A novel concept of steerable catheters actuated by muscle cells: the BioMeld project

C. Salvatori[1,2], L. Ricotti[1,2], and L. Vannozzi[1,2]
[1] *The Biorobotics Institute, Scuola Superiore Sant'Anna, Italy*
[2] *Department of Excellence in Robotics & AI, Scuola Superiore Sant'Anna, Italy*

***Abstract*—Localized (targeted) therapies allow increasing the efficacy of treatments for several diseases, including cancer. Within this view, the BioMeld project aims at proposing a pipeline to guide the fabrication of an innovative intravascular steerable microcatheter, actuated on its tip by muscle cell contraction. A simulation framework streamlines the process of design quoting, manufacturing, verification, and reporting, thus significantly reducing error-prone manual steps and making the process more efficient. This new generation of steerable microcatheter, fostered by the unconventional kind of actuation provided by muscle cells, will be investigated throughout this project to target localized treatments of deeper and tortuous regions within the cardiovascular systems. In this work we report the overall project vision and we describe some preliminary results on the microcatheter design.**

***Keywords*—catheter, biohybrid actuation, drug release, cancer.**

I. Introduction

Cancer, or neoplasia, is a disease that is spreading more and more in recent years, to the point of being called the "disease of the century". The American Cancer Society has reported that over 1.9 million new cancer cases are expected to be diagnosed only in the US in 2023 [1].

Many therapies are currently available to fight cancers, and several efforts have been conducted by the scientific community to develop more sophisticated treatments to improve patient quality of life and extend life expectancy. Nowadays, chemotherapy, surgery and radiotherapy represent the gold standard. Among them, chemotherapy stands as a treatment based on the administration of drugs, typically injected through catheters by conventional accesses of the cardiovascular system (*e.g.*, in a vein residing in the hand or arm), to fight cancer cells with a cytotoxic action. However, the absorption of a drug at the blood circulation level can cause harmful effects due to the intrinsic toxicity of the chemotherapeutic drug, combined with a non-specific absorption by out-of-target cells, and consequently, a lower therapeutic index.

Alternatively, the use of microcatheters to release the drug locally at the site of interest may enable a local drug release, thus limiting the spread of the drug in healthy organs and tissues. One recent application of local chemotherapy is the hepatic artery infusion (HAI), in which the chemotherapeutic drug is released slowly and steadily into the hepatic artery through a catheter connected with a needle through the skin [2]. In the scientific state of the art, an example of a microcatheter able to locally release drugs has been developed by Sarker *et al.* [3]. Starting from a commercially available catheter, the authors provided a few lateral holes on the catheter wall, and closing the distal end to obtain a localized radial release of drug. The main challenge still remains the guidance of the commercial catheter at increased curvatures and pattern tortuosity.

For this purpose, catheters with a steerable tip have been proposed, recently. Steerable catheters are mainly classified into two groups: those with force generation in the tip and those with force transmitted to the tip [4]. Focusing on the first group, Gopesh *et. al*. developed a hydraulically steerable tip with an outer diameter of 900 µm provided with four channels of 50 µm diameters, filled with a saline solution, symmetrically arranged, and controlled remotely [5]. Regarding the second group, an interesting study was conducted by Kim *et al.* [6]: they developed a remotely-controllable steerable magnetic catheter featured with an outer diameter of 500 µm, remotely controlled, which can navigate through narrow and constrained environments. The magnetic navigation system can assist in approaching the *in vivo* target using magnetic responsive materials within the catheter. However, some restrictions lie on the generation of the torsion movement, which is necessary to facilitate the direction of the tip [7].

In recent years, many advances in manufacturing methods have allowed the production of intravascular catheters with diameters up to 1.8 Fr (500 µm). Such diameter size can potentially enable reaching deep districts, which are intrinsically characterized by a significant tortuosity, thus reaching different targets within the body. However, remotely controlling miniaturized microcatheters on such a small scale remain a challenge. Thus, precise drug release towards hard-to-reach *in vivo* targets still has large margins of improvement.

II. The BioMeld project

BioMeld is a European project funded in the Horizon Europe framework. It aims to develop an intravascular steerable microcatheter actuated by muscle cells to enable drug release in hard-to-reach areas. The development of the microcatheter would benefit from an artificial intelligence-guided modeling and simulation framework to optimize the search for the most efficient design, that will be validated within a validation framework (Figure 1).

