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ARTIC

Nature-inspired micro-fluidic manipulation using artificial cilia

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Table of Contents

1 Introduction

This document presents a public summary of the technical achievements and dissemination and use within the project NMP4-CT-2006-033274, ARTIC - Nature-inspired micro-fluidic manipulation using artificial cilia

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Public Project Website

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http://www.artic-project.eu

2 Executive summary

The ARTIC project has developed magnetically actuated artificial cilia, inspired by biology, and proven that they can generate substantial fluid in micro-channels. Typical average net velocities are larger than 100 μm/s, and typical flow rates are 20 μL/,min. These values are comparable to other micro-fluidic principles such as electro-osmosis, but our approach has the advantages of simple actuation and compatibility with bio-fluids; next to pumping, the artificial cilia can also be used for fluid mixing. Altogether, the technology enables the active control of microscopic quantities of fluid in lab-on-chip biosensor applications, thereby creating the opportunity to conduct fast and efficient complex analyses, such as DNA profiling or pathogen identification, at a patient's bedside or in a doctor's surgery.

Next to this main achievement, by which the main goal of the project has been fulfilled, we have reached the following results:

- We have developed new advanced numerical models to simulate interactions between magnetically actuated mechanical structures and fluid flow, including behavior of complex fluids.
- These models have been applied to carry out simulations that show that fluid can be propelled with artificial cilia consisting of polymer films with dispersed PM or SPM particles that generate an asymmetric motion. In addition, it was shown that fluid inertia, metachrony, and complex fluid behavior can enhance the fluid flow.
- We have obtained more insight into processes at work in fluid manipulation by natural cilia, both by modeling and by experiments.
- Materials (polymers, magnetic nano-particles) and processes were established for the generation of magnetic cilia-like microstructures and transferred to a clean room environment.
- Reliable large area processing and integration of cilia arrays into a microfluidic system was achieved.
- Various microfluidic cartridges were designed and fabricated to meet the requirements for characterization of cilia and fluid flow.
- A fully functional experimental setup consisting of cartridge with integrated cilia array, magnetic actuation system and epifluorescent microscope was built.
- μPIV measurements were carried out of the flow generated by artificial cilia
- The project team has done scientific research on a very high level, as shown by a the large number of peer-reviewed publications that have been published, as well as by the number of (invited) lectures
- A plan for exploitation of the project results by all partners is in place.

All of the anticipated project results and contributions have been achieved.

3 Project Execution

3.1 Project objectives

One particular micro-fluidics manipulation process “designed” by nature is that due to a covering of beating cilia over the external surface of micro-organisms. A cilium can be viewed as a small hair or flexible rod (in protozoa: typical length 10 μm and diameter smaller than 100 nm) attached to the surface (see Fig. 3.1). The cilia move back and forth collectively in a particular concerted manner, and are in this way quite effective in generating flow: the swimming speed of the Paramecium, for example, can be more than 1 mm/s.

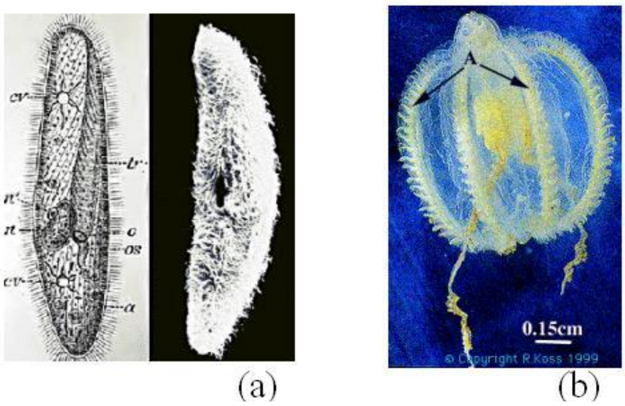

Figure 3.1: Two micro-organisms that make use of propulsion by cilia: (a) Paramecium, (b) Pleurobrachia.

The **overall objective** of the ARTIC project was to develop artificial cilia, on the basis of polymer micro-actuators, that can be integrated in micro-fluidic systems, and that can be used for fluid manipulation, in particular pumping. The movement of the artificial cilia has to be actively controlled, preferably using a magnetic field. To achieve this, we started by studying the natural cilia in terms of underlying mechanisms, energy consumption, and effectiveness. The knowledge obtained was translated into advanced mechanical, electro-magnetic, and fluid flow models, which were used to generate optimum designs and specifications for the artificial cilia to be made. Based on these specifications, (composite) materials were synthesized that can be used as a basis to fabricate the artificial cilia.

To validate the effectiveness of fluid manipulation using artificial cilia, we designed and set up a basic experiment. The final test consisted of fluid flow characterization in an elementary micro-fluidic device containing the micro-actuators or artificial cilia. It consists of a micro-fluidic channel device in which the artificial cilia are integrated. By magnetically actuating the artificial cilia, fluid flow should be generated. The flow was characterized using special flow velocity measurement techniques. The original aim of the project was to create a liquid pumping effect with typical flow rates in the order of 10 pl/min to 1μl/min, which is a suitable range required by biosensor-applications. The liquid has a viscosity around 10^{-6} m^2/s (water-like, suitable for many biological fluids), and the micro-channel has a typical cross-section of (500x500) μm^2 and a length in the order of 1 cm.

