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2020

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Adamopoulou, T. (2020). *Design and fabrication through additive manufacturing of devices for multidimensional LC based on computational insights*. [Thesis, fully internal, Universiteit van Amsterdam, Vrije Universiteit Brussel].

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Chapter 3

Active flow-confinement - Two-Dimensional Insertable Separation Tool (TWIST)

This chapter relates to the following publication:

T. Adamopoulou, S. Deridder, G. Desmet, P.J. Schoenmakers. Two-dimensional insertable separation tool (TWIST) for flow confinement in spatial separations. *J. Chromatography A*, 1577 (2018), pp. 120-123

Abstract

Spatial comprehensive two-dimensional liquid chromatography (^{x}LC×^{x}LC) may be an efficient approach to achieve high peak capacities in relatively short analysis times, thanks to parallel second-dimension separations [1,2]. A key issue to reach the potential of ^{x}LC×^{x}LC is to achieve adequate flow control and confinement of the analytes to the desired regions, *i.e.* confinement in the first-dimension direction and subsequently homogeneous flow in the second dimension. To achieve these goals, we propose the TWIST concept (TWo-dimensional Insertable Separation Tool), a modular device that includes an internal first-dimension (^{1}D) part that is cylindrical and rotatable. This internal part features a series of through-holes, each of which is perpendicular to the direction of the ^{1}D flow. The internal part is inserted in the cylindrical casing of the external part. The internal diameter of the casing is marginally larger than the external diameter of the internal part. The external part also comprises a flow distributor and second-dimension (^{2}D) channels. During the ^{1}D injection and development, the channel is placed in a position where the through-holes are facing the wall of the external part, such that the liquid remains confined within the ^{1}D channel. Thereafter, to realize the transfer to the second dimension (^{2}D injection), the ^{1}D channel is rotated, so that the holes of the internal part are aligned with the holes on the external part, allowing a transversal flow of the ^{2}D mobile phase from the distributor through the ^{1}D channel and eventually into the ^{2}D area.

3.1. Introduction

Comprehensive two-dimensional liquid chromatography (LC×LC) is indispensable for the characterization of very complex samples [3]. Greatly enhanced peak capacities relative to conventional one-dimensional (1D) LC may be obtained by LC×LC, which can be effectively realized if the two separation dimensions are sufficiently different (*i.e.* highly orthogonal).

One premise for successful comprehensive operation is that the entire first-dimension effluent must be transferred and subjected to the second-dimension separation. This requires the chromatographer to establish a compromise between the first- and second-dimension column dimensions and flow rates and the modulation time, which implies a sacrifice in performance. The need to compromise can be avoided with a perfectly operated spatial ^{x}LC×^{x}LC system. A suitable format for spatial separations may be realized through microfluidic devices [2,4]. However, perfect operation requires rigorous confinement of the flow of mobile phase and analytes in the desired (^{1}D or ^{2}D) direction. Incomplete confinement will greatly affect the separation efficiency.

The development of microfluidic devices is typically a stepwise process of design and prototyping. Actual prototyping can be a time-consuming and cumbersome task [5]. By using computational fluid dynamics (CFD), designs can be theoretically established and tested. Satisfactory designs are then prototyped and the resulting experimental performance can be used to enhance the design further. Previous CFD studies have been performed on flow distribution, ^{1}D injection volumes and channel discretization in the second dimension [1,6,7]. To facilitate rapid and easy prototyping, 3D-printing methods have been adopted. Stereo-lithography provides a high degree of accuracy and consistency with the original design. In the present study a novel flow-confinement concept (two-dimensional insertable separation tool or TWIST) for spatial comprehensive two-dimensional liquid chromatography (^{x}LC×^{x}LC) devices is presented.

3.2. Materials and Methods

3.2.1 Computational fluid dynamics (CFD) studies

For CFD simulations, ANSYS Workbench Fluids and Structures Academic Package (ANSYS, Pennsylvania, PA, USA; version 17.1) was used. The cases were solved as 3D domains and for the entire geometry to be simulated.