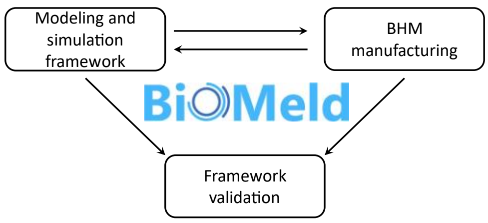

Figure 1: Scheme of a bio-intelligent manufacturing cell for design and production of the microcatheter within the BioMeld project. BHM = biohybrid microcatheter.

A biohybrid actuation paradigm, will be explored for controlling the microcatheter tip.

Biohybrid systems combine living organisms, such as contractile muscle cells, with engineered artificial structures [8]. Biohybrid actuators rely on their ability to convert the chemical energy of the environment into mechanical energy, thus there is no need to supply them when used in *in vivo* environments, avoiding the use of batteries.

One of the most significant challenges affecting current actuation technologies for in vivo applications is represented by the scalability of performance, especially for in vivo applications for which the requirement of biocompatibility is crucial.

Within the BioMeld project, we envisaged a reconfigurable and modular soft catheter bendable by the contractile force generated by the biohybrid actuator. The catheter will be composed of a magnetically-responsive catheter body and a catheter tip, equipped with: (i) a muscle cell-based actuator; (ii) a flexible electronic platform to trigger its activation and receive real-time feedback of catheter motion using flexible strain sensors; (iii) a bioreactor to keep it functional in the long-term.

The catheter body will include magnetically-responsive materials to allow its remote control. A good compromise towards guaranteeing a flexible body but magnetic responsiveness is represented by mixing polymeric materials (*e.g.*, silicones) with magnetic powder, such as NdFeB [9] and orienting them to maximize their responsiveness towards a specific magnetic field direction.

The catheter tip will be designed to host a biohybrid actuator based on skeletal muscle cells, which are controllable through electrical or optical stimuli to generate torque to the catheter tip. Muscle cell-based actuators, as the so-called bio-bots, can generate a relevant force (~100 µN) in the mm-size [10]. As mentioned, the biohybrid system also guarantees the maintenance of the contractile performance while keeping the actuation efficiency high with respect to other actuation technologies when scaled down.

Within the catheter tip, a flexible electronic platform will be integrated to provide muscle cells the electrical stimulation, and able to return the catheter deflection. This platform will exploit a low-voltage organic field-effect transistor fabricated on a polymeric substrate (*e.g.*, Parylene C) acting as a buffer through inkjet printing [11]. Such an electronic platform will also be provided with a deformation sensor to detect the curvature generated on the catheter tip by the muscle cells.

However, a disadvantage of using living materials as a source of actuation is the need to keep the environment parameters controlled with a bioreactor (pH and exchange of nutrients) to maintain muscle cells alive and functional over time [8].

All these components will be integrated inside the microcatheter, while maintaining the tip flexible and soft to be bent. Besides, the catheter will be provided with a hemocompatible coating, a crucial trait for all devices that encounter blood.

III. MATERIALS AND METHODS

A. Selection of the manufacturing techniques and material requirement

For the microcatheter fabrication, we considered molding, additive manufacturing, self-assembly techniques, and dip coating. Soft materials such as silicones (*e.g.*, PDMS, Dragonskin and Ecoflex) will be investigated at first instance. We do not exclude the use of thermoplastic polymers, such as polyurethane or Pebax®, and latex, since these materials represent suitable candidates already used for fabricating commercial devices. Our hypothesis assumes that the soft catheter will offer minimal mechanical resistance. For this purpose, we target materials with a Young's modulus lower than 1.5 MPa. Then, fabrication criteria will be directed to define geometrical parameters to decrease the catheter flexural rigidity.

B. Modeling and estimation of the flexural rigidity and deflection of the catheter

Apart from the magnitude of the force generated by the actuator, the catheter deflection is influenced by several parameters, such as internal and external diameter, wall thickness and elastic modulus [12].