At the start of the project, the following contributions by ARTIC to knowledge creation and technological innovation were defined:

- Generation of new knowledge in the field of fluid manipulation by natural cilia

- Dedicated mechanical, electro-magnetic, and fluid flow models including the interaction between these domains.
- Development of artificial cilia on the basis of magnetically or electrically actuated polymer nanostructures, and development of a technology to integrate these in a microfluidic system.
- A completely novel microfluidic manipulation means, opening new ways of very effectively transporting, mixing, or otherwise manipulating complex fluids in many critical applications, e.g. in the biomedical area.

The following main results were anticipated:

- New insights into the processes at work in fluid manipulation by natural cilia.
- New materials and processes for making electro-magnetic polymer-based artificial cilia.
- Models describing the mechanical, electro-magnetic, and fluid flow aspects of the complete system.
- A basic micro-fluidic device containing the artificial cilia and driving system.
- Experimental assessment of the fluid manipulation effectiveness of the technical system.

3.2 Contractors involved

Consortium overview					
#	Participant	Type	Country	Enter project	Exit project
1	Philips Electronics Nederland	IND	NL	M1	M48
2	University of Freiburg, Institute for Microsystem Technology	HE	GE	M1	M48
3	Liquids Research Ltd.	IND	UK	M1	M48
4	University of Groningen, Department of Applied Physics	HE	NL	M1	M48
5	"Politehnica" University of Bucharest	HE	RO	M1	M48
6	Centre for Biomimetics and Natural Technologies, University of Bath	HE	UK	M1	M48
7	Delft University of Technology	HE	NL	M1	M48
8	Eindhoven University of Technology	HE	NL	M1	M48

Table 1 : Type: HE (High Education Institute), IND (commercial manufacturer, Industry)

3.3 Work performed

The work was carried out in 4 workpackages:

- WP1: Modeling and design of ciliary motion
- WP2: Materials synthesis and analysis
- WP3: Technology and system integration
- WP4: Flow characterization

This section will describe the work performed, and main results obtained, in the workpackages.

Modeling and design of ciliary motion

During the first stage of the project, we made a full catalogue of existing biological liquid-moving/handling mechanisms. No classification of this kind was found in the scientific literature. A special emphasis was put on ciliated and flagellated biological systems, see Figure 1. On the basis of the insights obtained, we constructed a number of experimental scale models of ciliary actuators. This work resulted in guidelines for designing artificial cilia and, in particular, in a lithography mask for processing of artificial cilia.

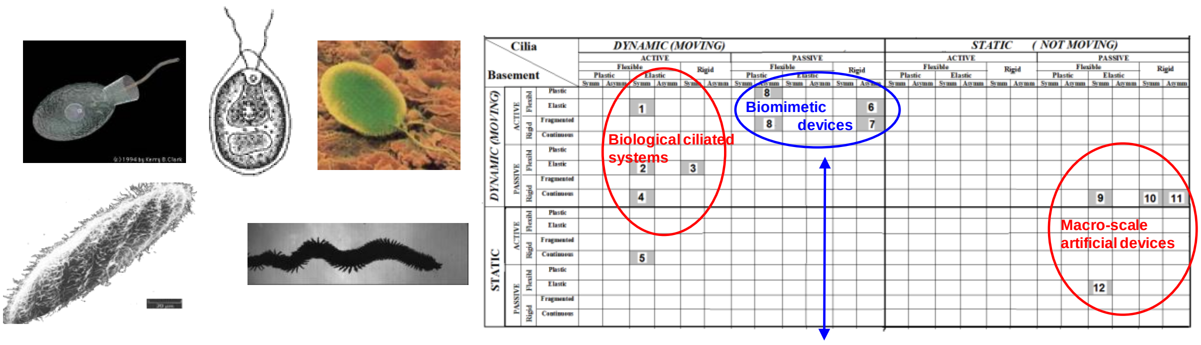

Figure 1: Examples of ciliated and flagellated biological systems (left), and a classification in terms of their properties (right).

In the second year we started to construct a mathematical model of biological cilia which incorporates their main structural features and functional components to help us understand the mechanical basis of their motion. The model consists of two microtubules with nexins links, behaving as slender beams. A motility function was introduced by using distributed loads acting in opposite directions for each filament. This model was extended by introducing design rules inspired by the description of the activation mechanism for the dyneins by motor proteins in natural cilia. Simulations were performed of the interaction between the two-microtubule artificial cilia and a viscous fluid. This helped us to understand the working principles of natural cilia.