The examined devices consisted of three main parts, *viz.* the flow distributor, the ^{1}D channel and the ^{2}D domain. To investigate (lack of) flow confinement, a solution of dye in water corresponding to three ^{1}D channel volumes was introduced to the ^{1}D channel at a flow rate of 5 mL min^{-1}. During the ^{1}D injection the ^{2}D inlet and outlet were kept closed.

All dimensions were chosen in accordance with our 3D-printing capabilities (see section 3.2.2 below). Simulations were conducted with both empty ^{1}D channels and channels filled with a porous structure. The computations involving empty ^{1}D channels were in compliance with previously fabricated and studied devices, in which iso-electric focusing was used as a separation method in the first dimension [4,8]. The cases simulated with a porous ^{1}D channel represented the presence of a monolith as stationary phase. The permeability of ^{1}D and ^{2}D porous structures was $1.7 \cdot 10^{-13}$ m^{2} [9].

All cases were meshed in a similar manner, with size inflation at the distributor, body sizing at the ^{1}D channel and edge sizing with divisions at the ^{2}D area. In the ^{2}D domain bias was imposed in order to have more resolution close to the wall and to the ^{1}D to ^{2}D transition area. These modifications were made to enhance the accuracy of the CFD results.

3.2.2 Designing and 3D-printing

The design process was facilitated by the commercial package Autodesk Inventor (Autodesk, San Rafael, CA, USA). The proposed design is depicted in Fig. 3.1 as an assembly. It consists of two parts: an internal (grey) and an external (blue) one. The internal part, also shown for clarity in the insert, is the channel in which the ^{1}D

separation takes place. Two diametric series of through-holes are created to allow a perpendicular flow to pass through the ^{1}D channel during transfer to the second dimension. The external part comprises a flow distributor (top), the ^{1}D channel casing in which the internal part is inserted, and a series of parallel ^{2}D channels (bottom).

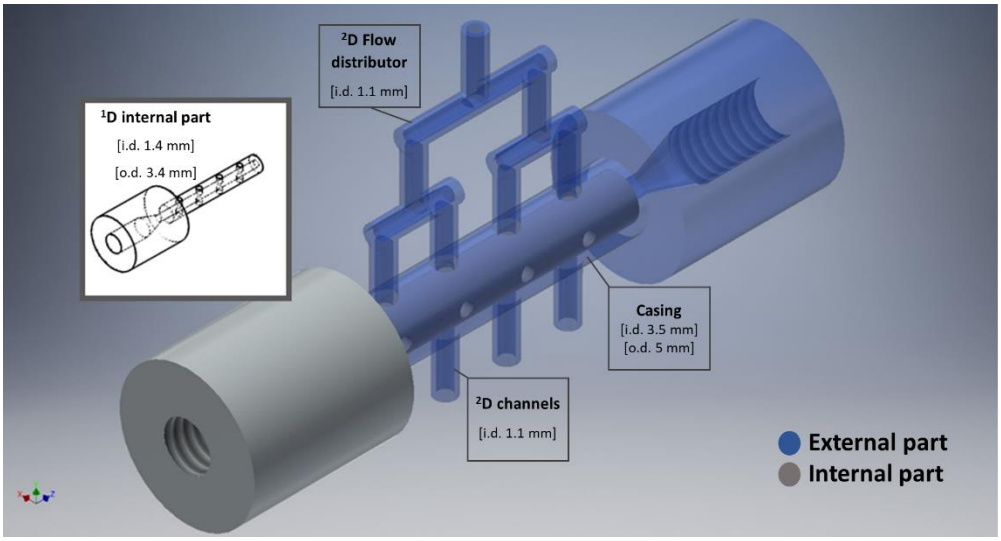

Fig. 3.1. The proposed device in assembly form, consisting of an internal (grey) and an external (blue) part. Insert: sketch of the internal part

