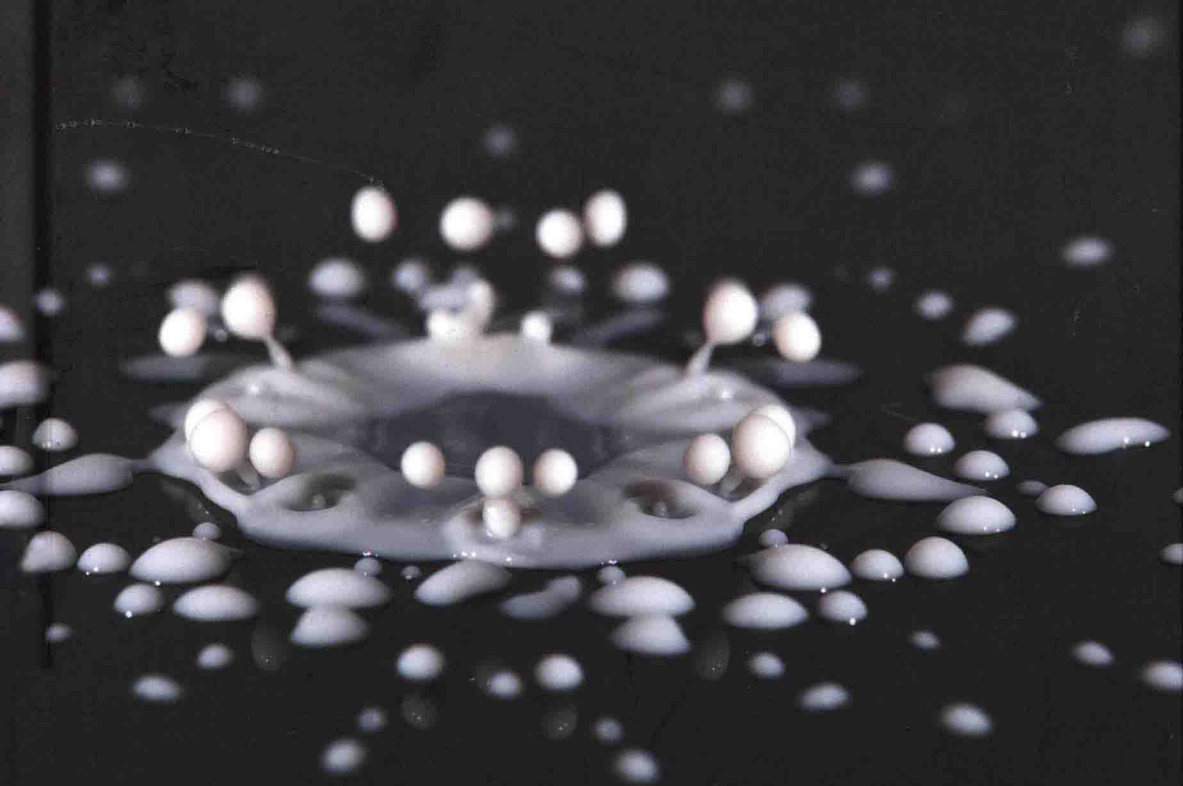
ADVANCES IN

MICROFLUIDICS

Edited by **Ryan T. Kelly**



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Preface

When the field of microfluidics emerged in the early 1990s, it was primarily focused on the development of analytical microdevices. Since then, microfluidics has expanded its influence into virtually every branch of science and engineering. There are many driving forces behind this explosive growth. To name a few:

- Scaling properties afforded by miniaturization are desirable for many applications. For example, enhanced mass transfer and heat dissipation enable faster chemical separations without sacrificing separation performance.
- Sample and reagent requirements can be greatly reduced.
- The unique properties of fluids when confined to small channels (e.g., laminar flow) make novel applications possible.
- Photolithographic patterning provides tremendous design flexibility. Rather than manually coupling different components and capillaries to create a microsystem, microfluidic design relies on the creation of photomasks that are drawn using computer aided design software.

These favorable conditions have led to a positive feedback loop in which new applications drive additional technology development and vice versa. Of course, such developments are ongoing, and we will undoubtedly continue to see brisk growth in both the research environment and in commercial settings for many years to come.

