# Design and Optimisation of a Microgripper: Demonstration of Biomedical Applications Using the Manipulation of Oocytes

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*Abstract* - **We present a bidirectional electrothermal microgripper for the advanced manipulation of single large cells. The device demonstrates excellent performance, and shows great potential as a supporting microtool for different biomedical procedures such as oocyte selection or electrofusion of cells. In particular, we focus on the operation of the device in real environments, i.e. integrated in a standard biological micromanipulation station and entirely submerged in a biological fluid, for the handling and transportation of 'live' specimens (in our case mice oocytes). A clamping mechanism is included in the design that limits the pressure exerted over the biological specimen to an approximate maximum of 40 µN, whilst maintaining a robust grip, with a force up to 300 µN, between the arms of the microgripper.**

## I. INTRODUCTION

Advances in biological and biomedical areas such as cloning, cell replacement therapy (CRT), stem cell research or in-vitro fertilisation (IVF) have demonstrated the need for complex micromanipulation strategies and tools [1]. Micromanipulation in these areas can be particularly challenging due to different factors: the size of the cells that have to be manipulated e.g. embryos and oocytes with diameters above 100 µm, their fragile nature against mechanical forces and chemical toxicity, and the environmental conditions under which they have to be maintained for their survival. All these factors, together with their operational implications — low actuating voltages (≤ 2V for un-encapsulated devices), low temperatures ( < 50 °C), and low and controllable handling forces (< 40 µN) — will strongly condition the kind of techniques and tools that can be envisaged.

Contact manipulation techniques based on microgrippers (miniaturised tweezers) offer several advantages over other well known non-contact techniques such as optical tweezers or electric/magnetic traps. They are generally cheaper, easier to operate and to integrate into standard manipulation stations and with a design, generally composed of an actuation mechanism and a pair of extended arms, which offers great flexibility. Furthermore, there is no risk associated with high fields, radiation or heat interacting with the cell. Microgrippers can also offer the possibility to transport and hold single cells over large distances.

Advanced microgrippers, equipped with sensing and actuating structures, can also be advantageous when compared to the use of the conventional pipettes which can only perform standard pick and place operations. Two different steps required in IVF and stem cell research procedures can directly benefit from the use of a microgripper. These are the quantitative selection of the most suitable oocyte based in the difference of the cell stiffness during meiotic maturation (nowadays, oocyte selection relies on human visual inspection) and pressurisation of the recipient cytoplast and donor cell during electrofusion procedures (one of the critical factors on the success of electrofusion is the good contact between the cell membranes).

In recent years, numerous basic and advanced microgrippers based on different mechanisms of actuation have been proposed for the manipulation of cells. However, very few among them have demonstrated the manipulation of actual biological specimens in liquid environments.

TABLE I
SUMMARY OF THE PERFORMANCE OF DIFFERENT ELECTROTHERMAL MICROGRIPPERS

| Electrothermal microgrippers | | | Experiments in air | | | | Experiments in aqueous solution | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Ref. | Year | Actuator type | Max deflection [µm] | Voltage [V] | Power [mW] | T tips [°C] | Max deflection [µm] | Voltage [V] | Power [mW] | T tips [°C] |
| [2] | 2004 | Double U-shaped | 100 | 10 | 50 | < 100 | - | - | - | - |
| [3] | 2005 | U-shaped | 12 | 0.45 | 5 | ambient | 12 | 2 | 10 | ambient |
| [4] | 2008 | Bimorph + U-shaped | 32 | 4.5 | 114 | ~ 180 | - | - | - | - |
| [5] | 2008 | Bimorph + U-shaped | 32 | 2.5 | 35 | ~ 250 | - | - | - | - |
| [6] | 2008 | V-shaped | 57 | 9 | - | ~ 47 | - | - | - | - |
| [7] | 2008 | V-shaped | 35 | 0.32 | - | ambient | 35 | 2 | 120 | ambient |
| This work | 2008 | U-shaped | 300 | 3.1 | 186 | ambient | 70 | 4.1(*) | 410 | ambient |

(*) In this work a working voltage of 4.1V in liquid is possible due to the encapsulation of the device anchor that contains the electrical connections preventing electrolysis. Failure of the device due to excessive heating occurs at 6 V.

