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Bio-Hybrid Steerable Catheter Fabrication and Assembly within the EC 'BioMeld' Project - Part 1: Manufacturing Process Steps

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Abstract

The Biological Transformation, or Biologicalisation, in Manufacturing is an emerging trend that concurs to the pressing requirements of sustainability and can beneficially exploit novel and more effective manufacturing methods to fulfil the demands of the coming generations, by leveraging on the increasing utilization of materials, structures and processes of living nature in production technologies with the goal of sustainable added value. These innovation achievements can only be attained through the convergence of biology and biotechnology, manufacturing processes and systems, and information and communication technology, which can provide the outlook for strikingly major changes in future advances in production engineering for substantial enhancement of sustainability and significant advancement of efficiency. In June 2021, within the Horizon Europe Programme Call HORIZON-CL4-2021-DIGITAL-EMERGING-01-27, the first EC call topic on Biological Transformation named "Development of technologies and devices for bio-intelligent manufacturing" was published, and the project proposal "A Modular Framework for Designing and Producing Bio-Hybrid Machines (BHM) - BioMeld" was submitted and approved in October 2022. The manufacturing process steps developed in the 'BioMeld' project for the fabrication and assembly of a BHM consisting of a bio-hybrid vascular catheter as novel medical device for drug delivery in hard-to-access regions of the human body are illustrated in this paper.

Peer-review under responsibility of the scientific committee of the 18th CIRP Conference on Intelligent Computation in Manufacturing Engineering (CIRP ICME '24)

Keywords: Bio-hybrid machine; Living cell actuator; Manufacturing processes

1. Introduction

The Biological Transformation, or Biologicalisation, in Manufacturing is seen by [1] as a breaking new trend in production engineering that concurs to the pressing needs for sustainability in manufacturing and can exploit new, more effective manufacturing methods to fulfil the demands of the future generations.

Biologicalisation in Manufacturing has been defined as the "use and integration of biological and bio-inspired principles, materials, functions, structures and resources from living nature for intelligent and sustainable manufacturing technologies and systems with the aim of achieving their full potential" [2].

From the perspective of practicability, Biologicalisation in Manufacturing crucially depends on the efficacious convergence of biology and biotechnology, manufacturing processes and systems, and information and communication technology, in order to provide the expected remarkable changes in future innovation for advanced manufacturing engineering, including substantial enhancements in industrial production sustainability and significant advancements in manufacturing operational effectiveness and facility resource utilisation.

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2. Bio-intelligent manufacturing of bio-hybrid machines

In June 2021, within the Horizon Europe Programme Call HORIZON-CL4-2021-DIGITAL-EMERGING-01-27, the first EC call topic on Biological Transformation with title "Development of technologies and devices for bio-intelligent manufacturing" was published [3].

The topic description stated that "the use of biological elements as key enabling technology for manufacturing is an emerging trend that concurs with the pressing requirements of sustainability, and the biological transformation of industry can harness innovative and more efficient modes of production which can satisfy the needs of future generations".

Responding to this call topic, the project proposal entitled "A Modular Framework for Designing and Producing Bio-Hybrid Machines (BHM) - BioMeld" was successfully submitted and approved in October 2022 [4].

The goal of the BioMeld project is to develop a modular modelling and simulation framework for the design and fabrication of bio-hybrid machines (BHM), focusing on bio-integration by merging living materials and artificial materials, within the broader framework of Biologicalisation in Manufacturing which encompasses bio-inspiration, bio-integration and bio-intelligence [2], with the main scope to achieve greater autonomy, flexibility and energy efficiency in comparison with existing customary solutions [4].

The 'BioMeld' project involves the development and application of artificial intelligence and machine learning models in the first phases of BHM manufacturing. The purpose is to identify the most appropriate BHM designs and improve the BHM fabrication and assembly processes via integration of the inputs gained from the constructed BHM into a modelling and simulation framework to downgrade the faults particularly due to manual operations.

This approach is employed in the 'BioMeld' project to develop and implement a BHM consisting of a bio-hybrid vascular catheter as novel medical device for enhanced drug delivery in difficult-to-access regions of the human body.