Firstly, we analyzed the catheter mechanical properties in terms of flexural rigidity (*Fl*). For a catheter, such parameter can be calculated as follows:

$$Fl = E * I_0 \qquad (1)$$

Where *E* is the Young's modulus of the material used to build the catheter, and *Io* is the moment of inertia that can be expressed for a hollow structure as:

$$I_0 = \frac{\pi(D^4 - d^4)}{64} \qquad (2)$$

Where *D* is the external diameter and *d* is the internal diameter. We analyzed the variation of the external diameter *D* (from 2 mm to 10 mm) and, for a specific *D*, the variation of the Young's modulus up to 1.5 MPa.

Then, we estimated the deflection of the catheter by assuming the force generated by the biohybrid actuator equal to 100 µN [10]. According to the Euler-Bernoulli's beam theory [13], the deflection (*δ*) can be estimated as:

$$\delta = \frac{M * L^2}{2 * E * I_0} \qquad (3)$$

Where *L* is the catheter tip length, set at 8 cm, while *M* is the torque generated by the biohybrid actuator, calculated as follows:

$$M = F * \frac{d}{2} \qquad (4)$$

Where *F* is the force produced by the biohybrid actuator. Figure 2 shows a schematic representation of model parameters.

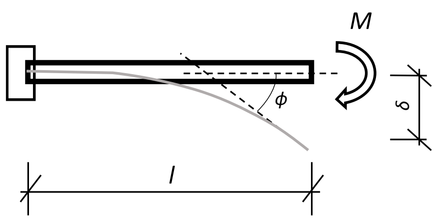

Figure 2: Depiction of the model applied to estimate the catheter deflection.

C. Analysis of the catheter kinking

When a catheter is curved under the application of a moment, the lumen may be occluded if the curvature radius becomes lower than a critical value ($R_{critical}$). This phenomenon is called kinking, and $R_{critical}$ is defined as:

$$R_{critical} = \frac{(1-\nu^2)*R^2}{K*t} \quad (5)$$

Where ν is the Poisson's ratio (set to 0.48, typical value for silicones), R is the external radius of the catheter, t is the wall thickness, and K is a constant (theoretically = 0.99; experimentally 0.72-1.14) [14].

IV. RESULTS AND DISCUSSION

A. Flexural rigidity

Figure 3 shows the influence of the catheter geometrical parameters in the estimation of the flexural rigidity.

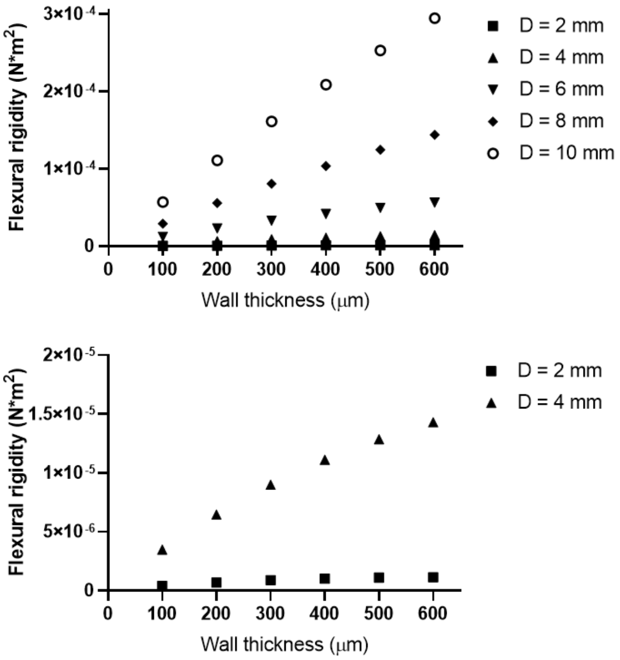

Figure 3: (top) Flexural rigidity estimated by varying the external diameter (D) from 10 to 2 mm, and the catheter wall thickness from 100 to 600 µm, and (bottom) a magnification for the cases D=2 and 4 mm. This estimation was performed by fixing the elastic modulus (E) of the catheter to 1.5 MPa.

