EndoMediskop
Trans-Endoscopic Microinjection for Flexible Endoscopy

K. Mutschler [1], W. Kunert [2], R. Ingenpaß [2], K. E. Grund [2], L. Tanguy [1], A. Ernst [1], R. Zengerle [1] and P. Koltay [1]
[1] Laboratory for MEMS Applications, Department of Microsystems Engineering - IMTEK, University of Freiburg, Germany, klaus.mutschler@imtek.uni-freiburg.de
[2] Surgical Endoscopy, University Hospital Tübingen, Germany, chir.endo@uni-tuebingen.de

Abstract

We report experimental work towards the development of an endoscopic instrument to enable the non-contact trans-endoscopic microinjection of liquids (e.g. drugs) within endoscopic surgery. The medical supply onto, into or through the tissue surface is realised in a needle-free manner by direct penetration of micro droplets or liquid jets through the tissue surface. A pressure driven experimental setup was established to characterize the requirements of liquid jets to penetrate the tissue. A minimum pressure of 20 bar using a nozzle with a diameter of 80 µm was required to penetrate the tunica mucosa of tissue samples derived from swine. Based on the results of these experiments an electromagnetic actuator was designed that can generate high pressure liquid jets in the range of 12 to 45 bar with durations of up to 15 ms. This proximal actuator with the distal nozzle for jet release connected by a tubing fits with the small dimensions of a working channel of a standard endoscope with a length of 1.5 m and a diameter of ~ 2.8 mm. The functionality of this portable system for trans-endoscopic microinjection was characterised by experiment at maximum dosage frequency of 5 Hz. A linear correlation of the actuation current to the jet pressure was found ($R^2 = 0.994$) and the penetration of the free jet was recorded by high speed video imaging.

1 Introduction

Needle-free liquid jet injection has the potential to prevent difficulties and risks associated with standard needle based injections used in surgical endoscopy up to date [1, 2]. The high relevance to improve endoscopic microinjection systems is demonstrated by the increasing number of clinical coloscopies. Nowadays worldwide approximately 20'000 polypectomies [3] are done every day. The resection of polyps is essentially supported by the injection of fluid to swell the Submucosa as a mechanical and thermal shield for safety reasons (avoidance of hemorrhage and perforation). Improved reinspection is realised by the injection of dye to mark the treated areas for easy relocation. These applications imply the importance of high safety and advanced handling of such systems. One approach to achieve needle-free injection is to use a mechanical proximal actuator as presented in [4]. An improvement is to apply an electrically driven actuator as presented in this work. The injection system is designed as portable system to be inserted into the working channel of a standard endoscope (Ø ~ 2.8 mm, l = 1.5 m). It allows for non-contact administration of liquids (e.g. drugs or colour markers) within surgical endoscopy. The needle-free liquid delivery onto, into or through the tissue surface is realised by the generation of high pressure liquid jets with adjustable impact pressure. The system consists of a handheld actuator, installed at the proximal end of the endoscope and the dispensing unit comprising the liquid supply channel and the injection nozzle at the distal end.

2 Evaluation of injection pressure

Starting point of the development of the endoscopic injection-system was to determine the physical boundary conditions in terms of hydraulic pressure, jet diameter and jet duration, that are required to inject a liquid aliquot successfully into tissue. To determine these physical parameters tissue from the colon of swine was used as tissue model, making reference to the potential use of the device in coloscopic endoscopy. In coloscopic applications the liquid is to be injected into the submucosa layer (cf. Img. 1) by perforating the tunica mucosa but not perforating the tunica muscularis. In order to determine suitable technical parameters to achieve this goal a pressure driven experimental setup was assembled like shown in image 2. This setup was not qualified for use through an endoscope due to its macroscopic dimensions, but only used for the experimental evaluation of injection pressure.

