BioMeld

A Modular Framework for Designing and Producing Biohybrid Machines

Newsletter #2

Message from the Coordinator

The past year has seen the BioMeld project make significant progress toward creating a new paradigm in medical device technology. Our interdisciplinary team spanning biotechnology, materials science, computer modeling, manufacturing planning, and medical engineering is pioneering a framework that could transform how we design and manufacture bio-hybrid machines.

As the project moves toward its final phase, our focus is shifting to integration — bringing together individual technological components and strengthening the link between simulation and experimental validation. This next stage will address key design and engineering challenges while consolidating the knowledge generated across the consortium.

At the same time, BioMeld is progressing toward a set of exploitable outcomes with strong potential for future medical innovation. In this Newsletter, we provide a closer look at these developments and outline the path forward toward translating project results into real-world impact.

Igor Balaž
BioMeld Project Coordinator

Poljoprivredni fakultet, Novi Sad, Serbia

Bridging the Digital-Physical Gap with Advanced Simulation

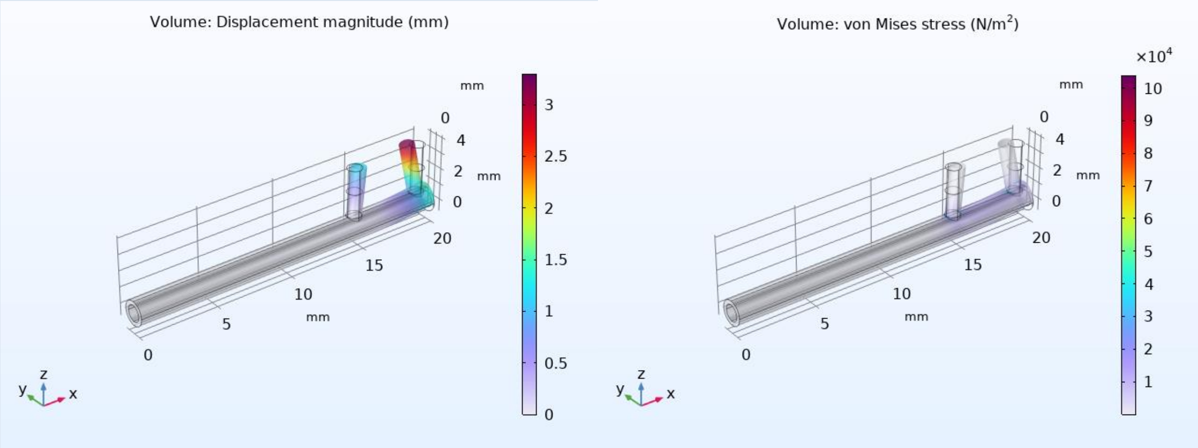
Our computational modeling team has made significant progress in developing a comprehensive framework to predict biohybrid catheter behavior across diverse configurations. Using multiphysics simulations, we have successfully conducted first round of parametric sweep analyses exploring a wide range of catheter geometries and material properties.

This systematic approach has yielded our first batch of high-quality synthetic data capturing the complex relationships between design parameters and functional performance. These simulations model critical aspects such as the interaction between muscle-based actuators and support pillars, their geometry and material properties. The next round of simulations will deal with sensor and biochamber integration effects, on overall catheter bending dynamics.

The synthetic dataset represents a crucial step toward our goal of creating a predictive AI system that can accelerate design optimization. Rather than relying solely on time-consuming physical prototyping, our approach uses these simulation results to pre-train neural networks that will ultimately be refined with experimental data.

As we await the complete simulation dataset, we are already preparing the neural network architecture and regression analysis framework that will transform this wealth of computational data into practical design insights.

With this work we are starting to bridge theoretical design and practical manufacturing, addressing one of the most challenging aspects of biohybrid technology development: accurately predicting how digital designs will perform in the physical world.



Figures 1. and 2. Simulating Catheter Displacement with COMSOL

We conducted a finite element analysis of a soft actuator-driven catheter using COMSOL Multiphysics. The simulations reveal the von Mises stress distribution and displacement magnitude within the catheter structure in response to actuator activity. As seen in the results, localized actuation produces significant deformation at the distal end, with peak displacement exceeding 3 mm. These insights support the design of responsive and minimally invasive biomedical devices.