The examined device was fabricated through 3D-printing using a Digital Light Processing (DLP) Asiga Pico 2 HD (385 nm). Printing orientation and settings were optimized for high resolution. After 3D-printing, post processing of the parts was necessary. This included sonication and flushing the channels with 2-propanol and nitrogen to remove any uncured resin. When all the undesirable material was removed, the parts were inserted in a Pico Flash UV chamber (type DR-301C, 36 W, 365 nm, 3DXS Germany) and cured between 30 and 90 min (depending on the part). To make the devices connectable, straight threads (#10-32 UNC, major diameter 4.83 mm, thread pitch 0.794 mm) were created using a hand tap, whereas the conical part at the end of the connection area was already incorporated into the print design. In order to connect the tubing to the flow distributor inlet, the tubing was inserted 2 mm in the inlet channel and glued with optical glue. The connection for the ^{2}D inlet was not

included in the design to stay within the surface area of the printer's build platform and the chosen printing orientation (the part was printed horizontally). The final connections were watertight at the pressures needed for testing.

3.2.3 Chemicals and Materials

Asiga PlasClear V2 resin was purchased from 3DXS (Erfurt, Germany). The same resin was also used for the fabrication of the devices described in Chapter 2, where the pressure resistance was briefly studied. 2-Propanol (Biosolve BV, Valkenswaard, The Netherlands) was used during the post-processing of the printed parts, as well as during the flow tests. The PME Natural Food Color –Red (product nr: PFC1022, www.deleukstetaartenshop.nl) and PME Natural Food Color –Blue (supplied by local source) were used during testing. Nitrogen used during the post-processing of the printed parts was supplied by Praxair to a laboratory gas-supply network. Optical glue was supplied by a local source.

3.2.4 Flow Testing

Two set of experiments had to be performed; a flow-confinement investigation during the ^{1}D injection and transfer from the ^{1}D to the ^{2}D. Flow-confinement tests were performed on the fabricated device. The device was empty and a mixture of dye dissolved in water was injected in the ^{1}D channel for flow visualization. Different flow rates in the range of 0.5 to 5 mL/min were studied. For the second investigation, the ^{1}D channel was rotated and water was injected at 1.5 mL/min from the inlet of the flow distributor. The flow profiles were recorded with a Canon EOS 1300D camera. The experiments were performed without a holder or additional sealing.

3.3. Results and discussion

All designs presented in this study consisted of three main parts, *viz.* a flow distributor, a ^{1}D channel and a ^{2}D domain. In this type of devices either a monolith is assumed to be present in both the ^{1}D and ^{2}D domains, or only in the ^{2}D domain, leaving the ^{1}D channel empty.

3.3.1 Flow confinement

Flow confinement is necessary during the ^{1}D step. Leakage during this step (from the first-dimension channel to the flow distributor or to the second-dimension channels) can undermine both the first- and the second-dimension separations. In Fig. 3.2 exemplary results are depicted of ^{1}D injections into devices without any confinement measures and assuming a monolithic packing in the ^{1}D channel (left) or an empty ^{1}D channel (right). The desired outcome is to have the dye present only in the ^{1}D channel (in high concentrations, *i.e.* red in the figure). Both cases in Fig. 3.2 are seen to result in excessive amounts of dye in other compartments of the device.