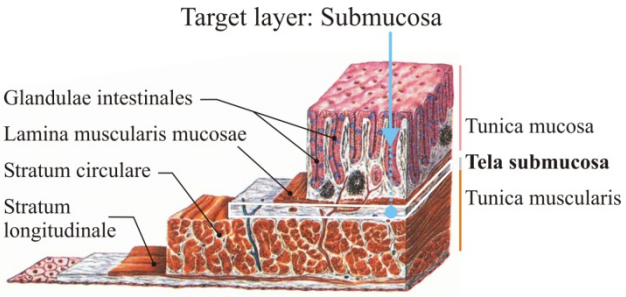

Image 1: Histologic scheme of the colon. Blue: illustration of the jet and its destination in the submucosa [5]

The main part of the pressure driven experimental setup was the SMLD 300 G dispensing valve from F. Gyger [6] Switzerland. This valve was screwed into a specific holder, to be connected via BSP-Tubing to a liquid filled bottle (not shown in image 2). This bottle then was pressurized with compressed air from a high pressure gas bottle using a manual pressure regulator. The individually adjustable

operating pressure in the range between 1 bar and 50 bar enabled to study the penetration depth of the liquid jets into tissue at different pressures. By variation of the valve opening time in the range of 0.5 ms to 16 ms the jet length and the liquid volume could be adjusted also. In image 2 the valve (L = 33 mm, outer Ø = 5.9 mm, nozzle Ø = 100 µm) is positioned at a distance of 5 mm to the tissue sample, which is a typical application distance within endoscopic interventions.

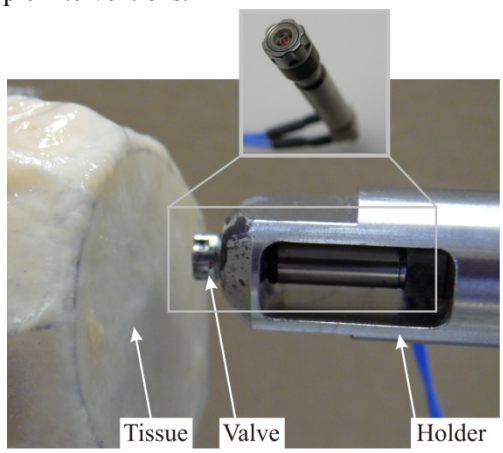

Image 2: Pressure driven setup with target tissue and Gyger Valve [7] in holder, which is the connection to BSP-Tubing

The tissue samples were freshly derived from the colon of a pig and fixed by a defined pre-stressing force to ensure the comparability between different experiments. To visualize the injected liquid, Indian ink (Pelikan [6]) was used as injection liquid. After performing the injection experiments, the colon tissue patches underwent histological section (formalin fixation, paraffin embedding, HE staining) to analyse the impact on the tissue considering penetration depth and amount of injected liquid (cf. Img. 3).
It turned out that approximately 100 µm wide jets generated at a system pressure between 20 and 40 bar at valve opening times of 0.5 ms already reached the submucosa layer in most cases. Jets beyond 50 bar mostly lead to penetration of the target.

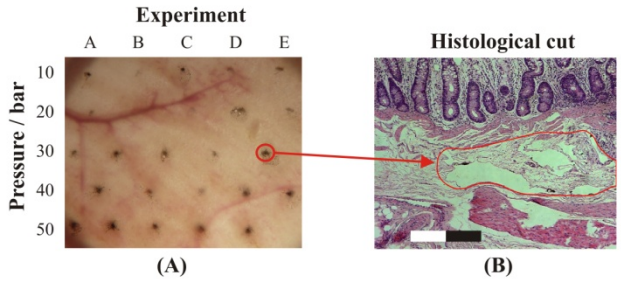

Image 3: Identifying the physical parameters for injection and penetration experiments. (A) View on the tissue directly after injection experiments, successful penetrations starting at 20 bar, (B) histological cut, red curve illustrating created excavation at 30 bar. (Scale: 400 µm)