University of the West of England, Bristol, UK

UWE team's efforts continued towards the optimization based on simulation of BHMs, since it will offer several key advantages over real-world testing. Simulations in general can run much faster and explore a wider range of conditions than physical prototypes. They are also more affordable and sustainable, as they do not require physical materials or specialized equipment. Additionally, simulations provide a safer testing environment by removing risks such as injuries or equipment damage. Another benefit is the ability to gather detailed insights into how a system behaves, as the virtual environment allows for easier control and measurement. While simulations may not always be perfectly accurate, their efficiency, safety, and cost-effectiveness make them valuable tools for designing and improving BHM systems.

During this second part of the project, the UWE team utilized the updated version of a soft-body physics engine, i.e. Voxelyze, as a testbed for optimization methodologies. In addition to the Age-Fitness-Pareto-Optimization (AFPO) methodology implemented and optimized to run 30% faster during the first year of the project, more complicated methods (that use not only mutation operations, but crossover too) were investigated. More specifically, NeuroEvolution of Augmenting Topologies (NEAT) and Hypercube-based NeuroEvolution of Augmenting Topologies (HyperNEAT) were compared with AFPO and both managed to produce more robust morphologies of soft actuators in silico tests as illustrated in **Fig. 1**.

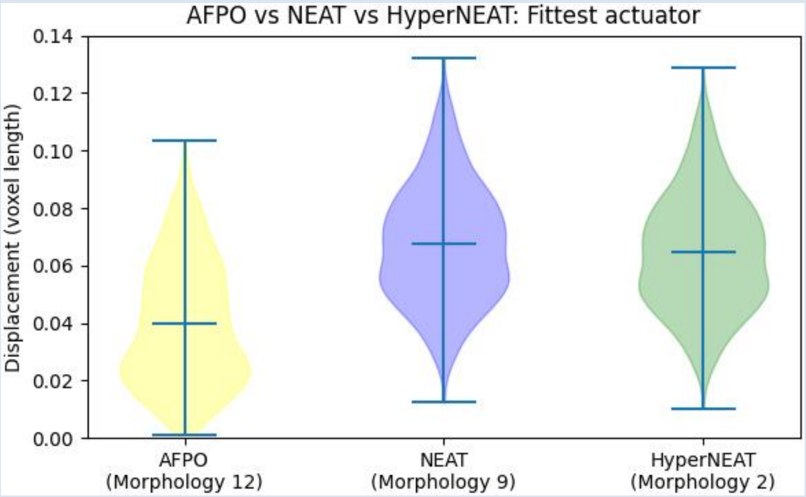


Figure 1. Violin plots comparing the performance of the fittest actuator morphology produced by AFPO, NEAT and HyperNEAT. Each violin presents the kernel density estimation of the frequency distribution of 1000 random controller scenarios.

These NeuroEvolution algorithms were implemented to optimize not only the physical morphology of actuators (like the ones presented in **Fig. 2**), but also the controller's synchronization of the active components of these actuators. Namely, the phase offset of each active voxel's expansion and contraction is considered as the controller strategy of each actuator morphology and is optimized through AFPO, NEAT and HyperNEAT.

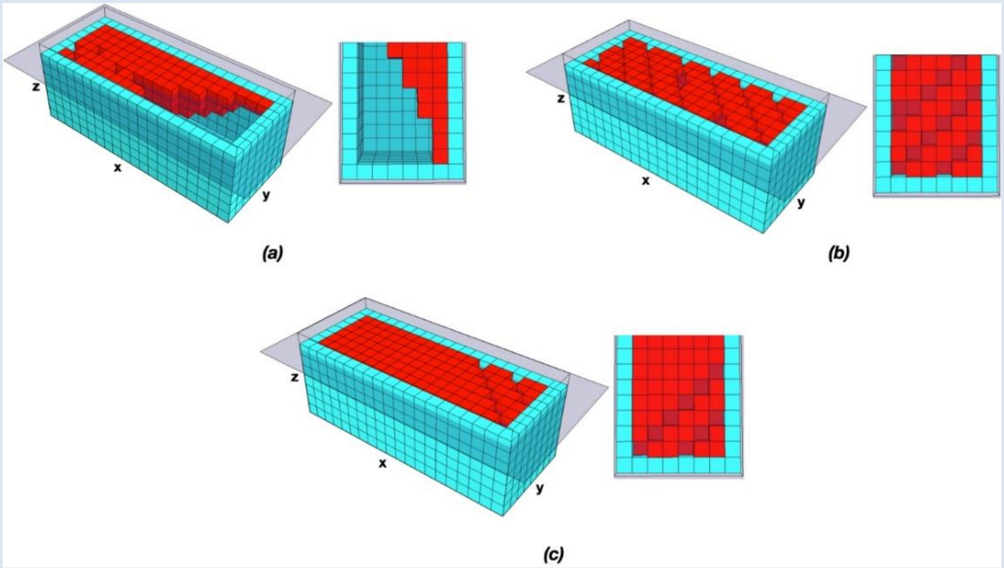


Figure 2. Morphology of the fittest actuator under: (a) AFPO; (b) NEAT; and (c) HyperNEAT. Blue voxels represent passive tissue; red voxels represent contractile tissue.