Results showed a strong dependence of the flexural rigidity towards the geometrical parameters defined for the catheter, with a difference of two orders of magnitude between the larger (D = 10 mm) and the narrower case (D = 2 mm), for example, from $1.15*10^{-6}$ N*m^2 for D = 2 mm to $2.95*10^{-4}$ N*m^2 for D=10 mm, at a wall thickness of 600 µm. Typical values of flexural rigidity of catheters range from 1 to $50*10^{-4}$ N*m^2, mainly due to the stiffness of the material used to fabricate the catheter [15]. Here, the objective of designing a soft catheter for being actuated by muscle cells implicates the achievement of lower flexural rigidity for the catheter.

We also analyzed the influence of the elastic modulus for a specific case (D = 6 mm) The results are reported in Figure 4.

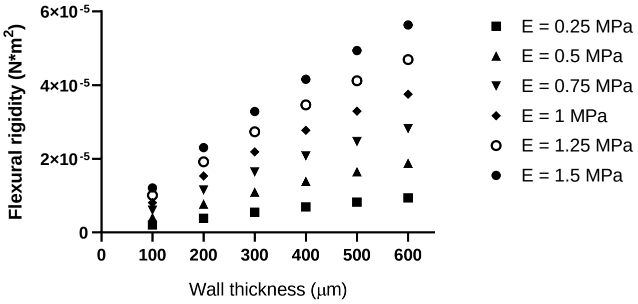

Figure 4: Flexural rigidity estimated by varying the elastic modulus (E) from 0.25 MPa to 1.5 MPa, and the catheter wall thickness from 100 to 600 um. This estimation was performed by fixing the external diameter (D) to 6 mm.

The graphs show that the wall thickness and the elastic modulus influence flexural rigidity. A non-linear trend can be observed with the variation of the external diameter, while a linear trend is noticeable while Young's modulus decreases. As a rule of thumb, flexural rigidity decreases by decreasing the external diameter, wall thickness, and elastic modulus.

B. Deflection

Figure 5 shows the influence of the catheter geometrical parameters in the estimation of the catheter deflection, according to the Euler-Bernoulli's beam theory.

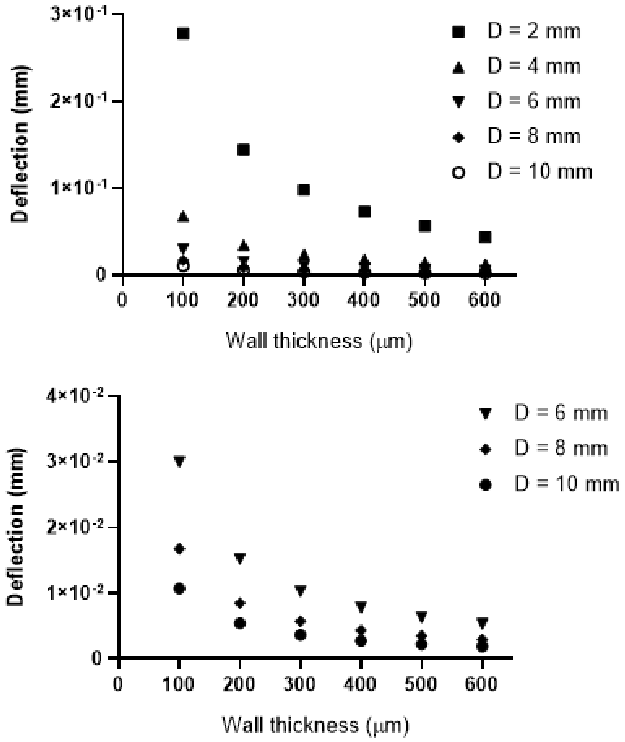

Figure 5: (top) Deflection estimated by varying the external diameter (D) from 10 to 2 mm, and the catheter wall thickness from 100 to 600 µm, and (bottom) a magnification for the cases D=6, 8 and 10 mm. This estimation was performed by fixing the elastic modulus (E) of the catheter to 1.5 MPa.

Results show a strong dependence of the flexural rigidity towards the geometrical parameters defined for the catheter, with a difference of one order of magnitude between the larger (D = 10 mm) and the narrower case (D = 2 mm). The deflection increases by decreasing the wall thickness. For example, for a diameter of 2 mm, and a wall thickness of 0.10 mm, the deflection will be 0.28 mm while for a higher thickness, such as 600 µm, the deflection becomes less than 100 µm. These results are intuitive since an increase in the wall thickness means an increase in mass, therefore, a higher moment of inertia.