3 System description

3.1 Momentum generating actuator

Based on the determined pressure requirements to successfully achieve penetration of liquid into the tunica submucosa, a proximal driven momentum generator was designed to be used as liquid actuator suitable for endoscopy. The reason for using a proximal drive as actuator and not an ultra-miniaturized valve similar to the presented experimental setup are twofold: First an ultra-miniaturized valve would have to be disposable or cleanable which is an additional challenge. But more importantly, an ultraminiaturized valve that fits into the endoscopic channel would not be able to operate against the high pressures. Therefore, an actuator generating the pressure outside the endoscopic channel at the proximal end and transferring the pressure to the nozzle located at the distal end through stiff tubing is much more feasible. The actuator device studied in this work is based on a momentum transfer principle, where the momentum is generated by a magnet that is accelerated via the magnetic field of a coil. The magnet is travelling a distance of 2.7 cm until it hits the piston of a 1 ml syringe (see Img. 4). The piston of the syringe transfers the generated momentum to the liquid inside the syringe, which is connected via a 1.5 m long FEP-tube (ID = 0.75 mm, AD = 1/16") to the distal injection nozzle (ID = 80 µm). The impact of the magnet thus creates a short defined pressure pulse leading to ejection of a liquid jet out of the nozzle.

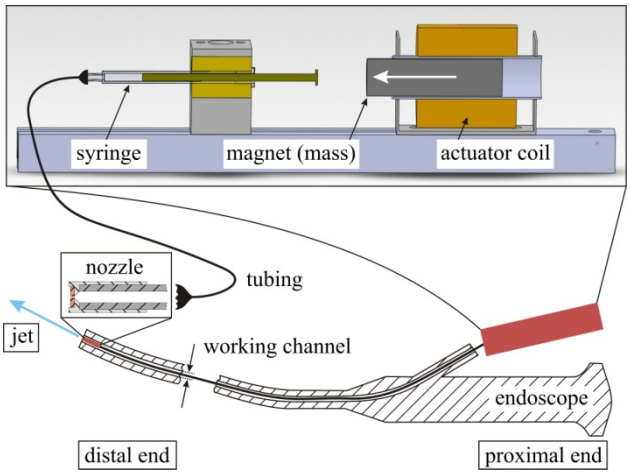

Image 4: Sectional drawing of the injection system for use through the working channel of an endoscope. A permanent magnet is accelerated and impacts with a defined momentum on the piston of a syringe.

3.2 Theoretical assessment of jet pressure

For further quantitative characterization of the impact of the liquid jets generated by the presented actuator system, liquid jets with durations of about 15 ms were injected onto a force sensor having a resolution of 1 mN. The jet was ejected in perpendicular direction onto the sensor surface with a distance of 5 mm, typical for endoscopic applica-

tion. The force measured by the force sensor can be transferred to pressure applying the formula:

$$P = F/A \quad (1)$$

Where P is the pressure, F the force and A the area on which the force is acting. The area was approximated using the diameter of the jet, which is assumed to be equal to the diameter of the nozzle (80 µm). A free flying jet has not only a dynamic pressure. There is an additional pressure due to surface tension (capillary pressure), which is given by [9]:

$$P_{surf} = \frac{\sigma}{r} \quad (2)$$

where σ is the surface tension of the liquid and r the radius of the jet. In case of Indian ink P_{surf} calculates to 0.18 bar and has been neglected due to the small amount in comparison to the considered pressure range.
Considering Bernoulli's law,

$$p + \frac{1}{2}\rho v^2 = \text{constant} \quad (3)$$

where p is the static pressure, ρ the density and v the velocity, the following formula can be derived, describing the velocity of the jet at the nozzle as a function of the impact pressure:

$$v = \sqrt{\frac{2 * p}{\rho}} \quad (4)$$

Thus, one can determine easily jet velocity and pressure from the experimental results presented below, to extrapolate physical requirements for other tissues types than investigated in this work.

