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COMSOL assistance for the modeling of cellular microsystems

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Abstract:

The developments of microsystems for biotechnology have been fast in the last few years, and no sign of slowing down is observed. It has begun with lab-on-chip for genomics, especially for the recognition of DNA sequences, followed by protein reactors and immunoassays, and today the emphasis is on cellomics.

Cell-chips are design to monitor the behavior of cells, individually or as a group, and to estimate parameters such as cell signals, cell response to drugs, and cellular differentiation.

In this paper, we present some examples of cell manipulation in chips—which is often called cellular biomicrofluidics [1]—and cell-chips, and show how their functioning and numerical simulation and COMSOL in particular can contribute to their design.

Keywords: cell culture, cell-chips, concentration gradient, separation, pinched channel, sheath flow.

1. Introduction

Cell chips have become essential tools in the development of biotechnology. Since a small population of cells, or even a single cell, can be isolated and closely monitored, new information on the cellular behavior can be obtained.

Such information can be the mechanism of cellular communication, or the cell response to a particular chemical species or a drug, or the cell differentiation in function of its chemical and/or physical environment, etc.

In this text, we present some examples of cell manipulation in microsystems and of cell-chips, and we show how the use of the numerical modeling can lead to a better design and a more efficient functioning of the device.

2. Single-phase flow focusing

Focusing cells or particles in a microfluidic channel is an essential step for all cell-chips. Two types of flow focusing exist: the two-phase flow focusing that is used to encapsulate biological objects and cells [2,3], and the single-phase flow focusing which is used to concentrate or focus a "beam" of liquid inside a sheath flow [4,5]. The biologic targets transported by the flow are focused or confined in a fraction of the cross section of the channel. Depensing on the device, the focusing can be made along a wall of the microchannel or in a pinched streamflow (fig.1). In the first case, the flow rate ratio is

$$\frac{Q_1}{Q} = \frac{1}{2}\frac{w_1}{w} \qquad (1)$$

where Q_1 and Q are respectively the sample fluid flow rate and the total flow rate, and w_1 and w are respectively the width of the focused region and the total width of the channel. In the second case, the characteristic size of the pinched flow R is

$$\frac{Q_1}{Q} \approx \frac{9}{4}\frac{R^2}{w\,d} \qquad (2)$$

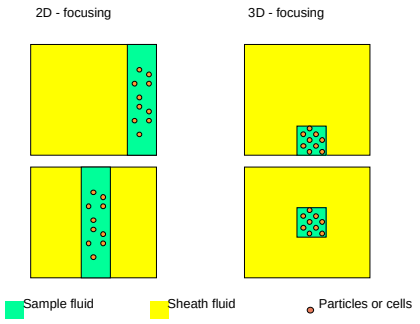

Fig.1. Principle of single-phase flow focusing

The first case can easily be numerically modeled (fig.2); note that the focusing of the flow by the sheath flow can be tuned by adjusting the sheath flow rate.

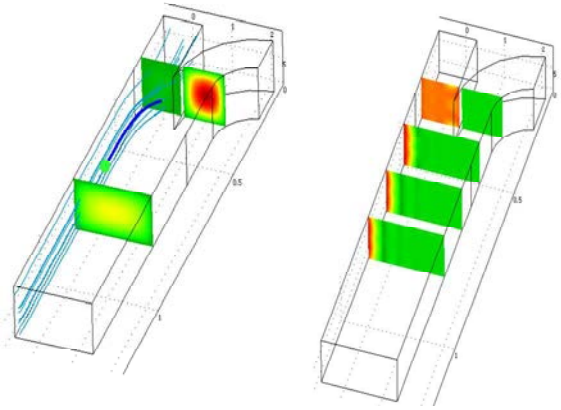

Fig.2. Single-phase flow focusing: left, streamlines are (continuous line) are concentrated along the wall under the action of the incoming sheath flow; a trajectory of a 10 µm particle is shown in dark blue; right, concentration slices in the channel showing the focusing.

Three-dimensional focusing can be achieved by a more elaborate device like that shown in figure 3, initially proposed by Kennedy and colleagues [4].

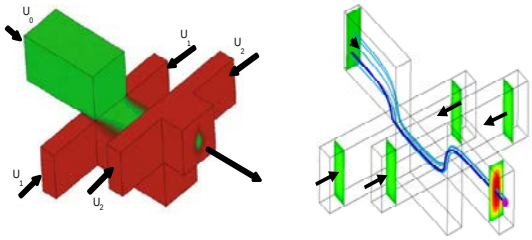

Fig.4. Left: Principle of 3-D single-phase flow focusing; right: streamlines obtained by using COMSOL numerical program, showing the focusing.