The main objectives of the 'BioMeld' project are the following [4]:

- Setting up a robust and adaptable fabrication process of the BHM consisting in a bio-hybrid vascular catheter.
- Developing a modelling and simulation framework for BHM digital design.
- Organising a bio-intelligent manufacturing system for BHM construction.

This paper is focussed on the first objective, aiming at the development and implementation of the fabrication and assembly processes for the bio-hybrid catheter manufacturing.

3. Fabrication processes for BHM manufacturing

The BHM consists of a flexible, reconfigurable and modular steerable vascular catheter able to undergo controlled bending under the application of the force produced by the contraction of muscle cell fibres in a bio-hybrid actuator (Fig. 1).

The bio-hybrid catheter is composed of the following components:

- Basic plastic catheter made of three modules (Fig. 2)
- Muscle fibre-based bio-hybrid actuator (Fig. 3).
- Flexible electronic platform for bio-hybrid actuator stimulation and real-time feedback on motion (Fig. 4).
- Bioreactor chamber to keep the muscle tissue cells alive and functional in the long-term (Fig. 4).

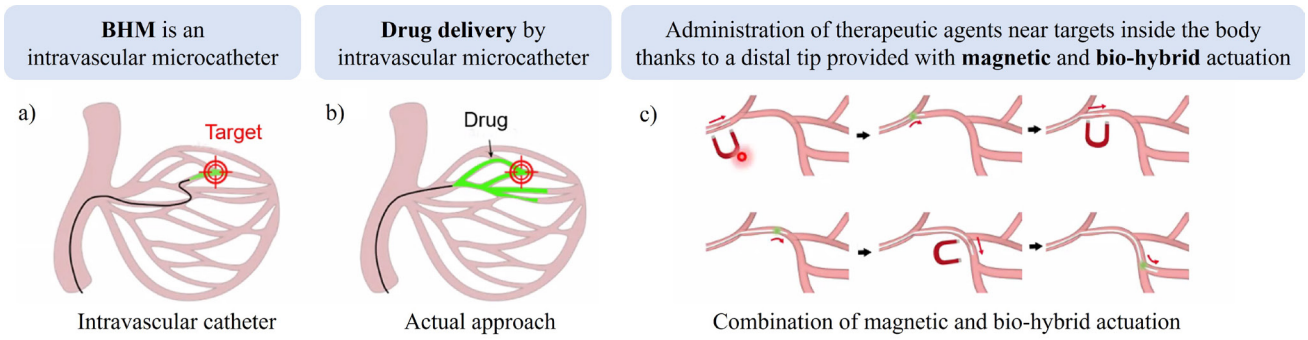

Fig. 1. The 'BioMeld' bio-hybrid machine (BHM) consists of a reconfigurable and modular soft steerable catheter which is flexible to produce a bending deformation depending on the force generated by living muscle cells in a bio-hybrid actuator [4].

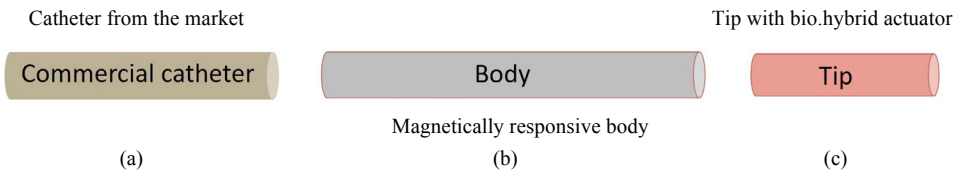

Fig. 2. Catheter made of three components: (a) commercial catheter component, (b) magnetic responsive body component; (c) soft distal tip component [4].

The diverse manufacturing steps needed for BHM fabrication and assembly as well as their sequence in the production cycle were identified as follows (Fig. 5):

- Catheter components manufacturing.
- Flexible electronic platform manufacturing.
- 3D muscle tissue bio-manufacturing.
- Bioreactor chamber manufacturing.
- Assembly of bio-hybrid catheter modules.

Each of manufacturing step in Fig. 5 is specified and detailed in the next sections.

3.1. Fabrication of the bio-hybrid catheter modules

The basic plastic catheter comprises three modules (Fig. 2):

- Harder magnetic-response catheter module.
- Softer distal tip catheter module.
- Commercial catheter module (procured on the market).