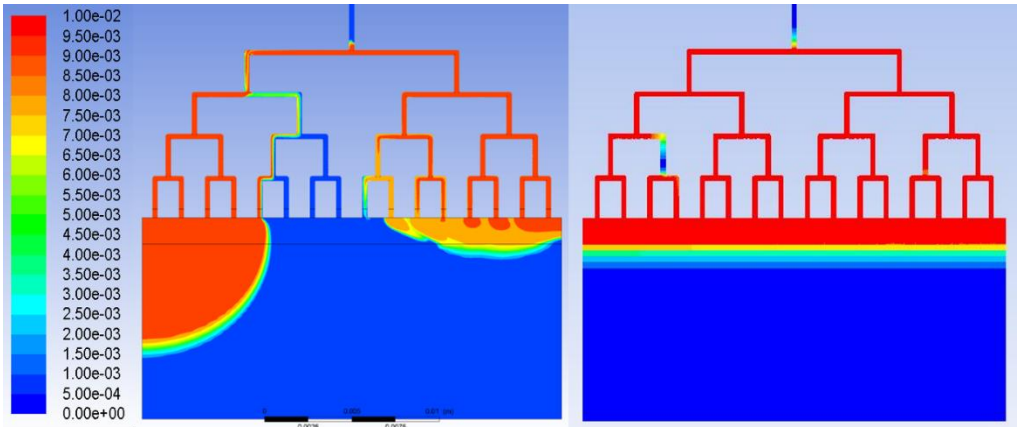

Fig. 3.2. Concentration profile of dye solution after injecting three channel volumes into the ^{1}D channel. Devices with porous (left) and with empty ^{1}D channel (right). The permeability of ^{1}D and ^{2}D porous structures was $1.7 \cdot 10^{-13}$ m^{2}.

In case of an empty ^{1}D channel (right) leakage is observed mainly towards the flow distributor area. In the case with a porous ^{1}D channel (left), dye penetrates both to the distributor and the ^{2}D area. The dramatic dye distribution in the latter case can be understood by realizing that the flow in the ^{1}D direction creates a pressure gradient from left to right in the figure. This gradient makes the liquid follow the path of the least flow resistance on its way to the outlet, making a detour through the ^{2}D flow distributor before exiting along the exit of the ^{1}D channel. One way to enhance flow confinement would be to keep the ^{1}D channel empty (right panel) and to create

constrictions, such as monolithic frits, at the outlets of the distributor, minimizing the leakage of dye to the ^{2}D flow distributor (result not shown). However, an empty ^{1}D channel leaves few separation options other than IEF. A different design is needed that allows a stationary phase to be present in the ^{1}D channel, while achieving flow confinement and effective flow control.

As a solution to the above problem, we propose a concept wherein the ^{1}D separation takes place in a channel with a cylindrical external geometry [nr. WO2020/016426 A1, EP18184801.1]. This channel can be inserted in a cylindrical housing in the ^{2}D device. Both the ^{1}D channel and the housing contain through-holes. During the operation of the device for the ^{1}D separation the through-holes of the chamber are not aligned with the through-holes of the ^{1}D channel. During the subsequent second-dimension separation, the through-holes of the chamber are aligned with the through-holes of the insertable channel, allowing a perpendicular flow through the ^{1}D channel. A great additional advantage is that the insertable ^{1}D channel can easily be replaced, allowing different stationary phases to be used for the ^{1}D separation. The ^{1}D separation may also be performed in a different housing (off-line), for example one that allows higher pressures for the flow to pass through the full length of the channel.

3.3.2 Flow testing

Some leakage (through the first hole in the internal cylinder) was observed at very low flow rates (0.5 mL/min) at the inlet side of the channel probably related to the residence time of the dye solution. Also, some leakage (between the internal and the external parts) was observed at high flow rates (5 mL/min) or upon prolonged flushing. No leakage was observed during standard operation at 1.5 or 2 mL/min. These results were obtained without any sealing in place. Leakages can be reduced by incorporating sealing in the device e.g. by incorporating frits or membranes in the holes and adding O-rings or sleeves.

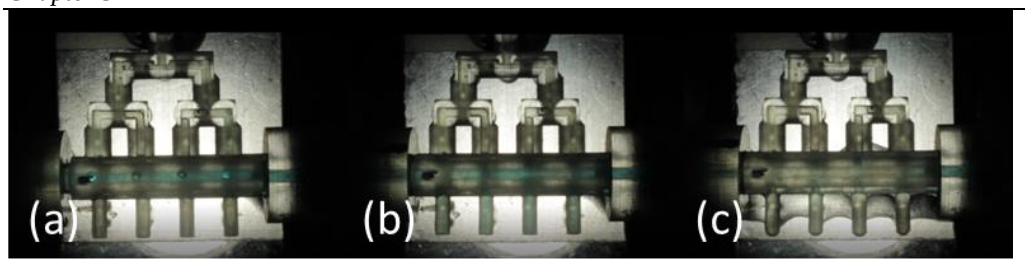

Fig. 3.3. Pictures of the device containing dye solution (a) following injection in the ^{1}D channel, (b) just at the start of the ^{2}D injection, (c) at the end of the ^{2}D injection.