Depending on the different sheath flow rates, the focusing may be adjusted inside the channel cross-section as shown in figure 5.

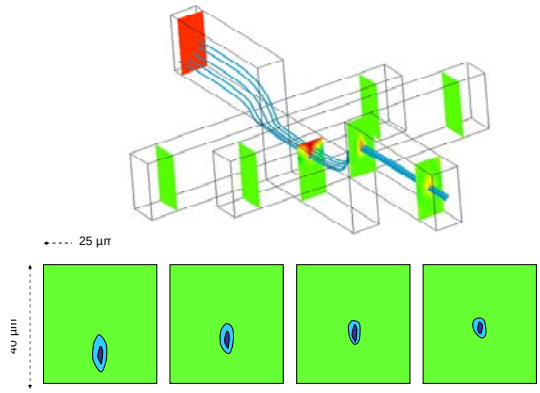

Fig.5. Top: Slices showing the concentration in the device and the focusing at the outlet. Bottom: different focusing obtained by tuning the different sheath flow rates.

3. Pinched channels

Separation of cells is fundamental for the study of a precise type of cell. Cells are often sorted out according to their size. A simple, yet efficient method is that of “pinched channel”.

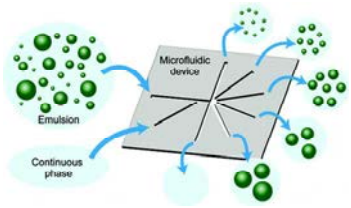

Fig.6. The principle of cell sorting by pinched channel method [6].

Pinched channel geometry has been found to be an efficient way to separate particles and cells according to their size [6,7]. A first step is to concentrate all cells or particles alongside a wall. This step is called “2D focusing” and has been presented in the preceding section. The targets are then transported towards a sudden enlargement (fig.7). Small particles have their mass center closer to the wall than that of larger particles. In the enlargement, their trajectories will be different, the small and large targets not belonging to the same trajectory. Let us denote w_1 the half-width of

the pinched channel and w_2 the half width of the enlarged channel, and d the sphere (particle or cell) diameter, then the homothetic rule yields

$$\frac{y}{w_2} \approx \frac{w_1 - d/2}{w_1} \qquad (1)$$

which leads to

$$y \approx (w_1 - d/2)\frac{w_2}{w_1} \qquad (2)$$

If we write relation (2) for two different types of cells, characterized by a difference of diameter Δd, the increase of vertical distance between the two trajectories is

$$\Delta y \approx \frac{\Delta d}{2}\frac{w_2}{w_1} \qquad (3)$$

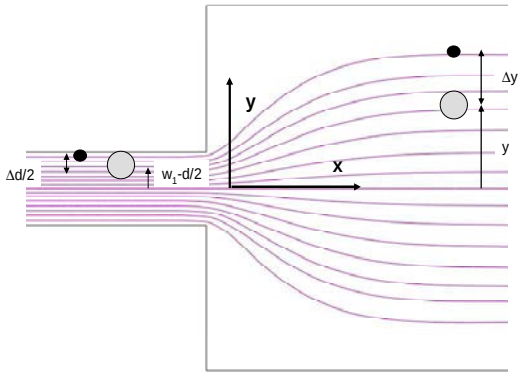

Fig.7. Principle of pinched channel.

Such a behavior can be obtained using COMSOL (fig.8) with a simple expression for the drag force

$$F_{drag} \approx C_D \left(V_f - V_p\right) \qquad (4)$$

where C_D is the drag coefficient ($C_D \approx 6\pi\eta R_H$) and V_f and V_p are respectively the fluid and particle velocities.

The modeling with COMSOL in three-dimensions is shown in figure 8. Streamlines and trajectories for 5 µm radius spherical particles have been added to the graph, showing that the hypotheses of the simplified analytical model are approximately justified.

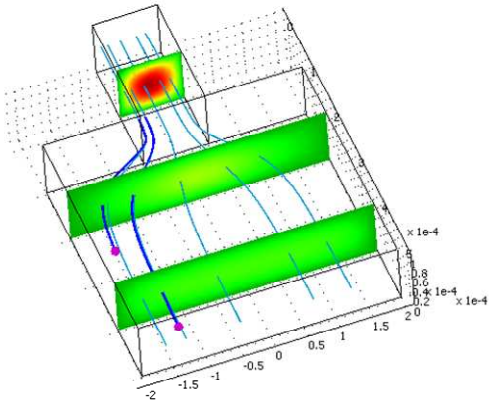

Fig.8. Pinched channel and sudden enlargement: streamlines (continuous light blue lines) and trajectory separation of particles according to their focusing at the wall. Note that particle trajectories are not exactly identical to streamlines.