This book provides a current snapshot of the field of microfluidics as it relates to a variety of sub-disciplines. The chapters have been divided into three sections: Fluid Dynamics, Technology, and Applications, although a number of the chapters contain aspects that make them applicable to more than one section. It is hoped that this book will serve as a useful resource for recent entrants to the field as well as for established practitioners.

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Part 1

Fluid Dynamics

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Microfluidic Transport Driven by Opto-Thermal Effects

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1. Introduction

Microfluidic applications to biology and chemistry rely on precise control over the transport of (bio-)molecules dissolved in tiny volumes of fluid. However, while the rigid environment of a microfluidic chip represents a convenient way to impose flows at the micrometer scale, an active control of transport properties usually requires the action of an external field (Squires & Quake, 2005).

Can light provide such control? Light indeed has several specific assets. First, as optical methods are contact-free, they are intrinsically sterile. Second, light fields can be tightly focused, providing by the way a very local and selective action. Third, light excitation can be totally disconnected from the chip (even though integration is possible (Monat et al., 2007)), therefore no microfabrication or specific treatment of the chip are required. This also provides a high degree of reconfigurability and versatility. The interest of applying optical fields to lab-on-a-chip devices is therefore evident.

Optical forces, which rely on the exchange of momentum between a light beam and a material object at a refractive index discontinuity (Ashkin, 1970), have led to the development of optical tweezers (Ashkin et al., 1986), themselves having opened a huge field of applications (Jonáš & Zemánek, 2008). However, the use of optical forces in the scope of microfluidic transport is limited by their very weak amplitude—typically, in the picoNewton range.

To circumvent this limitation, several alternatives have been proposed. The basic idea is to use light to induce hydrodynamic forces. A convenient means of doing this is to use a light source as a localized heater. The light beam thus provides a direct transfer of energy, rather than a transfert of momentum. Indeed, as the photon momentum equals its energy divided by the velocity of light, the total impulsion which can be communicated to an object is weak at given energy per photon. A direct transfer of energy therefore appears more favorable than a transfer of momentum to provide mechanical effects.

Besides the assets mentioned above, the use of focused light as a heating source has two extra advantages. On the one hand, it allows for producing very strong temperature gradients with a moderate heating. On the other hand, the possible disconnection from the chip, and the ability to duplicate or displace at will a laser beam (through galvanometric mirrors or holographic methods) provide two complementary ways of using the heating source: (i) a

'remote controlled' mode, in which the source is static, and (ii) a 'writing' mode, involving a continuously moving source. This complementarity opens the way to various opportunities.

How can the heating affect the transport properties of a fluid, or of a solute carried by this fluid? A first method consists in directly tuning the concentration of the solute, providing that the thermally-induced transport is strong enough to overcome the natural Brownian diffusion. Alternatively, the manipulation of the carrier fluid provides another way to control the transport of reagents. Such a manipulation can be achieved by tuning the fluid properties, density and viscosity, which are both temperature-dependent. On the other hand, diphasic flows are particularly relevant in lab-on-a-chip applications since they allow for the manipulation of calibrated volumes of reagents, while preventing from potential cross-contamination according to the immiscible character of the fluids involved (Song et al., 2006; Theberge et al., 2010). From the viewpoint of fluid manipulation, diphasic flows add another degree of freedom, namely, the interfacial tension, toward the control of fluid transport. Finally, a last possibility consists in performing phase changes, involving liquid-gas or gas-liquid transitions.

These two families of flows—mono- or diphasic flows—build the structure of the present chapter, basically constituting its two main parts, inside which we overview the main approaches developed in the literature. The scope of this review includes the transport of fluids and macromolecules of biological interest in the view of—proven or potential—lab-on-a-chip applications. Our purpose is not to give an exhaustive overview of the literature (especially, the manipulation techniques of small molecules, colloids, and nanoparticles, are not included in the present chapter), but rather to give a comprehensive survey, centered on the main physical mechanisms, and then to bridge the gap between the highly diverse opto-thermal approaches.

2. One-fluid flows

This section reviews the main transport phenomena involved in monophasic flows. We will first remind the main principles involved, then we will show two major research directions combining these methods, namely, the generation of channel-free microfluidic flows, and the manipulation of biological molecules.

2.1 Basic principles and methods

Three basic mechanisms, as summarized in Fig. 1, are involved in monophasic solutions: thermophoresis, thermal convection, and thermoviscous expansion. A more anecdotic alternative, involving a thermally-induced sol-gel transition, will also be briefly presented.