In Fig. 3.3 the three main steps of operation are presented. Initially the ^{1}D injection takes place, while the through-holes on the ^{1}D channel are not aligned with the distributor and the ^{2}D channels (a). Afterwards the ^{1}D channel is rotated to achieve the desired alignment (b). Here, the liquid present in the dead zone inside the holes can be observed. Dead zones can be minimized, for example by placing a frit or a membrane. Finally, frame (c) depicts the successful emptying of the ^{1}D channel to the ^{2}D, proving the principle and correct operation of the device. The video of this flow-test can be found by scanning the QR-code.

3.4. Conclusions

Rigorous flow confinement in the ^{1}D channel is required for optimal operation of spatial comprehensive two-dimensional liquid chromatography (^{x}LC×^{x}LC) devices. To achieve this a two-dimensional insertable separation tool (TWIST) is proposed. This concept allows confinement of the flow and independent separations to be performed in the different dimensions. A prototype was made using 3D-printing technology. Further research is required for device and material optimization, incorporation of stationary phases and for performing actual separations. Furthermore, use of an external holder could offer stability during the rotation of the ^{1}D channel and accuracy for the required alignment. Finally, with some modifications, the

TWIST concept may provide an attractive option to realize flow confinement in spatial three-dimension liquid chromatography.

3.5 Supplementary information

The device described in this chapter is covered by the patent "Device for multidimensional liquid analysis" (EP3598125A1; WO2020016426A1). The general concept of the separation devices described in this patent is that they are comprised of a flow distributor, a ^{2}D compartment, a chamber for the ^{1}D channel, and an insertable ^{1}D separation channel. Both chamber and ^{1}D channel contain through-holes (or a permeable slit). During the operation of the device for the ^{1}D separation the through-holes of the chamber not aligned with those of the ^{1}D channel, so that the channel is closed, except for the terminal inlet and outlet openings. For the ^{2}D separation the through-holes of the chamber are completely aligned with the through-holes of the insertable ^{1}D channel. A great advantage is that the device is modular. The insertable ^{1}D channel can easily be exchanged, so that, for example, different first-dimension stationary phases can be used. Below is a figure from the patent, which can be found here

(54) Title: DEVICE FOR MULTI-DIMENSIONAL LIQUID ANALYSIS

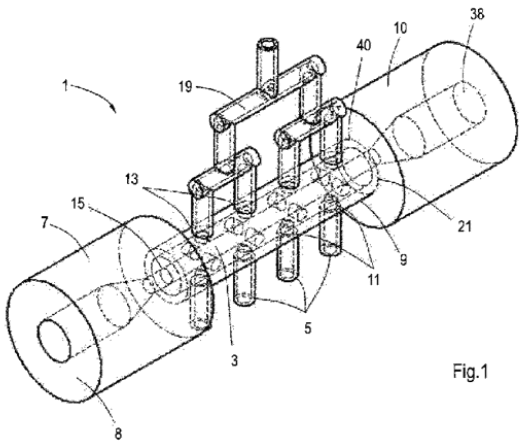

Fig.1

(57) Abstract: Device (1) for multi-dimensional liquid analysis, such as chromatography. The device comprises a first analysis channel (3) and one or more second analysis channels (5). The first analysis channel comprises a channel wall (21) with outlets (11) connecting the first analysis channel to one of the plurality of second analysis channels, and a valve (7) for opening or closing at least one of the one or more outlets (11).

A. Alternative designs

In the case of the TWIST (TWo-dimensional Insertable Separation Tool) described in this chapter, the alignment and misalignment of the through-holes is based on a rotating-valve mechanism. Another arrangement that follows the concept of the invention and is covered by the patent (*i.e.* the SLIT – Simple Liquid Transfer) will be described in Chapter 5. The TWIST device presented in this chapter comprised a cylindrical ^{1}D channel, which was inserted in a cylindrical slot of the external part, which comprised a flow distributor and ^{2}D channels. Different geometrical arrangements are possible within the concept of a rotating-valve mechanism.