We also analyzed the influence of the elastic modulus for a specific case (D = 6 mm). Results are reported in Figure 6.

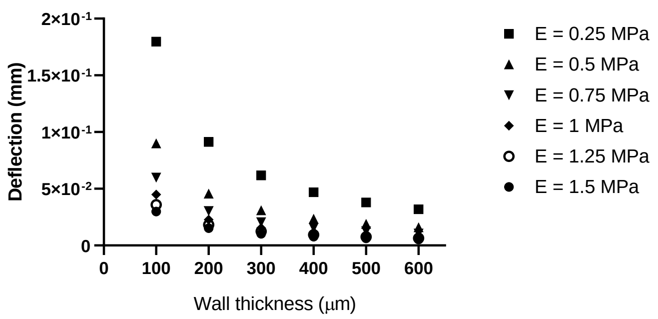

Figure 6: Flexural rigidity estimated by varying the elastic modulus (E) from 0.25 MPa to 1.5 MPa. This estimation was performed by fixing the external diameter to 6 mm.

Results show the effect of the elastic modulus decreasing in the increase of the expected deflection. Indeed, an increase in elastic modulus means a higher material rigidity, which reduces the expected deflection. Such deflections are relatively low and probably not sufficient to navigate vascular branches, and a process of parameter optimization will be necessary to provide a futuristic usage of biohybrid technology.

C. Kinking

Figure 7 shows the influence of the catheter geometrical parameters in the estimation of the critical radius.

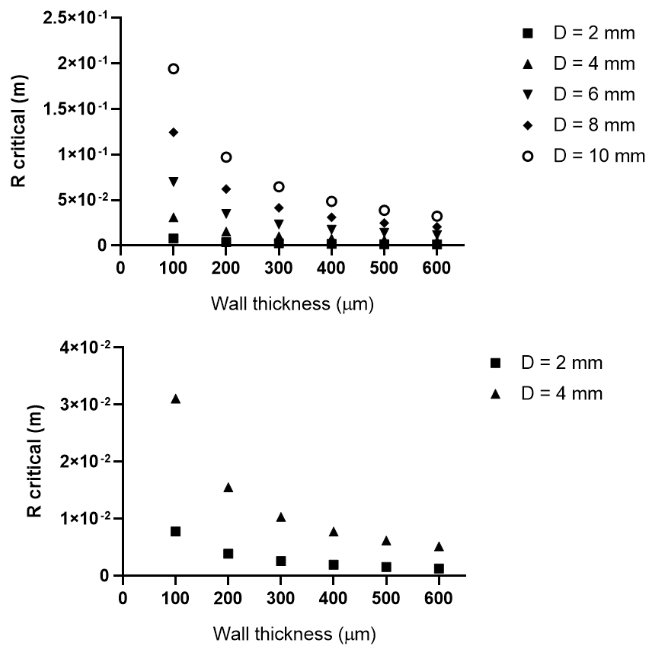

Figure 7: (top) Critical radius estimated by varying the external diameter (D) from 10 to 2 mm, and the catheter wall thickness from 100 to 600 µm, and (bottom) a magnification for the cases D=2 and 4 mm. This estimation was performed by fixing the elastic modulus (E) of the catheter to 1.5 MPa.

Results highlight that the $R_{critical}$ is strongly dependent on the geometrical features of the catheter. From the anatomical point of view, the angle of curvature expected to surpass the first branch of the hepatic artery is equal to ~45° [16], with a radius of curvature ranging between 1-4 cm. Catheter size and wall thickness will be chosen among the cases with the $R_{critical}$ lower than the targeted radius of curvature.

V. CONCLUSION

Within the framework of the BioMeld project, catheter design and manufacturing are encountering the technical challenges of integrating several components. Indeed, it must fit with the integration of an electronic platform and a bioreactor to enable the correct functioning of the biohybrid actuator, while maintaining good flexibility. Beyond the choice of materials and processing techniques, fabricating a soft catheter also involves the investigation of parameter designs. The next steps will be directed towards the definition of suitable geometrical parameters to target components integration, while maximizing the catheter flexibility.

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