2.1.1 Thermophoresis

Thermophoresis, also called thermodiffusion, or Ludwig-Soret effect, takes place in solutions submitted to a temperature gradient (Piazza & Parola, 2008; Würger, 2010). The macroscopic effect is the creation, at steady state, of a concentration gradient overtaking the natural smoothing due to the Brownian diffusion (Fig. 1(a)). While this effect has been discovered in the mid-nineteenth century (independently by Ludwig and Soret), its theoretical

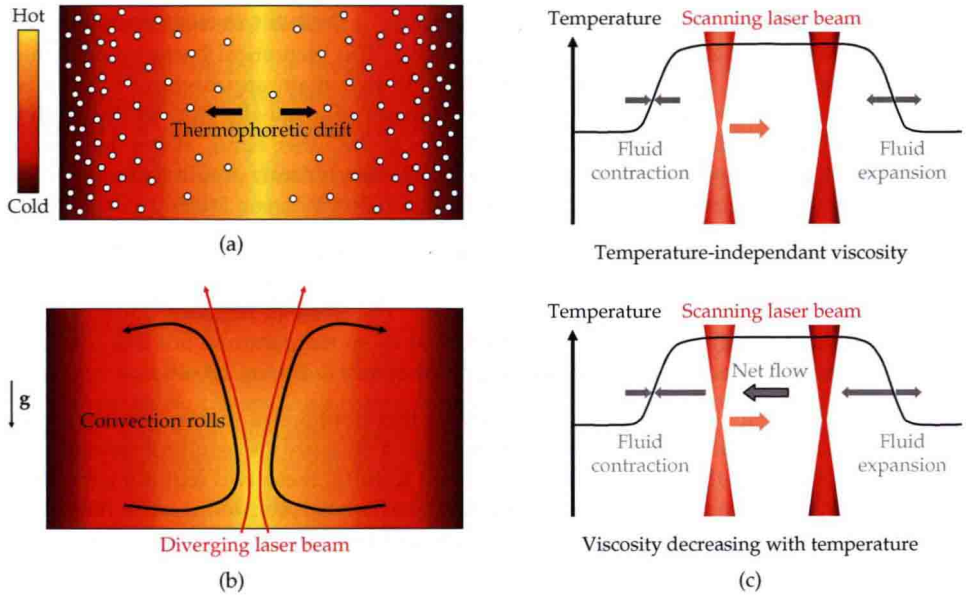

Fig. 1. Schematic illustration of the three main mechanisms involved in monophasic opto-thermal transport. (a) Thermophoresis of (here thermophobic) molecules, (b) laser-induced convection, and (c) thermoviscous expansion (adapted after Weinert & Braun (2008b)).

understanding is still controversial. The recent review by Würger (2010) provides significant insight on the different mechanisms which can be involved.

From a phenomenological point of view, the motion of particles submitted to a temperature gradient can be described as a thermophoretic drift of velocity

$$\mathbf{u}_{\text{Soret}} = -D_T \boldsymbol{\nabla} T, \tag{1}$$

with D_T the thermophoretic mobility. Note that the word 'particle' should be understood here in a generic meaning, including both molecules, nanoparticles, microbeads, etc. Indeed, while biomolecules will mainly be considered in the following, thermodiffusion applies to a broad range of systems. Even though fundamental differences exist in the involved physical mechanisms (more details can be found in (Würger, 2010)), the phenomenological description we provide here keeps its generality.

Comparing thermophoresis to the Brownian diffusion leads to the definition of the Soret coefficient,

$$S_T = \frac{D_T}{D}, \tag{2}$$

with D the Brownian diffusivity. This coefficient has the dimension of the inverse of a temperature. It can be either positive or negative and then determines both the direction and amplitude of the overall particle drift. To date, no unified theory is able to predict either the sign or the order of magnitude of the Soret coefficient, which have been observed to

usually depend on both solute and solvent parameters, as well as external conditions such as temperature (Piazza & Parola, 2008; Würger, 2010). The theoretical background aiming at describing the fluidic thermophoresis is built upon two main approaches. On the one hand, hydrodynamic descriptions rely on the hypothesis of quasi-slip flow at the particles boundary (Weinert & Braun, 2008a; Würger, 2007). On the other hand, at the microscopic scale, thermodynamic approaches assume the local thermodynamic equilibrium to account for solvent diffusivity and fluctuations (Duhr & Braun, 2006b; Würger, 2009).