Table I shows a summary of the performance of different electrothermal microgripper designs. In air as well as in underwater manipulation, our microgripper provides the largest deflections at appropriate voltages and temperatures. The devices in [3,7] have comparable performances to ours at low displacements, but due to the smaller maximum deflections they are limited in the range of cell sizes that can be manipulated. In some biological applications, such as stem cell research, deflections of at least 50 µm are required in order to allow for the cell size variations that can occur either between cells of the same type (e.g. oocytes) or within different cells (e.g. mice oocytes versus human oocytes).

The microgripper presented here is a compliant polymeric structure that controllably deforms in response to asymmetrical heating of its constituent parts (Fig. 1). The overall design consists of two parts: a pair of extended arms and an actuation mechanism. The extended jaws are a pair of cantilever-like beams that amplify the motion of the actuators and act as end effectors. The actuation mechanism, composed of two highly efficient U-shaped thermal actuators, is able to deflect when a current is passed through the device. Both parts, the actuators and the arms, are built of the same structural material, the polymer SU8, and are fabricated at the same time. The actuation mechanism is a multi-layer structure which encapsulates a conductor between two layers of the polymer.

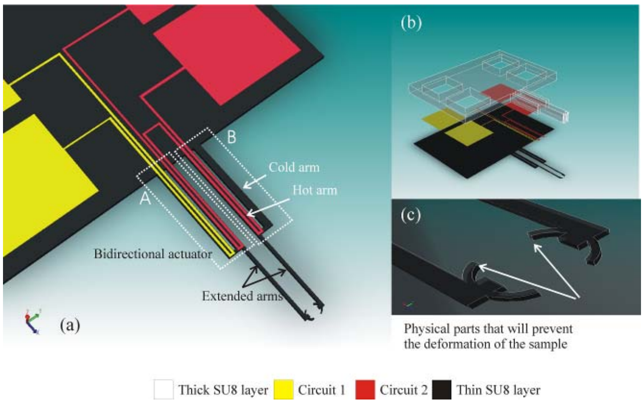

Fig. 1. (a) Microgripper design (b) Multilayer structure (c) Detail of the end effectors.

## II. DESIGN AND FABRICATION

The microgrippers can be fabricated using an improved version of the process discussed in [8]. The new process incorporates a thermal oxide in-situ mask that enables the $XeF_2$ release and the dicing of the structures in a more effective and reliable manner. After the release of the microgrippers, which now include silicon anchors, the devices are diced, bonded and wired into a PCB. In the last step of the fabrication the electrical contact pads are encapsulated using glue.

The asymmetrical heating of the structure is achieved by embedding a gold resistor in just one arm of the actuator B (Fig. 1(a)) or by actuating just one of the gold resistors in the actuator A (Fig. 1(a)). The opening or closing of the microgripper ultimately depends on the difference in temperature ($\Delta T$) established between the hot and cold arms of the actuator. Since no heat is generated in the cold arm, this temperature difference is maximised for a given voltage, power and maximum temperature. A detailed description of the efficient thermal actuators included in design and their full modelling and characterisation have been reported elsewhere [8]. Here those models will be used to predict the microgripper operating temperatures for a given voltage and displacement.

The microgripper presented here differs from previous designs in that it includes two separate heating elements (circuit 1 and circuit 2) which permit the bidirectional in-plane movement of the arms (Fig. 2(a)). The operation of circuit 1 and circuit 2 increases and decreases respectively the spacing between the arms (Fig. 2(b)). More versatile designs could be considered by the split of circuit 1 into two separate circuits. Some of the advantages conferred by bidirectional movements of the arms can be summarised as follows. First, it allows for the manipulation of cells with broad size dispersion with a minimal heat generation, second, it permits to exert a controlled deformation over the cell (with a maximum pressure fixed by the geometry of the arms tips (see detail in Fig. 2(c)). Finally, it permits to clamp (or tighten) the arms of the device once the cell has been encapsulated (Fig. 1(c)).