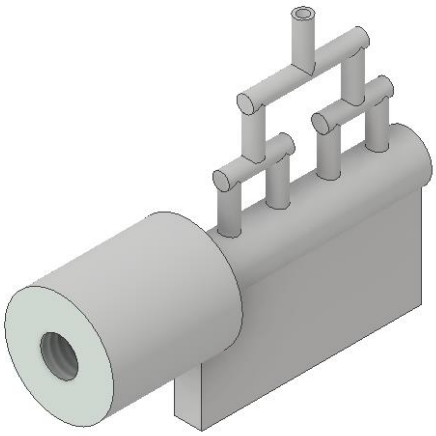

Fig. S3.1. External part of a TWIST device with a ^{2}D compartment in the form of a flat bed.

In Fig. 3.1S an external part is depicted in which the ^{2}D domain takes the form of a flat bed. The internal part in this case could be in as before (with through-holes in both sides), could have through-holes in one side and a rectangular slit on the other side (Fig. 3.2Sa), or open slits on both sides (Fig. 3.2Sb). The challenge in the two last arrangements will be to make a continuous frit where the open slits are located. If the 1D stationary phase is a monolith, the need for a frit may be avoided.

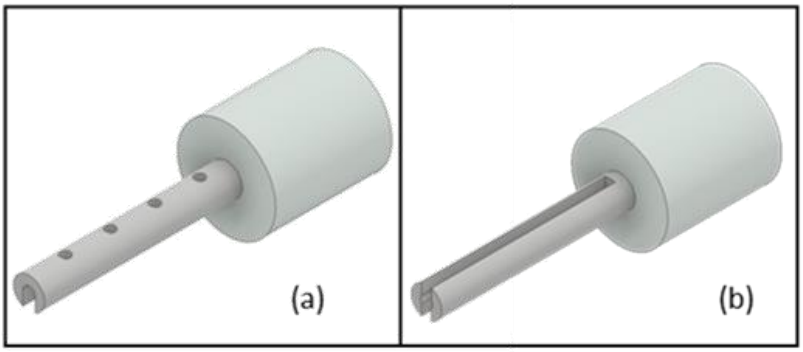

Fig. S3.2. Internal part of a TWIST device with a ^{2}D compartment in the form of a flat bed. Frame (a) comprises through-holes and a slit while frame (b) two open slits.

B. Effect of gap between the two parts

In order to investigate the effect of the suggested 0.1mm gap between the two parts, computational fluid dynamics (CFD) simulations were conducted. The geometry examined here comprises a ^{1}D channel of 50 mm length, a flow distributor with channels of 1-mm i.d. and sixteen outlets, and a ^{2}D bed with a length of 20 mm. The ^{2}D bed had a permeability of $1.7 \cdot 10^{-13}$ m^{2}, while the ^{1}D was either empty or filled with a stationary-phase material. The flow rate used during both the ^{1}D and the ^{2}D steps was 1 mL/min. For the evaluation of the ^{1}D flow confinement a continuous injection of a mixture of dye and water was incorporated from the ^{1}D inlet for the duration of three ^{1}D channel volumes. At this stage only the ^{1}D channel and the gap were taken into account to reduce computational cost. As shown in Fig. S3.3, in the case of an open ^{1}D channel the dye moved mainly within the ^{1}D channel, while only a small fraction moved towards the gap, exclusively in the vicinity of the inlet area. When the ^{1}D channel contained stationary-phase material, after entering the ^{1}D channel the dye and followed the path of the least resistance, which in this case implied that it moved through the 0.1 mm gap towards the ^{1}D outlet.