4 Results

4.1 Experimental characterization of the momentum generating actuator

Liquid jets were generated applying an actuation current of about 3.2 A and the force sensor data was recorded over time. The conversion of the recorded force signals, created by an impinging jet on the force sensor, to the equivalent pressure was performed using formula (1). Image 5 shows the time course of two pressure signals generated by the momentum generating actuator in comparison to the experimental setup with the valve described in section 2.
In comparison to the pressure driven setup, the jet duration is increased from 3 ms to 12 ms. One reason for this is that the pressure driven setup has no long tubing to connect to the nozzle such that there are less capacitive effects, which explains the faster rise and fall of the pressure for the valve based setup. Furthermore, the jet generated by the impact actuator is also influenced by the opposing effect of inertia (fluidic inductance), as the mass of the fluid in syringe and tubing has to be accelerated, till the signal reaches its maximum after approximately 2 ms.
Nevertheless, both jets generated with the impact actuator shown as example in Img. 5 reach the same maximum pressure, which is high enough to penetrate the tissue in a similar way like the valve based setup. Thus, the pressure signal generated by the momentum generator fits the needed specifications for a needle-less injection through the endoscope.

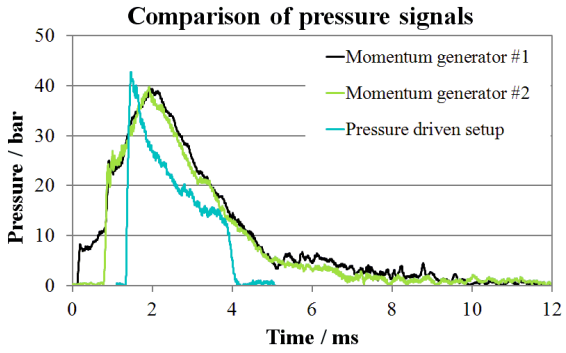

Image 5: Quantitative comparison of two measured pressure curves of ejected jets by using a driving current of about 3.2 A and the pressure driven setup, working with a high precision valve.

As shown in Img. 6 the system can be adjusted to deliver peak pressures between 12 and 45 bar, by adjusting the actuation current of the momentum generator. This is a big advantage compared to previous mechanical actuators.

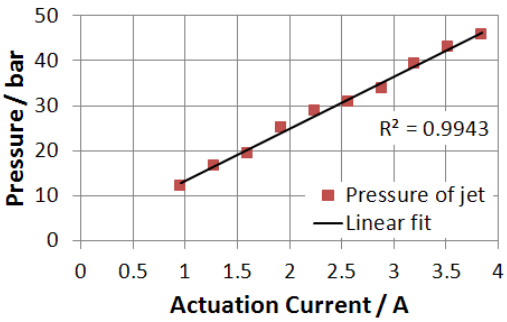

Image 6: The experimentally measured maximal pressure scales linearly with actuation current of momentum generator.

The correlation between actuation current and the maximal pressure of the jets, taken from the maximum peak signal of the measurements, is linear with a quality criterion of $R^2 = 0.994$. For future clinical use this linearity enables a simple adjustment of the desired pressure and with it the impact and penetration behaviour of the jet. Though, the maximum pressure is within the experimentally determined specifications of 20 to 40 bar, the longer duration of the jets created by the impact actuator could still lead to a different penetration behaviour into tissue. Therefore, further experiments have been performed to investigate the jet impact into tissue.

4.2 Experimental validation of penetration into tissue

Experiments with the impact actuator and patches of fresh tissue samples as described before have been conducted analogous to the valve based experiments in section 2. The pressures of the ejected jets have been varied according to the calibration line given in Img. 6. The results shown in Img. 7 confirmed the expected ability of the jets to achieve penetration into the tissue in the range from 20 to 40 bar. These experiments have led to the creation of cavities in the tissue, of approximately 2 mm width, filled with ink.

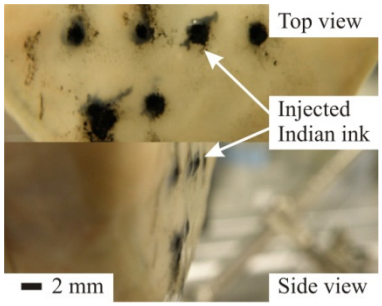

Image 7: First successful penetrations with momentum generator setup in colon tissue.