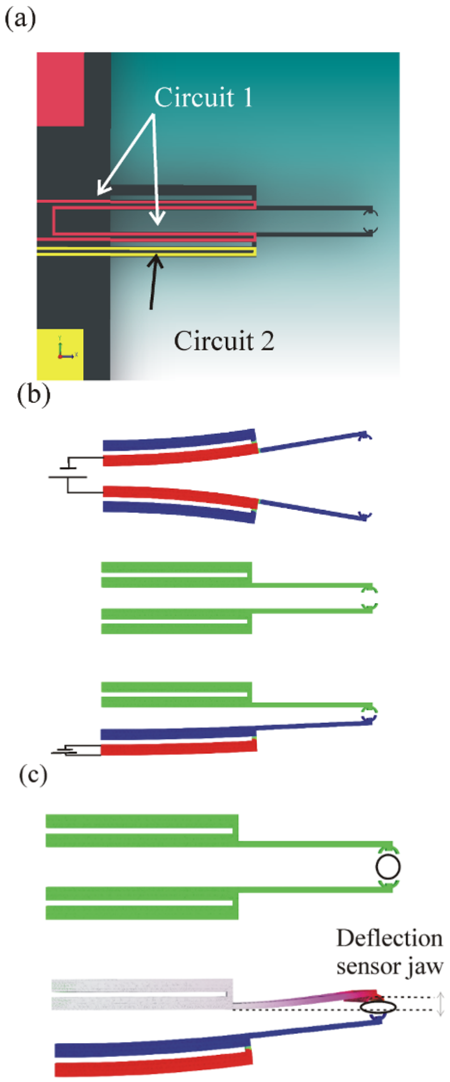

Fig. 2. (a) Detail of circuits 1 and 2 (b) Different modes of actuation: (top) normally closed (bottom) normally open (c) Force measurement technique.

Microgripper prototypes with the characteristic dimensions shown in Table II have been fabricated, modelled and tested in air and liquid environments. The material properties used for the models are listed in

Table III. The resistance and the movement of the microgripper at different input currents have been recorded. The resolution of the images is 0.45 microns (1 pixel), but a certain level of blur in the images (due to out-of-plane deflection and focus adjustment) results in an estimated accuracy of ± 5 pixels (approx. error = ± 2 µm).

TABLE II
CHARACTERISTIC DIMENSIONS OF THE MICROGRIPPER

| Geometrical characteristics [µm] | |
|---|---|
| Length actuator | 2000 |
| Length extended arm | 1600 |
| Device thickness | 100 |
| Width actuators arms | 140 |
| Width extended arms | 60 |
| Gap actuator arms | 60 |
| Resistor width | 40 |
| Resistor thickness | 0.289 |
| Initial arm's spacing | 120 |

TABLE III
MATERIAL AND MODEL PROPERTIES

| Material properties and heat transfer coefficients | Value | Units |
|---|---|---|
| SU8 thermal conductivity | 0.2 | W/m-K |
| Coefficient of thermal expansion SU8 | 64 | ppm |
| Au thermal conductivity | 297 | W/m-K |
| Resistivity | 2.08E-08 | Ω-m |
| Temperature coefficient of resistance Au | 0.0039 | 1/K |
| Cell culture thermal conductivity | 0.8 | W/m-K |
| Air thermal conductivity | 0.026 | W/m-K |
| Heat transfer geometrical factors(*) | 1.24 | - |
| Intra-heat geometrical factors(*) | 2.34 / 0 (liquid) | - |

(*)As defined in [8]

The modelling technique used to extrapolate the temperatures combines two models: an electrothermal analytical model and a FEA thermomechanical model. In both models the variation of the material properties with temperature are taken into account. The main characteristic of the electrothermal model used in this work is that it takes into account the heat exchange between the arms of the actuators through the air gap. In addition it takes into account the heat losses to the ambient by conduction as well as convection (external beams only).

## III. DISPLACEMENT RESULTS

Fig. 3 shows the measured displacements as a function of voltage and current. It can also be seen the detail of the validation of the models (Fig. 3 (b)) and the associated predicted temperatures (Fig. 3 (c)).