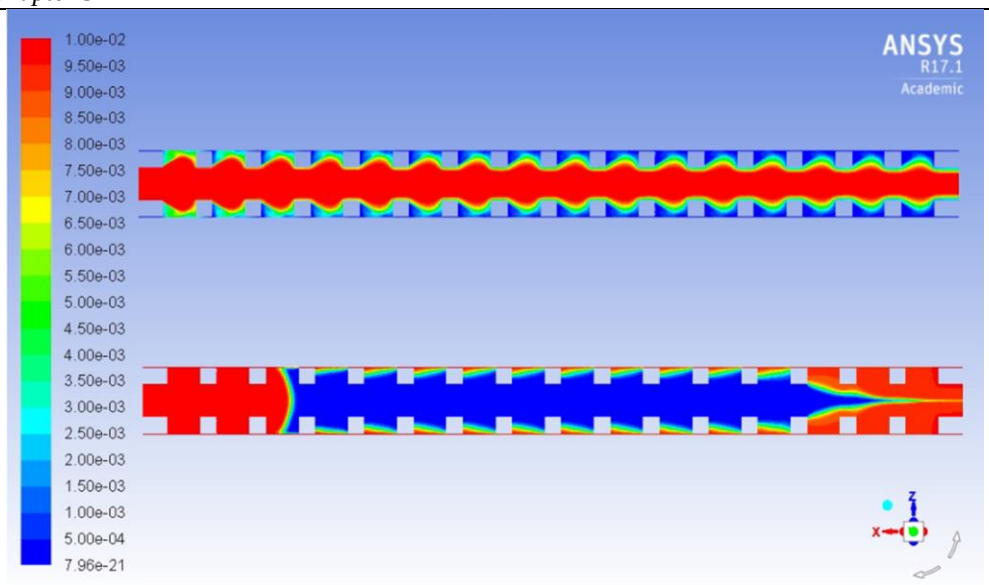

Fig. S3.3. Contour plots resulting from the injection of three channel volumes of dye into a ^{1}D channel, without (top) and with (bottom) stationary-phase material present. Simulations present the end of the simulation at a *y*-direction middle plane. The ^{1}D channel has an internal diameter of 1 mm and an external diameter of 3 mm The through-holes are 1 mm in diameter and a gap of 0.1 mm is assumed around the ^{1}D insert with through-holes.

To evaluate the effects of the gap during the transfer of the dye from the ^{1}D to the ^{2}D (i.e. the ^{2}D injection), a pulse injection of a mixture of dye and water through the inlet of the flow distributor was implemented at the beginning of the ^{2}D step and it was flushed into the device with half a device volume of water. In Fig. S3.4 the contour plots of the dye profiles are depicted for a ^{1}D channel without (frames A and B) and with (frames C and D) stationary-phase material after completing 30% of the process (frames A & C) and at the end of the simulation (frames B & D).