A large part of our modeling efforts have gone into the development and use of advanced numerical models to simulate the magnetic actuation of artificial cilia, and the interaction between the cilia and the surrounding fluid. Magnetic models describing the interaction between a magnetic excitation field and magnetic materials, from the macroscopic scale down to the nanoscopic scale, were made. The results led to the design of the first magnetic actuation prototype, and to guidelines for the required distribution of magnetic nano-particles in the artificial cilia. Subsequently, a magneto-mechanical model of an individual artificial cilium in a fluid was made. This model was extended with a cilia-fluid interaction model, and this enabled us to design optimal artificial cilia and driving magnetic fields for fluid flow generation. The basic geometry of the artificial cilia were micro-flaps, with a rotating magnetic field applied. A parametric study carried out using the new and truly unique model gave guidelines for the detailed design of our artificial cilia and the final magnetic excitation system (see below). In addition, the simulations provided guidelines for optimization of the channel height and cilia spacing. Important conclusions of the simulations were that even at these small length scales, fluid inertia can play a substantial role in net flow generation by artificial cilia. In addition, out-of-phase beating of the artificial cilia, leading to wave-like motion of a collection of cilia, can significantly enhance the generated flow. Figure 2 shows some simulation results.

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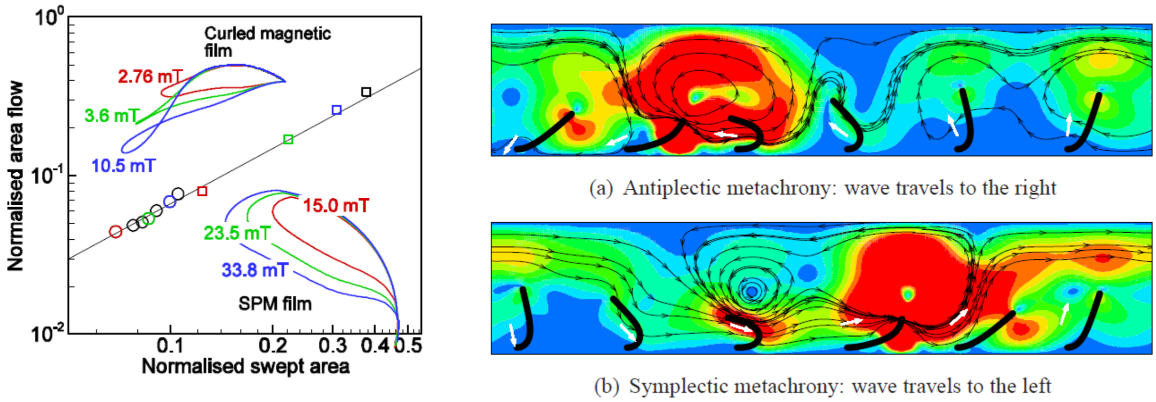

(a) Antiplectic metachrony: wave travels to the right

(b) Symplectic metachrony: wave travels to the left

Figure 2: Results of the numerical simulations. Left: from this plot the relationship between artificial cilia properties, applied magnetic field, and the induced fluid flow can be determined. Right: images showing streamlines, fluid velocity (represented by the colors) of flow generated in a microchannel by cilia moving out-of-phase under the influence of an applied magnetic field (white arrows).

As a sideline, the dynamics of an electrostatically (rather than magnetically) actuated micro-fluidic mixing channel based on artificial cilia have been modelled. From the results we concluded that inertia, next to asymmetric motion, can play an important role in determining the flow direction even at this small length-scale.

Finally, the modelling of the cilium/fluid interface was greatly improved by adapting a new embedded boundary scheme which made it possible to simulate the interaction between actuated cilia and non-Newtonian fluids, rather than just for Newtonian fluids like water. For practical applications, this is highly relevant since in many microfluidic applications (e.g. lab-on-a-chip) the fluids to be manipulated are complex non-Newtonian fluids, for example blood or saliva. The new and accurate scheme allowed the simulation of a cilium propelling a shear thinning fluid such as saliva. It was shown that fluid propulsion in a shear thinning fluid is much more sensitive to the applied time scale than a Newtonian fluid. This effect can even be used to enhance the fluid flow of a cilium, see Figure 3.

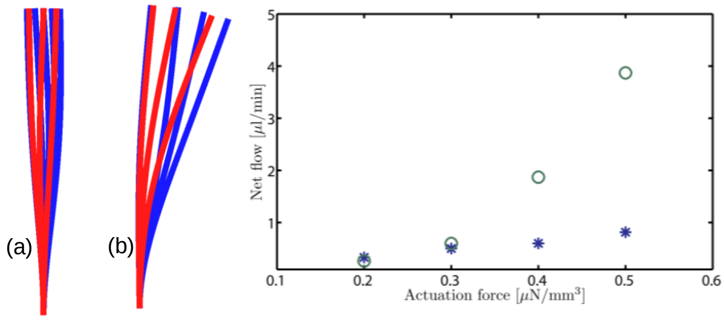

Figure 3: Simulation results showing the effect of non-Newtonian behavior of the fluid. Left: The motion of a cilium in forward (blue) and backward stroke(red) for the Newtonian case (a) and shear-thinning case (b). Right: The net flow for a Newtonian fluid (closed symbols) and a shear thinning fluid (open symbols).