The usefulness of such devices for cell separation is shown in figure 9.

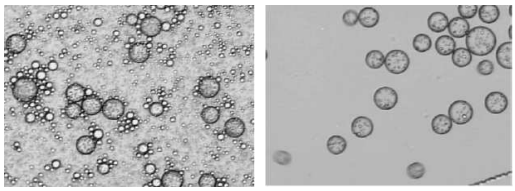

Fig.9. Separation of dispersed particulate suspension by pinched channel device [3]

4. Microsystems for cell culture

The control of chemical delivery in microfluidic cell culture is a major research topic at the present time. The solution for the precise delivery of a chemical signal to a large group of cells without disturbing the cellular environment is a challenge. On one hand, the conventional use of passive diffusion gradients leads to overly slow and very approximate signal delivery. On the other hand, active methods using convective flow profoundly disturb the cellular environment: cells can be removed by the flow, shear stress modifies the direction of cellular chemotaxis, and the natural cell signals are blurred; active methods can deliver the chemical signal, but their effect on the cell culture is too invasive.

A proposed solution is to combine the two approaches: a convective microchannel is used to quickly transport towards a microchamber the chemical signals, and a nanoporous membrane (porosity ~10%) is used to protect the microchamber from flow convective motions (fig.10) [8]. Chemical signals can then be delivered quickly to a large cell culture area without the drawbacks of the conventional active or passive methods.

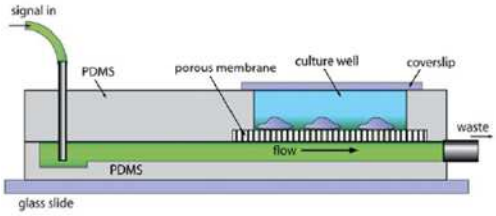

Fig.10. Schematic view of the cell culture system by VanDersarl et al. [8].

At the LETI, a similar solution is investigated, but with micro-apertures instead of the nanoporous membrane, which makes the microfabrication easier. A calculation can easily be done with COMSOL for the system described in figure 11.

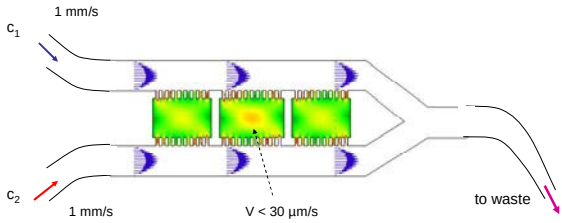

Fig.11. Velocity field inside the microsystem: in the cell culture microchambers, the fluid velocity is smaller than 30 µm/s.

Even if the velocities in the "feeding" channels are large (1 mm/s) the velocities inside the chambers stay small (less than 30 µm/s).

On the other hand, the diffusion of species to the cell culture chambers is quite fast, as shown in figure 12. A bolus of concentration at the "top" inlet propagates very fast in the system: in less than 0.3 seconds it affects the cell culture.

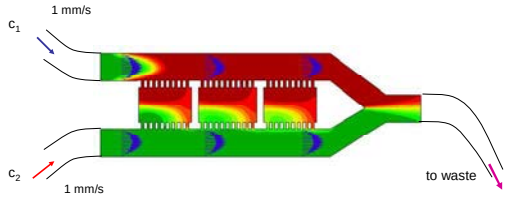

Fig.12. A bolus of concentration at the inlet reaches the cell culture areas in less than 0.3 seconds.

Moreover, a progressive gradient can be achieved across the system, as shown in figure 13 where a stable (steady) gradient is obtained across the cell chambers.

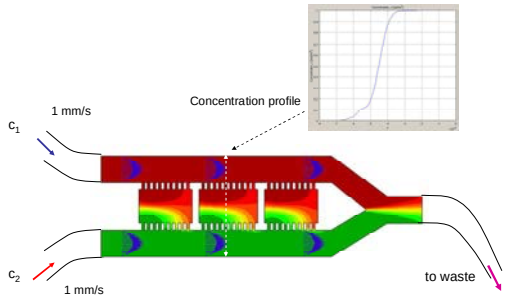

Fig.13. Concentration map in the system.

5. Conclusions

Cellular biomicrofluidics and cell-chips are perhaps the fastest developing area in biotechnology. Great expectations are associated to these new methods and microdevices.

The few examples presented here enlighten the possibilities of advances in this domain. New designs are to be found and adapted numerical tools like are essential to help this search.

These tools must deal not only with conventional convection-diffusion-migration but also with accurate trajectory calculations with the taking into account of different local forces, like lift forces, Dean forces, etc. An open, easy-to-use sub-toolbox in the MEMS toolbox, dealing with these forces, would be of great use to the developer.

6. References

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