A positive value of the Soret coefficient thus corresponds to a migration toward the colder regions ('thermophobic' behavior, as shown on Fig. 1(a)). Conversely, a solute with a negative Soret coefficient will be said 'thermophilic'. For DNA in aqueous buffer solution Braun & Libchaber (2002) measured $S_T = 0.14\ \mathrm{K}^{-1}$ at room temperature, but this coefficient has been observed to change of sign with temperature (Duhr & Braun, 2006b).

From an experimental point of view, the study of thermophoresis requires (i) to apply a temperature gradient to the test cell, and (ii) to detect and measure the resulting concentration distribution. Optical methods are indeed well suited to fulfill these two requirements. First, as already pointed out, a much higher temperature gradient can be produced by direct laser heating of the fluid than by externally heating the cell boundary. Second, the same laser beam can also be used to characterize the concentration gradient. One possible method relies on the thermal lensing effect: as the concentration gradient created by thermal diffusion modifies locally the refractive index of the solution, the transmitted beam is either focused or spread (effect called 'Soret lens'), depending on the direction of the solute migration (Giglio & Vendramini, 1974). An alternative method makes use of a fluorescent marker grafted to the particles of interest, or of the particles fluorescence themselves if applicable, to reconstruct the concentration profile in real time by microscope imaging (Duhr et al., 2004). Moreover, the temperature profile can also be monitored by using a temperature-dependant fluorescent marker.

2.1.2 Thermoconvection

Thermoconvection relies on the difference of density of an homogeneous fluid heated inhomogeneously. As density usually decreases with temperature, the local heating of a fluid leads to its dilatation. Considering the heating induced by a collimated laser beam with radial symmetry, the thermal expansion would also be axisymmetric, and no net flow would appear even in the case where the laser beam moves. Inducing a net flow in this case would require to break the heating symmetry. This can be done if the laser beam is divergent, as shown in Fig. 1(b): the fluid more heated at the bottom side raises up by buoyancy, then loses its heat and falls down, creating convective rolls (Boyd & Vest, 1975). This mechanism, generally known as Rayleigh-Bénard convection, is involved in many processes at the macroscopic scale, ranging from the cooking of pasta to atmospheric currents. However, in the micrometer-scale, gravity is not the predominant force, and the heating symmetry breakup induced by gravity is rather limited because the Rayleigh number, which controls the convection onset, behaves as the cube of the heated layer width. In that sense, thermal convection is usually not relevant at this scale. Microfluidic applications of thermoconvection can nevertheless be developed provided that the sample is thick enough, or that the other forces (essentially, viscous or capillary) can be efficiently reduced.

2.1.3 Thermoviscous expansion

Another elegant means of breaking the heating symmetry to induce a net flow has recently been proposed by Weinert & Braun (2008b). This method relies on the temperature dependance of viscosity of the fluid submitted to a scanning heating beam (Fig. 1(c)).

Let us consider a confined fluid, in which the influence of gravity is negligible. We first assume that the fluid viscosity does not depend on temperature, as shown on the top part of Fig. 1(c). As the laser beam moves, the fluid at the front of the spot scanning expands due to its decrease in density while, on the other hand, the fluid at the rear of the spot scanning contracts as well. As this thermal expansion is a linear process, expansion and contraction balance, and no net fluid flow is produced.

Let us now add the temperature dependence of fluid viscosity. As viscosity usually decreases with temperature, the expansion and contraction processes will be favored in the heated regions, as shown on the bottom part of Fig. 1(c). This dissymmetry results in a net flow, directed in the direction opposite to the scanning.