Materials synthesis and analysis

Based on the guidelines resulting from the numerical simulations, we developed new materials and processes to create artificial cila. Our chosen strategy for artificial cilia fabrication is to disperse magnetic nanoparticles in thin polymer films, and structure these lithographically to obtain micro-flaps that can be actuated magnetically (see Figure 5). For the polymer film two classes of polymer materials have been developed: a (swellable) hydrogel, polydimethylacrylamide (PDMAA), and a (non-swellable) rubber, polybutylacrylamide (PBA). In addition, we developed both super-paramagnetic and remanent magnetic nano-particles. The super-paramagnetic particles are magnetite. The magnetite particle system was improved by optimizing the average size of the particles and thus increasing the magnetization by 25% at 30mT. For the remanent systems, nanoparticles of both pure and mixed ferrite (cobalt ferrite) were produced. We explored new routes for making the Co-containing particles, which has successfully led to remanence values that are increased by 106% compared to conventional production techniques. An important development was the choice of surfactants to functionalize the nanoparticle surfaces, so that they could be homogeneously dispersed in both polymer materials. See Figure 4 that illustrates the results.

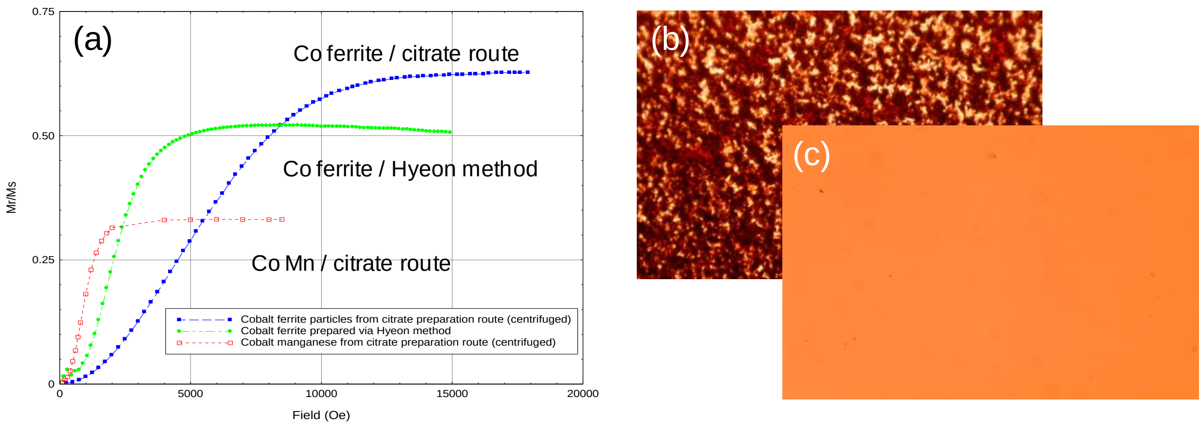

Figure 4: Result for magnetic particles. (a) Magnetization curves for our Co-ferrite particles, illustrating the high remanence level we can achieve. Right: pictures of dispersion of superparamagnetic nanoparticles in a PBA-film, with a non-optimized (b) and an optimized (c) surfactant system; the latter clearly shows a very good homogeneous particle dispersion.

Parallel to the development of the materials, a novel processing route was developed for manufacturing the artificial cilia. The method is based on two-color lithography and is sketched in Figure 5. This allowed us to generate anchor/release structures and artificial cilia flaps using crosslinkable polymer layers processed at two different wavelengths. To this end, two new crosslinkers were developed to improve the sacrificial layer properties. One was based on oxypropylacrylate (OPA) and the other was based on oxypropylmetacrylate (OMA). As a result a very robust polymer-composite multilayer system was obtained. A flap surface functionalization was performed to control the bending of the flaps after the release in aqueous fluids. This was done by coating the cilia with a hydrophobic layer permanently linked to the surface. The release itself is the final processing step of the cilia. This step can be performed within the microfluidic device, right before use of the cilia. This keeps the fragile cilia protected in the sacrificial layer, and is a proper way to protect them until usage so that the shelf life is extended.

