate ratios and the external A layer thickness

The A layer thikness was determined for the different flow rate ratios presented in this study Figure S13). On the transversal A and B concentration profile, the thickness of the A layer is defined by the intersection between two consecutive streams where $c_A > c_B$ for the first one and $c_B > c_A$ for the other one.

The decrease of the A layer thickness is linear for $0.5 < Q_A / Q_{A,Ref} < 1$ and amplified after ($Q_A / Q_{A,Ref} < 0.5$) which results in the strong gain increase observed in Figure 6-A in the manuscript.



Figure S13: Relation between the lateral stream flow rate and the transversal diffusion length. (Simulated data in red. The black line is the extrapolated linear correlation for the first points).

References

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