The gripping force has been measured using the induced deflection of the static arm as a reference for the force measurement (Fig. 2 (c)). The spring constant of the actuator is 40 times larger that the spring constant of the extended arm. Therefore, it is appropriate to consider that when a perpendicular force is applied to the tip of the microgripper only the extended arm deflects. Measured the deflection and using classical beam equations the gripping force can be extrapolated. Fig. 4 shows the measured forces which have been measured up to a force of 300 µN.

Other experimental results include the measurement of the response time of the devices which is approximately 700ms for the heating and 900ms for the cooling, and repeatability tests which demonstrate a variation of up to 7 microns at the maximum displacement in air.

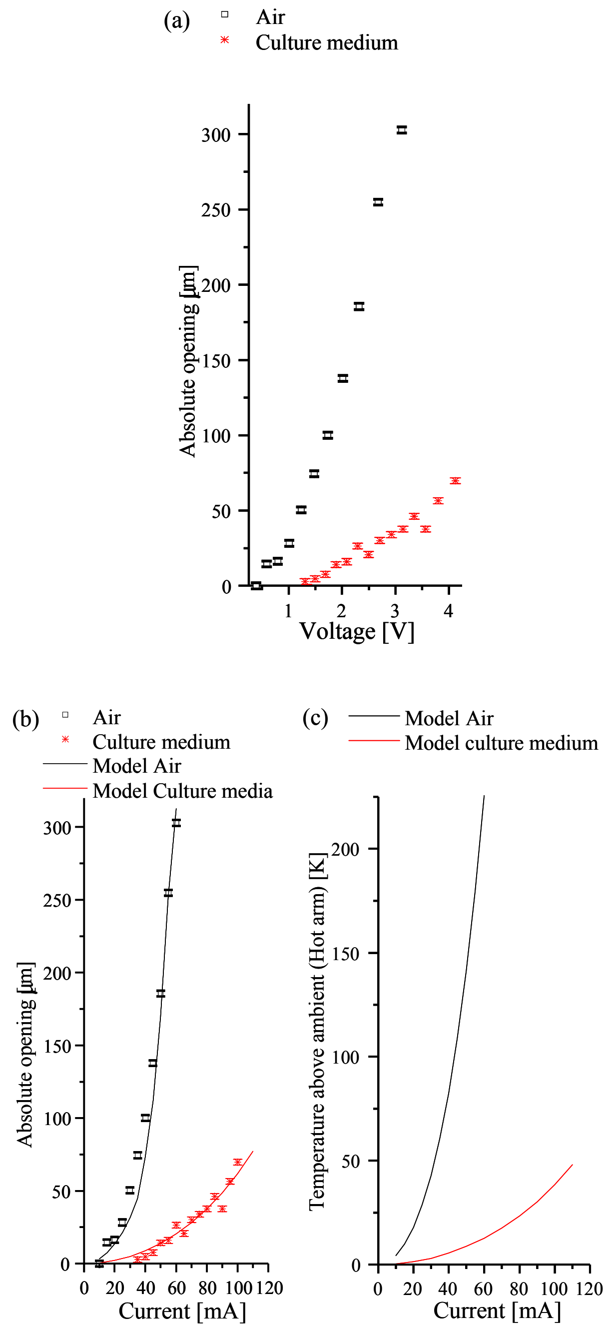

Fig. 3. Measurements in air and in liquid cell culture medium (M2 + IBMX from Sigma) with thermal conductivity ~ 0.8 W/m-K (a) Absolute opening versus voltage (b) Absolute opening versus current (c) Extrapolated temperatures in the hot arm of the actuator for different versus input current.

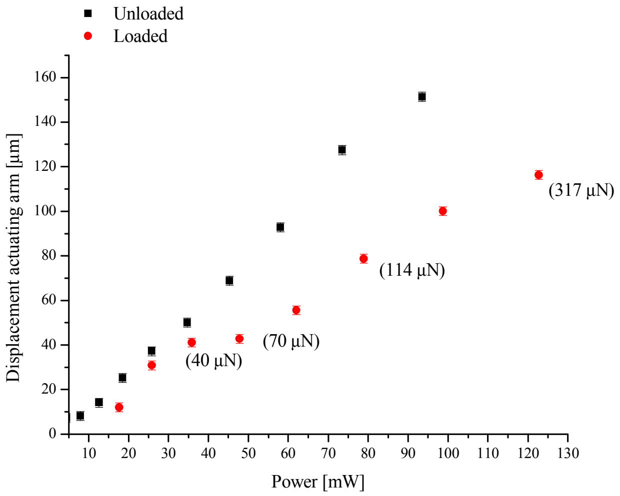

Fig. 4. Deflection of the extended arm (Fig. 2(c) in blue) when the clamp is activated (Loaded) and unloaded versus power. In brackets the value of the extrapolated clamping forces.