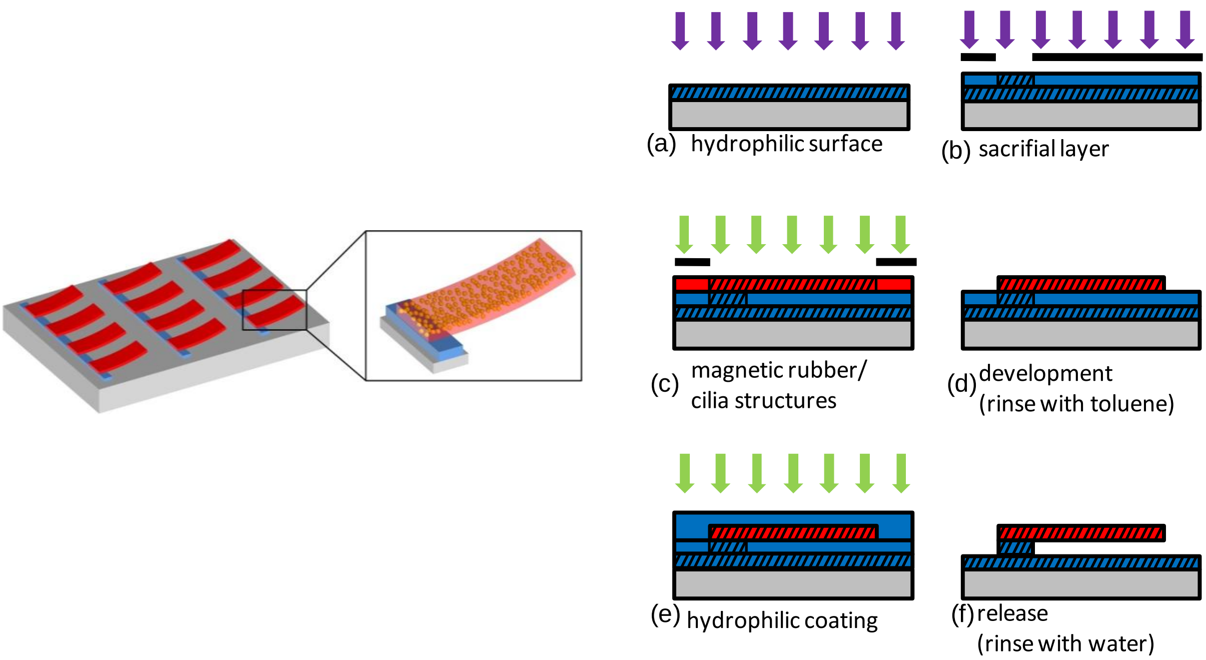

Figure 5: Left: sketch of our magnetic artificial cilia array, and an individual cilium. Right: processing route. a) The substrate is coated with wetting layer of hydrogel, b) The hydrogel sacrificial/anchor layer is deposited and structured; c) The magnetic rubber is deposited from toluene and structured; d) The cilia structures are developed; e) Hydrogel is deposited by dry deposition to protect cilia; f) The cilia are released by dissolving the sacrifical layer.

During the final stage of the project, the developed materials and processes were implemented in the cleanroom at IMTEK, so that cilia arrays could be produced in a well-controlled environment and on a regular base, see Figure 6. Functional samples were shipped to partner TUD for fluidic characterization (see below). Several masks designs were proposed and various structures made of magnetic composite materials were fabricated, see Figure 6. We have shown in proof-of-concept experiments that the released cilia responded to external magnetic fields: using an external permanent magnet, the cilia could be actuated, exhibiting substantial strokes.

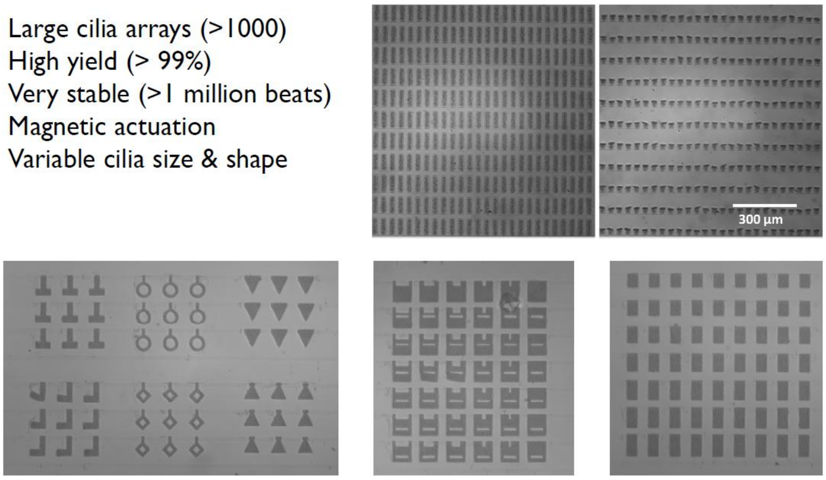

Figure 6: Images of artificial cilia we have fabricated, illustrating that we can produce large cilia arrays, with different shapes, and that they can be actuated by a magnetic field.

Technology and system integration

To be able to create a proof-of-concept device that makes it possible to characterize the capability of our artificial cilia to create flow, an integrated experimental system had to be realized. This consists of a microfluidics device in which the artificial cilia are integrated, a magnetic excitation system, and an optical system for flow visualization. After an extensive inventory of possibilities, we selected the following concept for the micro-fluidic device. The final microfluidic system has a sandwich structure composed of three parts: the substrate with the artificial cilia, a polydimethylsiloxane (PDMS) layer to define the channel geometry and a top optical part to allow optical access. The approach has the tremendous advantage that the connection between the cilia substrate and the microfluidics structure is not permanently fixed, as is usual for micro-fluidic assemblies, and this offers the possibility to re-use the cover substrate with connections for many experiments with varying cilia lay-out. Additionally we developed a second option in which the microfluidic part and the optical part are fabricated as one piece in a process of injection moulding of silicone rubber, see Figure 7. An additional, unique, feature was added in the form of an optical prism integrated in the microfluidics device, allowing optical access in the vertical plane, and enabling the observation of the artificial cilia from the side rather than from the top.