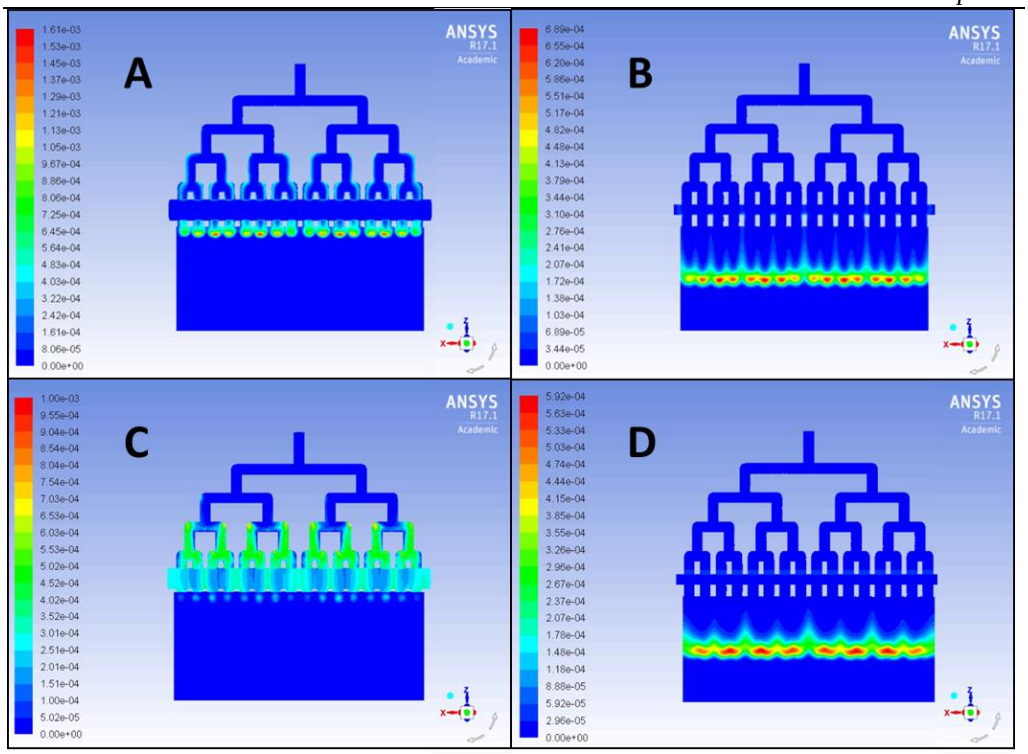

Fig. S3.4. Results (volume rendering of mass fractions, shown at a y-direction middle plane) of simulations of a pulse injection of dye, followed by flushing with half a device volume of water. (A) device with an empty ^{1}D channel (without stationary-phase material) after completing 30% of the process and (B) at the end of the simulation; (C) device with a ^{1}D channel with stationary-phase material after completing 30% of the process and (D) at the end of the simulation.

From Fig S3.4A it is found that in the case of a ^{1}D channel without stationary-phase material the flow passes through the ^{1}D channel without entering the gap and is transferred to the ^{2}D bed, while in case of Fig. S3.4C the dye entered the gap while the flow was moving towards the ^{2}D. This can be seen more clearly from a different perspective, as shown in Fig. S3.5. In Fig. S3.5A the dye is seen to not penetrate the full area (the middle of which is partly obscured by the inlet connector), while in in Fig. S3.5B the dye is seen to move around the first-dimension channel through the narrow (0.1 mm) space surrounding it. In Figs. S3.4B and D we can observe the band in the ^{2}D bed. In the case of the ^{1}D without stationary-phase material the band is more

homogeneous but tailing is observed, while in case a stationary-phase is present the band exhibits more heterogeneities, but the observed tailing is less severe.

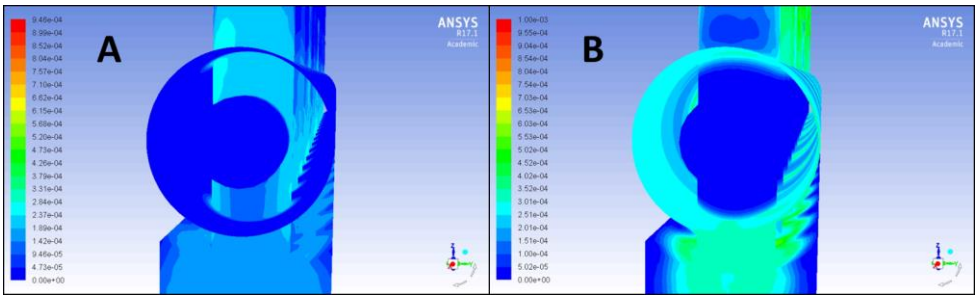

Fig. S3.5. Results (volume rendering of mass fractions) of simulations of a pulse injection of dye, followed by flushing with 15% of a device volume of water. (A) device with an empty ^{1}D channel (without stationary-phase material) and (B) device with a porous ^{1}D channel (with stationary-phase material). Zoomed-in trimetric view of the side of the ^{1}D inlet, which acts as a wall in these cases.

From these outcomes we must conclude that the gap between the outer diameter of the inserted ^{1}D channel and the inner diameter of the housing must be reduced. This may be achieved through narrower manufacturing tolerances or by additional sealing between the two parts, for example using an elastic material in the form of a continuous sleeve. For an example used in a later study see Fig. 5.10.

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