As thermal diffusion is faster, by several orders of magnitude, than the fluid flow, the fluid warms and cools down in milliseconds, so scanning can be operated at rates in the kiloHertz range. The resulting pump velocity can be expressed in a simple manner, dropping a numerical prefactor of order unity, as (Weinert & Braun, 2008b)

$$\begin{aligned} u_{\text{thermoviscous}} &= \text{scanning velocity} \times \text{thermal expansion} \times \text{thermal decrease of viscosity} \\ &= -f\ell_{\text{th}}\alpha\beta T^2. \end{aligned} \tag{3}$$

In this expression f is the scanning rate, ℓ_{th} the heating spot length scale, T the temperature rise, $\alpha = (1/\rho)(\partial\rho/\partial T)$ and $\beta = (1/\eta)(\partial\eta/\partial T)$ the thermal expansion coefficient and temperature dependance with temperature, respectively. For water, $\alpha = -3.3 \times 10^{-4}$ K^{-1} and $\beta = -2.1 \times 10^{-2}$ K^{-1}, then considering a heating spot size of 30 μm, a scanning rate of 5 kHz and a temperature rise of 10 K lead to a pump velocity of 104 μm s^{-1}.

2.1.4 Thermally-induced sol-gel transition

An alternative way, inducing a local phase transition in the fluid, should also be mentioned. As the thermoviscous expansion presented above, this approach relies on a thermally-induced change in the fluid viscosity, but in the framework of a phase change. Krishnan et al. (2009) used a thermorheological fluid (water containing 15 % w/w of Pluronic F127, a tribloc copolymer) flowing in a channel including an absorbing substrate. The laser heating induced a reversible gelation of the fluid, resulting in the interruption of the flow. A flow switch without any moving part was then achieved. A similar approach was also used to perform fluorescence-activated cell sorting (Shirasaki et al., 2006).

2.2 Channel-free microfluidic flows

The direct manipulation of volumes of fluid allows for the controlled creation of arbitrary flows without the need of a rigid microfluidic channel. In particular, Weinert & Braun (2008b) have shown that flows can be driven along complex patterns by thermoviscous pumping (Fig. 2). As illustrated in Fig. 2(a), an infrared laser beam writing the words 'LASER PUMP' can

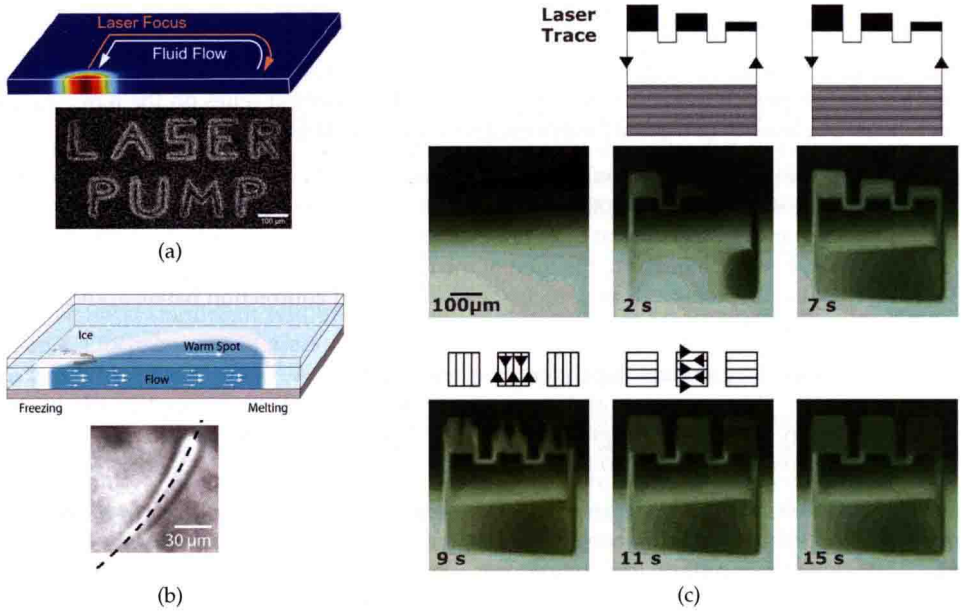

Fig. 2. Examples of channel-free flows performed by thermoviscous expansion. (a) A water flow is induced by a laser beam scanning in the opposite direction, and visualized by fluorescent tracer particles. From Weinert & Braun (2008b). (b) Thermoviscous motion in an ice sheet: the ice melts in front of the heating spot, and moves in the same direction due to the thermal expansion. The image is a superposition of frames of the molten spot along a curved path, shown in dashed line. From Weinert et al. (2009). (c) Optical creation of a dilution series of biomolecules. The system is composed of two neighboring gels, one of them (at the bottom) containing fluorescein-marked biomolecules. The laser beam first creates a liquid channel including three chambers of distinct volumes (upper panel), then mixes the content of these chambers with the ambiant fluid by pumping along a pattern alternating horizontal and vertical stripes. From Weinert & Braun (2008b).

produce a flow, in a 10-µm-thick water layer, in the direction opposite to the laser scanning. Due to the very small thickness of fluid involved, the thermoconvection cannot be invoked as a driving mechanism in this case.