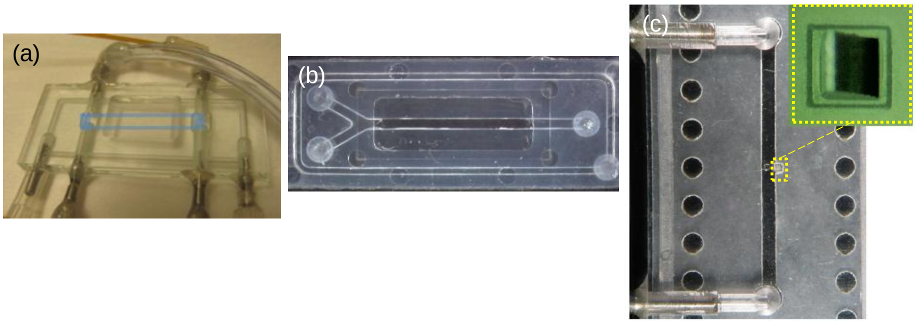

Figure 7: Pictures of the microfluidic cartridge we developed. (a) The sandwich cartridge; (b) the injection moulded cartridge; (c) cartridge with integrated a micro-prism for a cross-sectional view.

The magnetic excitation system we developed, consisted of four magnetic coils that can be individually driven through a custom made software program in order to control the magnetic field orientation and magnitude as a function of time. The micro-fluidic device containing the artificial cilia is placed in the center between the poles. The maximum field that can be generated is about 80 mT. An alternative magnetic actuation module was fabricated as well: a rotating magnet is placed under the microfluidic cartridge. Although the field uniformity depended on the magnet geometry, this system had the advantage that the actuation fields were almost double in strength at high actuation frequencies (e.g. 20Hz) compared to the electromagnet system.

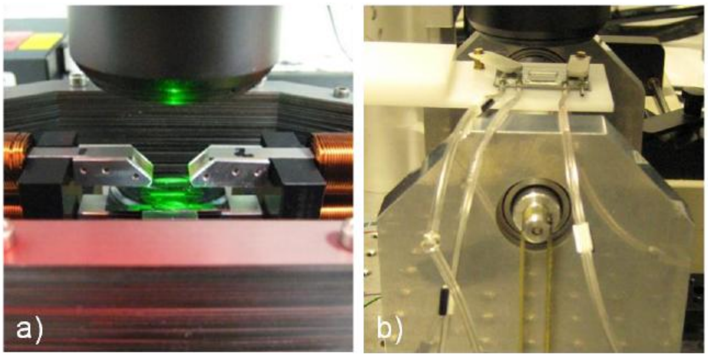

Figure 8: Images of the magnetic excitation systems we developed. (a) magnetic coil-based; (b) rotating permanent magnet.

The set-up was completed by the optical system. This includes an upright fluorescence microscope, a dual-cavity laser, two 12-bit double-frame CCD-cameras and a built-in PC trigger and timing unit for synchronizing the laser, the cameras, the data acquisition, and data. The laser, the cameras and the microscope are operated with commercial PIV software, so that Particle Image Velocimetry (PIV) measurements can be performed. Figure 9 shows a sketch of the complete set-up used in the final experiments.

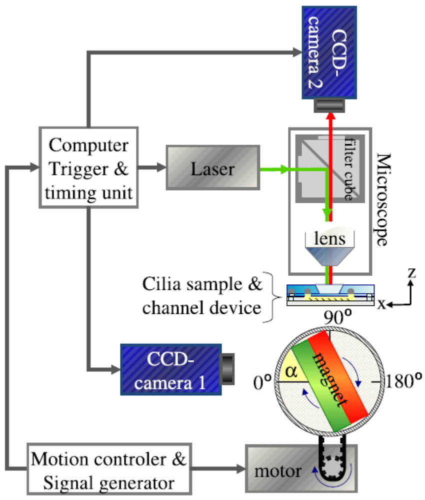

Figure 9: Sketch of the complete set-up used for the final experiments.

Flow characterization

In flow characterization, the focus was initially on measurements of natural cilia systems (cilia of a worm and lung cilia of a mouse). In particular the motion induced by mouse lung cilia was studied. The particle and fluid transport by the cilia was successfully measured. The flow was quantitatively studied using micro-Particle Image velocimetry (μPIV), see Figure 10, demonstrating for the first time that directed fluid transport is achieved by airway cilia in the absence of a mucus layer.

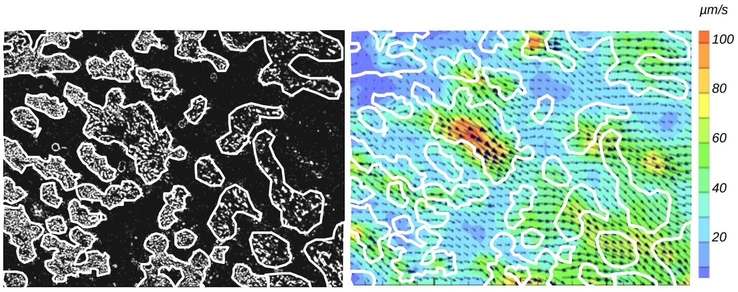

Figure 10: Left: Biological cilia of a mouse trachea. Right: Fluid velocities induced by the biological system in a plane 15 μm above the tissue surface, measured by μPIV.