To obtain a better understanding of the jet and its impact behaviour, high speed videos of the injection process were recorded at 25'000 fps @ 96 dpi. When a jet approached the tissue surface, as shown in image 8, first the jet squirted back at the surface of the colon (1 ms), until the jet overcame the critical level of about approx. 20 bar (estimated value). Then the jet entered the target tissue and bulged it due to injection of liquid. At 6.7 ms (Img. 8) a nearly completed injection is shown. Excess fluid formes a droplet pending over the point of injection (16.2 ms). After rinsing the target with water the tissue looked as one of the injections displayed in image 7.
The total actuation time of the impact actuator to accelerate the magnet, generate a jet and bring back the magnet to its original position is approximately 200 ms. Therefore, the jet generation frequency can be as high as 5 Hz, which seems to be sufficient for clinical applications.

5 Conclusion

An electrically driven portable device providing adjustable high power liquid jets for injection through an endoscopic instrument has been presented and characterized by experiments. The experimental setup shown here can be used for systematic studies to precisely determine parameters like penetration depth, layer selectivity, dispensed volume and positioning accuracy. One challenging issue for the near future research is to realize disposable nozzles and to avoid partial obstruction of the tinny nozzle due to desiccation of the fluid that can occur. Another important issue is how to realize shorter jets to avoid excess fluid on the tissue surface.

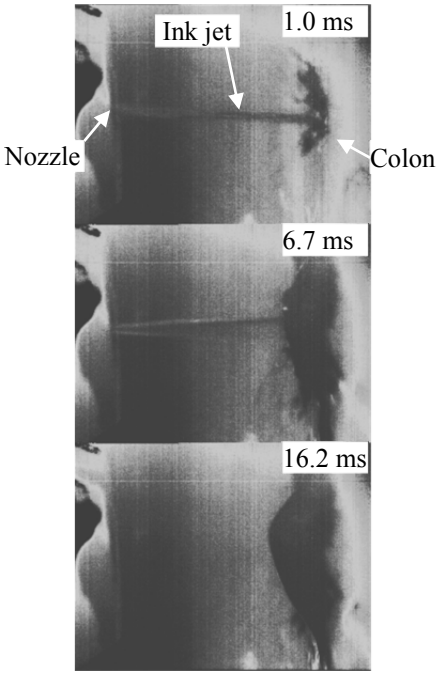

Image 8: High-speed recording showing penetration of the colon tissue with Indian ink through an 80 µm nozzle. (Camera: MotionBLITZ EoSens mini2 Mikrotron GmbH) Distance between nozzle and target: 5 mm; Total application time: 15.2 ms

6 Acknowledgement

The authors thank the Baden-Württemberg-Stiftung, Germany, for financial support of the project "MST II 5" in microsystems technology.

7 References

[1] A. Arora et al, "Needle-free delivery of macromolecules across the skin by nanolitre-volume pulsed microjets", University of California, Santa Barbara, USA, published by PNAS, 2007

[2] R. Higson, J. Hughes, "Clinical Studies with Jet Injection. New method of drug administration", Anesth. & Analg. 26, 225-230, 1947

[3] Statistisches Bundesamt Deutschland, 2012, www.destatis.de

[4] D. B. Özmen, „Eine neue Methode zur Injektion und Markierung in der Chirurgie", Inaugual-Dissertation, University Hospital Tübingen, 2002

[5] Speckmann / Wittkowski, Praxishandbuch Anatomie, Area Verlag, 2006

[6] Tusche A 17 Black, Pelikan, Hannover, Germany

[7] F. Gyger Company, Thun, Switzerland www.fgyger.ch

[8] K.E. Grund "Patentschrift DE 19607922 C2", published 29.01.1998

[9] Henrik Bruus, Theoretical Microfluidics, Oxford University Press, 2008