The thermoviscous paradigm has also been extended to the case of melting ice (Weinert et al., 2009). In that particular case, the scanning laser first melts the ice, the liquid motion is then driven by thermal expansion, and finally the liquid refreezes (Fig. 2(b)). The motion can be described as a thermoviscous pumping in the case where the water does not freeze in the channel, when the chamber is cooled above 0°C. However, as the water density increases with temperature below 4°C the fluid flow takes same direction as the scanning. Pumping velocities of several cm s^{-1} can be reached.

The creation of fluid flows along arbitrarily complex patterns can, in principle, provide an alternative to the design of rigid dedicated channels. To highlight the potentialities of the method for (bio)chemical applications, Weinert & Braun (2008b) created a dilution series by

thermoviscous expansion. To this aim, they used a drop of agarose gel, gelated at room temperature, and molten by moderate heating (Fig. 2(c)). Biomolecules (30 kDa dextran marked with fluorescein) were added at the bottom part of the drop only, with a large amount of saccharose in order to avoid diffusion across the interface between the two halves of the gelated drop. The laser first draws a liquid channel along the two parts of the gel, creating in particular three liquid chambers of 65, 40, and 20 pL, respectively, in the upper part (initially without biomolecules). This step is represented in the upper row of Fig. 2(c). In a second step (lower row of Fig. 2(c)), the laser scans the gelated zones surrounding these chambers, along successive crossing lines. This scan enlarges the actual chambers, and dilute the biomolecules by mixing them with the molten agarose gel. As a result, a dilution series is created, with volume ratios of 4:1, 1:1, and 1:4 in equal volumes.

2.3 Manipulation of biological molecules: Diluting, trapping, replicating, and analyzing

Besides setting in motion a fluid, manipulating directly molecules of biological interest which might be dissolved in it is also of particular relevance. Such direct manipulation should indeed allow for precise tuning of the molecule concentration, and, further, for inducing particular reactions (especially, DNA replication).

2.3.1 DNA dilution or accumulation

As stated above, DNA exhibit a thermophobic behavior at room temperature (Braun & Libchaber, 2002). Therefore, the laser heating of a buffer solution of DNA deplete the zone at the vicinity of the spot due to the DNA thermophoretic drift, as illustrated in the right image of Fig. 3(a). Thermophoresis is therefore a convenient way of locally diluting a DNA solution. However, the most relevant issue is rather to concentrate molecules at a given point. Duhr & Braun (2006b) observed that the thermophoretic behavior of DNA could be reversed by simply cooling the sample: at 3°C, the DNA molecules become thermophilic and can therefore be trapped at the hot spot (left image of Fig. 3(a)). Besides this very simple method, several alternatives exist to perform effective DNA trapping.

One elegant way consists in opposing a liquid flow to the thermophoretic drift (Duhr & Braun, 2006a). This method seems particularly relevant in the lab-on-a-chip context due to its easy integrability into microfluidic channels. A 16-fold increase in DNA concentration was reached, at about 10 μm upstream from the beam axis, with a peak flow velocity of 0.55 $\mu m\,s^{-1}$. However, the time required to reach the equilibrium concentration profile is about 15 min, which limits the potentiality of the method for high-throughput applications.

By increasing the vertical temperature gradient effects, thermal convection can become significant. Figure 3(b) represents the effective DNA trapping by the interplay between these two mechanisms, as observed by Braun & Libchaber (2002). They considered a 50-μm-thick chamber, in the center of which a heating beam was focused. The top and bottom walls of the chamber were cooled to enhance the axial thermal gradient. The trapping mechanism is made of four main steps. First, the lateral thermophoresis drives the DNA molecules away from the heating spot (step 1). Then, the convection rolls carry the molecules downward, as the upward part of the rolls occur in the depleted zone close to the beam axis (step 2). The axial thermophoresis holds the DNA molecules at the chamber floor (step 3), where they finally accumulate at a radial position which result from the balance between lateral thermophoresis