## IV. CELL MANIPULATION

Cell manipulation experiments were conducted at the Newcastle Fertility Centre[1] using mice oocytes (diameter = 100 µm) in a Petri dish culture. Fig. 5 shows schematically the experimental set-up. With this set-up the microgripper has been validated as a complementary and unique tool for the single-cell manipulation experiments that are normally carried out by IVF biologists.

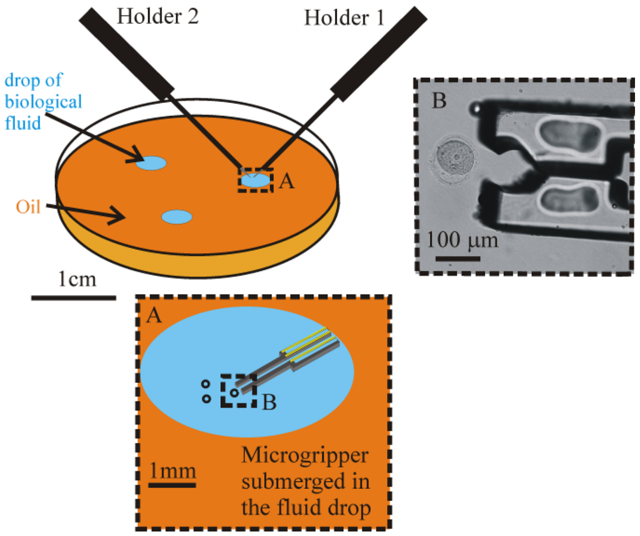

Fig. 5. Schematic experimental set-up. During the manipulation the microgripper is submerged in the biological drop.

Fig. 6 shows the images captured during a manipulation experiment where a mouse oocyte is held using a standard glass pipette and a microgripper. The microgripper, attached to the holder 1 (see Fig. 5) and on the right of the image, is able to grasp and detach the mouse cell from the suction of the pipette in holder 2 on the left of the image. This demonstrates that the grip generated by this microgripper is enough for standard manipulation procedures, or at least the same that are produced by the pipettes.