Subsequently, microfluidic experiments with our artificial cilia were performed using the set-up described above and shown in Figure 9. Tracing the cilia deflection was successfully performed making use of bright field high speed recordings at 100-500Hz. Fluid manipulation by cilia was measured with μPIV. The fluid transport over the entire actuation cycle was established by correlation of the tracer particles images with the same phase. The flow induced by the artificial cilia is strongly oscillatory with a flow reversal during the upward cilia stroke, see Figure 11.

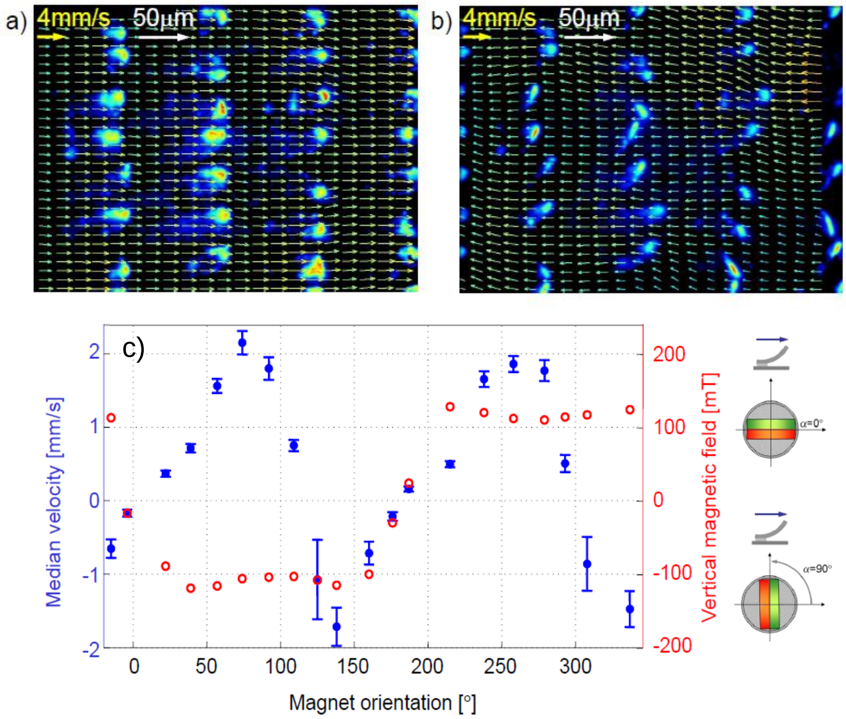

Figure 11: Cilia-induced flow 60μm above the channel bottom; a) during the cilia downward stroke (162° magnet orientation) and b) during the cilia upward stroke (234° magnet orientation). Cilia are displayed coloured in the background. c) Ensemble-averaged median

fluid velocities during one actuation cycle in a measurement plane 60 μm above the channel bottom for 10Hz actuation; red curve: measured, vertical magnetic field component

The major result was the proof of concept for generating fluid flow by magnetic actuation of our cilia arrays. Average fluid velocities of over 100µm/s were demonstrated in the proximity of the cilia when actuation frequencies were of 10Hz and above, in a channel with a cross section of (500x1000) μm^2 and a length of 2 cm. Figure 12 shows the measured phase-averaged velocity profile, which can be described by the superposition of a Poiseuille and a Couette profile. The corresponding generated flow rate equals 19 µl/min under a zero backpressure condition, which is exactly within the targeted range as stated in the original goal of the project (see above).

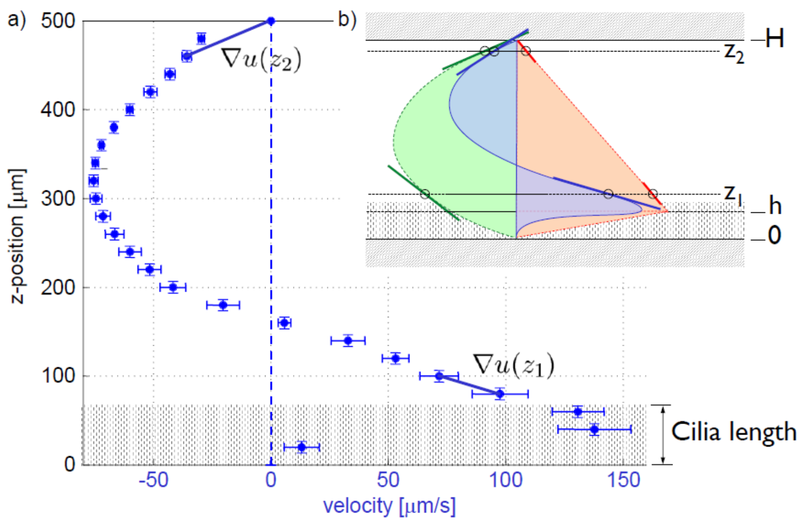

Figure 12: a) Cilia-induced phase-averaged velocity distribution over the channel height at 10 Hz actuation frequency in a closed channel; b) sketch of the velocity profile approximated as superposed Poiseuille and Couette profile.