After fabrication or procurement, these three catheter modules are assembled together by manual bonding using surgical or silicone glue.

Both the magnetic-response catheter module and the distal tip catheter module consist of hollow cylinders manufactured by mould casting.

The harder catheter module incorporates magnetic-responsive fillers for magnetically controlled catheter displacement using a magnetic field applied from the outside of the human body.

The softer distal tip catheter module is provided with flexible pins (anchors) manufactured by extrusion-based 3D printing for the incorporation of the muscle fibres into the bioreactor chamber.

3.2. Bio-fabrication of living muscle tissue for the bio-actuator

The bio-fabrication of the living muscle fibres having the purpose to act as the motor in the bio-actuator is performed by technologies such as mould casting, extrusion-based bio-printing and light-based bio-printing (Fig. 3).

The 3D muscle cells are cultured in a cell culture dish with differentiation medium, in a biological biosafety cabinet and sterile environment, to promote phenotypic cell change from a less specialized type to a particular one specialized in form and function for the bio-actuator task.

Once the muscle cells bio-fabrication process is completed, the muscle fibres can be moved by hand, using sterile metal tweezers, from the cell culture dish into the bioreactor chamber, previously assembled together with the flexible electronics on the catheter soft distal tip. Thereafter, the bioreactor chamber walls can be sealed with a cap attached to the bioreactor chamber top.

3.3. Fabrication of the flexible electronic platform

The flexible electronic platform (FEP) is designed for the purpose to trigger the activation of the muscle fibre-based motor in the bio-actuator and to provide in real-time the sensorial feedback for direct monitoring of the bio-actuator movement using strain sensor response (Fig. 4).

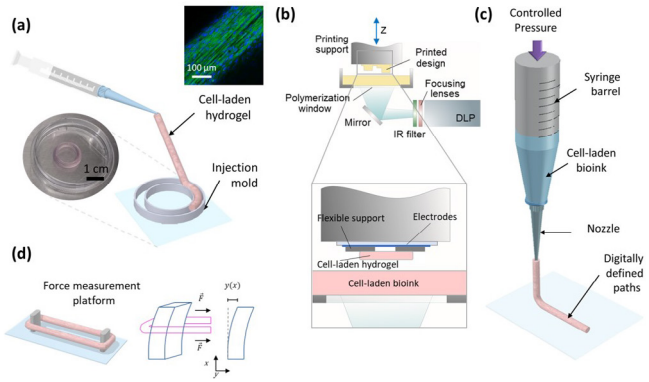

Fig. 3. Bio-fabrication processes of muscle-based bio-actuator and scheme of force measurement system: (a) mold casting; (b) extrusion-based bio-printing; (c) light-based bio-printing; (d) platform for measuring the muscle cell generated force [4].

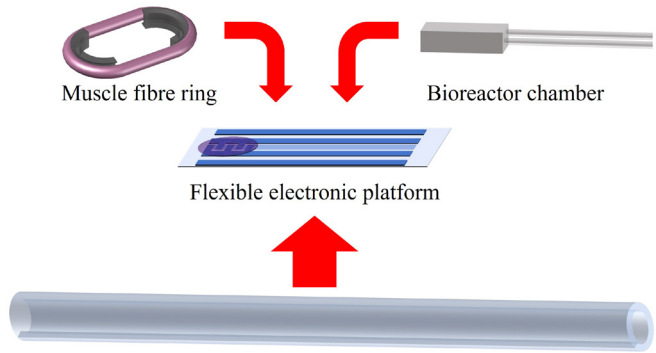

Fig. 4. Flexible electronic platform (FEP) for bio-actuator stimulation and feedback from catheter distal tip motion [4].

The FEP is made of a very thin (⩽ 2.5 µm) flexible plastic support accommodating a strain sensor, based on an organic field-effect transistor, and electrodes for electric stimulation of the bio-hybrid actuator.

Once the FEP manufacture is completed using different technologies, such as laser cutting, spin coating, chemical vapour deposition, inkjet printing, for the fabrication of its diverse electronic components, the FEP can be laminated on the soft distal tip of the catheter prior to the bioreactor chamber wall assembly and the muscle tissue manual transfer.