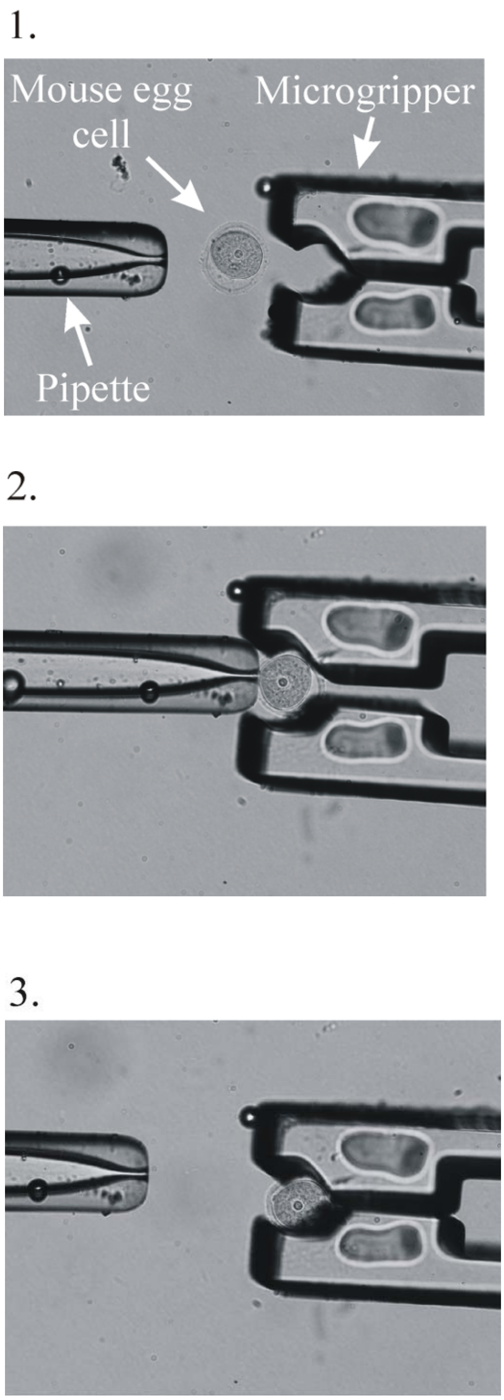

Fig. 6. Manipulation experiment where the microgripper is able to detach a mouse oocyte (diameter 100µm approx.) from the suction pipette.

As can be seen in Fig. 7(a), with this technique the microgripper can hold the cell even if it is detached from the bottom of the Petri dish (see cells on the bottom which are out of focus). The gripping is also strong enough to be able to transport a cell from one drop of biological media to

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[1] Newcastle Fertility Centre, International Centre for Life, Central Parkway, Newcastle upon Tyne, UK, NE1 3BZ

another through the oil media (Fig. 7(b)). Standard pipettes lose the grip when leaving the first drop. This makes the microgripper a unique tool for this application.

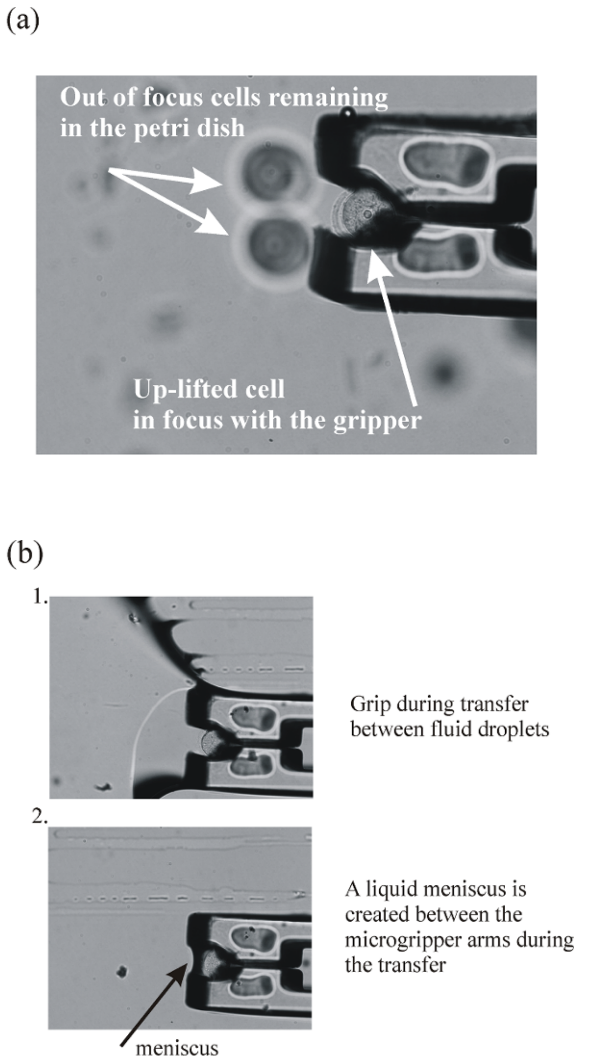

Fig. 7. (a) Microgripper up-lifting the cell above the bottom of the Petri-dish (b) Transfer of a cell from one biological drop to another through the oil media.

Future work includes the incorporation of a force sensor in one of the arms of the microgripper. First analysis of the performance of the strain sensor indicates that an eventual force sensor design has a sensitivity of 2.75 µV/µm with a force resolution of approximately 5 µN. At present the force resolution is limited by the geometry of the sensor beam and the minimum size of the resistors. Both things are in turn conditioned by fabrication constraints. Simulations using FEA software are on going to find the optimised design.

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