3.4 Relevance

The new technology developed within the ARTIC project is relevant for any application in which small amounts of liquid need to be controlled, i.e. pumped, dosed, mixed, etc. Particular applications include micro-channel cooling for electronics, controlled drug delivery systems, pharmaceutical and chemical high-throughput testing, and biosensor chips for medical diagnostics. Especially the latter application area is expected to have a large socio-economic impact, including lab-on-a-chip devices for personalized medical diagnosis and treatment. The development towards such medical systems promises to contribute to high-quality medical care at sustainable cost.

The fluid flow generated by our artificial cilia is at least comparable to other micro-fluidic principles such as electro-osmosis, but has the advantages of simple actuation and compatibility with bio-fluids; next to pumping, the artificial cilia can also be used for fluid mixing. Altogether, the technology enables the active control of microscopic quantities of fluid in lab-on-chip biosensor applications, thereby creating the opportunity to conduct fast and efficient complex analyses, such as DNA profiling or pathogen identification, at a patient's bedside or in a doctor's surgery.

3.5 Conclusions

We have developed magnetically actuated artificial cilia, inspired by biology, and proven that they can generate substantial fluid in micro-channels. Typical average net velocities are larger than 100 μm/s, and typical flow rates are 20 μL/,min. These values are comparable to other micro-fluidic principles such as electro-osmosis, but our approach has the advantages of simple actuation and compatibility with bio-fluids; next to pumping, the artificial cilia can also be used for fluid mixing. Altogether, the technology enables the active control of microscopic quantities of fluid in lab-on-chip biosensor applications, thereby creating the opportunity to conduct fast and efficient complex analyses, such as DNA profiling or pathogen identification, at a patient's bedside or in a doctor's surgery.

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- Various microfluidic cartridges were designed and fabricated to meet the requirements for characterization of cilia and fluid flow.
- A fully functional experimental setup consisting of cartridge with integrated cilia array, magnetic actuation system and epifluorescent microscope was built.
- μPIV measurements were carried out of the flow generated by artificial cilia

All of the anticipated project results and contributions (see section 3.1) have been achieved.

4 Dissemination and use

The project, as defined from the start, has been highly explorative and long-term as it has developed a truly new and advanced technology that asked for the integration of functional features from the nanometer range (polymer particle hybrids) up to centimeters (device). Still, some of the results produced within the project are being exploited by the partners already now. The application of the artificial cilia in microfluidic devices, however, will still need years of further development towards industrialization, but the foundation for this has been laid by the successful proof of concept in ARTIC.

We found that the subject of this project is extremely suited to create enthusiasm and awareness about science not only in the scientific world, but also in society in general. The idea of mimicking nature to achieve a breakthrough for biomedical applications in an elegant way as we have done, turned out to appeal to many people.

4.1 Exploitable knowledge and its Use

Some of the results produced within the project are being exploited by the consortium partners already now. In particular:

- The “two colors lithography” approach is being used at for the generation of complex – i.e. more three dimensional – microstructures on surfaces by IMTEK.
- Process for producing magnetic nanoparticles, developed within ARTIC, have allowed the expansion of product portfolio of LRL.
- Microfluidic laminated cartridges, for which the technology was developed within ARTIC, are being used in projects within Philips Research for the fast development and testing of novel microfluidic modalities.
- Two invention disclosures in connection to ARTIC have been submitted by Philips.
- The results are being used by the academic partners in educational programs, and for promotional activities.

4.2 Dissemination of knowledge

A substantial number of articles and conference papers have been written along the duration of the project. We would like to emphasize our significant presence at the European conferences in the field of micro-fluidics. For the last two editions of the European Conference on Microfluidics (µFLU) we have been present with representative work from each consortium member. Furthermore during µFLU 2010, Patrick Onck and Jaap den Toonder, WP and project leader of ARTIC, organized a special session: Cilia - Driven Flows. Invited speakers from groups with similar research topics were present. Our consortium presented a selected set of results per work-package so that the concept of our project was clearly described.

Press releases have been published both at the start and at the end of the project.

Figure 13 Poster of the 2nd European Conference on Microfluidics. Special Session: Cilia-Driven Flows.

List of publications

Year 2007

1)J. den Toonder, Micro-fluidic manipulation using artificial cilia, BIONIS, Bath (UK), 2007.

2)S. N. Khaderi, D. Ioan, J. M. J. den Toonder, P. R. Onck: Nature-Inspired Microfluidic Manipulation Using Magnetic Actuators. In: Microelectromechanical Systems - Materials and Devices, edited by D. Lavan, M. Spearing, S. Vengallatore, M. da Silva (Mater. Res. Soc. Symp. Proc. Volume 1052, Warrendale, PA, 2007), 1052-DD08-06.

Year 2008

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A number of publications are in preparation at the time of publication of this report. We expect at least 6 more publications to be published in the coming year.