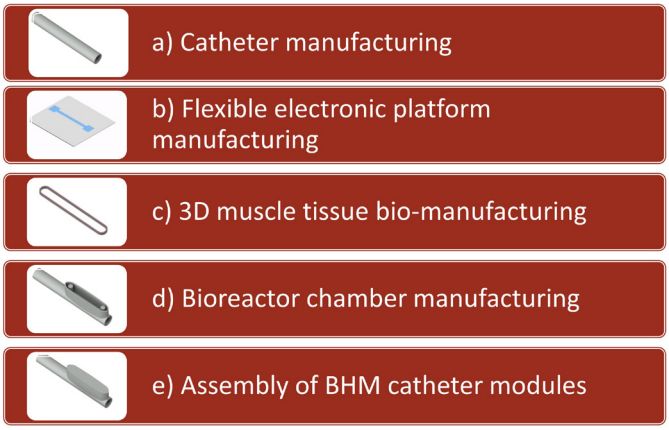

Fig. 5 - Manufacturing steps for bio-hybrid catheter fabrication and assembly and their sequence in the production cycle.

3.4. Fabrication of the bioreactor chamber

The bioreactor chamber is a microfluidic device designed for accommodating the bio-hybrid actuator, performing fluidic transport for cell culture medium supply, and monitoring the 3D muscle cell culture conditions.

The bioreactor chamber has an elliptical shape and is provided with an inlet hole and an outlet hole located at the right and left extremities of the chamber base where the inlet and outlet tubings will be connected to supply the nutritional liquid to feed and maintain alive the muscle fibres (Fig. 4).

The manufacturing processes used for the bioreactor chamber fabrication are 3D printing and replica moulding. The mechanical properties of the bioreactor chamber materials are compatible with those of the catheter soft distal tip module. 3D printing is also employed to fabricate the moulds for casting the bioreactor chamber components.

The assembly of the bioreactor chamber on the catheter soft distal tip is carried out through bonding by employing suitable adhesive agents and once completed the bioreactor chamber requires sterile handling and storage conditions.

3.5. Assembly processes for bio-hybrid catheter completion

The assembly processes needed for the final completion of the bio-hybrid vascular catheter comprise a number of steps as reported below.

Firstly, the flexible electronic sensor is assembled with the flexible pins (anchors) integrated on the catheter soft distal tip for the subsequent placement of the muscle fibres.

Secondly, the bioreactor chamber walls are mounted on the catheter soft distal tip and the inlet and outlet tubes are connected to the inlet and outlet holes at the base of the bioreactor chamber.

Thirdly, the muscle fibres are assembled with the flexible electronic sensor already integrated on the flexible pins (anchors) of the catheter soft distal tip inside the bioreactor chamber walls and the nutritional fluid supply is provided via the tubing system.

Finally, the roofless bioreactor chamber walls incorporated on the soft distal tip of the bio-hybrid catheter are covered with a rooftop cap to achieve microfluidic device leakage-proof conditions.

Every step for bio-hybrid catheter fabrication and assembly need to be carried out in a clean room and every procedure for manipulating muscle cells require to be performed in a biological safety cabinet and sterile environment.

4. Conclusions and outlook

The Biological Transformation, or Biologicalisation, in Manufacturing, has been presented as an emerging new trend that can provide solutions to the pressing requirements of sustainability in manufacturing technology and systems in the digital era by the increased utilisation of materials structures and processes of living nature in production engineering.

In the context of the Biologicalisation in Manufacturing, the Horizon Europe project “A Modular Framework for Designing and Producing Bio-Hybrid Machines - BioMeld”, was submitted to the HORIZON-CL4-2021-DIGITAL-EMERGING-01-27 Call Topic “Development of technologies and devices for bio-intelligent manufacturing”, and positively approved in Oct. 2022.

Among the main objectives of the ‘BioMeld’ project, the development of the manufacturing process steps for the fabrication and assembly of the bio-hybrid machine, constituting a bio-hybrid vascular catheter as innovative medical device for improved drug delivery in hard-to-access parts of the human body, is presented in this paper.

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