The UWE team has been cooperating with other teams within the project to optimize the geometric characteristics of the tip of the catheter with Evolutionary Algorithms and simulations based on Abaqus software and to predict the response of the BioHybrid catheter prototype under different stimulation signals with a Deep Neural Network. The investigation of all these methods and their implementation are aimed to form a pipeline of AI-enabled BHM design tool.

Fundacio Institut de Bioenginyeria de Catalunya
Barcelona, Spain;
Scuola Superiore Sant'Anna
Pisa, Italy

Fabrication, Assembly and Actuation of the Biohybrid Catheter Powered by Skeletal Muscle Constructs

Scuola Superiore Sant'Anna Pisa in collaboration with Fundacio Institut de Bioenginyeria de Catalunya

Over the past year, SSSA and IBEC have worked closely together to develop the Biohybrid Catheter and assess its performance. The manufacturing of a biohybrid machine (BHM) requires the incorporation of a skeletal muscle-based bioactuator capable of controlling the catheter motion.

To achieve the strongest contraction force, IBEC explored how tissue size impacts performance. Using mold casting, we fabricated circular-shaped muscle tissues of various sizes and cultured them in a flexible two-post system with different post distances (**Figure 1**). This system is crucial for proper muscle maturation, as it provides the necessary tension during muscle cell differentiation. Through these experiments, we found that muscle tissues formed with 9 mm diameter molds and assembled in 9 mm distant posts exhibited the highest contraction force, suggesting this setup is optimal for muscle development.

For integration, SSSA manufactured a hollow catheter through the molding technique and a custom material blend designed to improve its flexural capabilities. In addition, two pillars were added on its surface, allowing for easy assembly of the muscle tissue. Finally, once the muscle-catheter system was fully assembled, we evaluated its performance under different electrical stimulation protocols, marking a significant step forward in biohybrid technology (**Figure 2**).

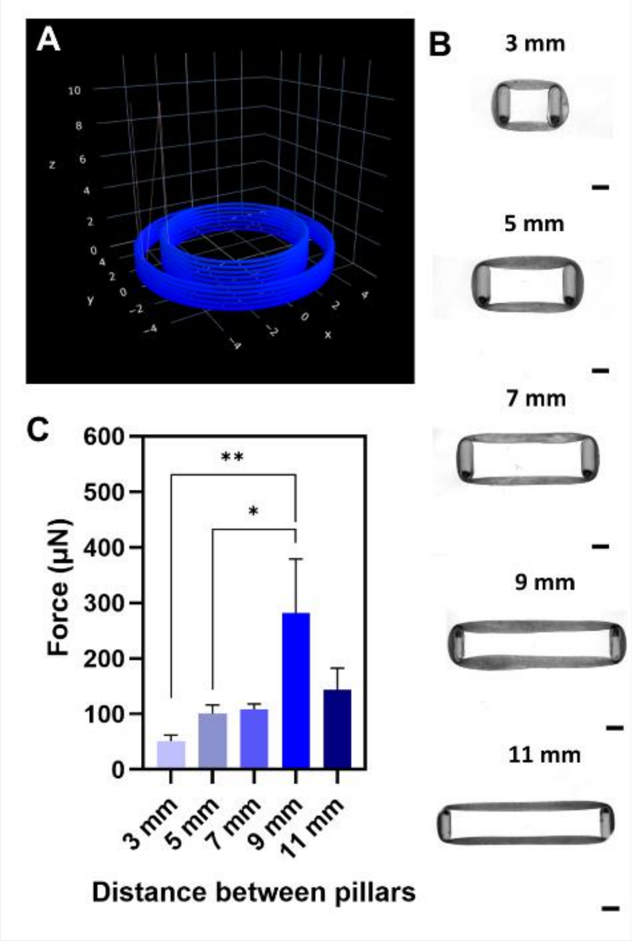


Figure 1. Characterization of circular-shaped mold casted muscle bioactuators. A) Example of a CAD design of a circular mold, which is fabricated using extrusion-based 3D printing. B) Images of the muscle tissues of different sizes assembled on the two-post system with different distance. Scale bar: 1mm. C) Force measurements of bioactuators of different diameters.

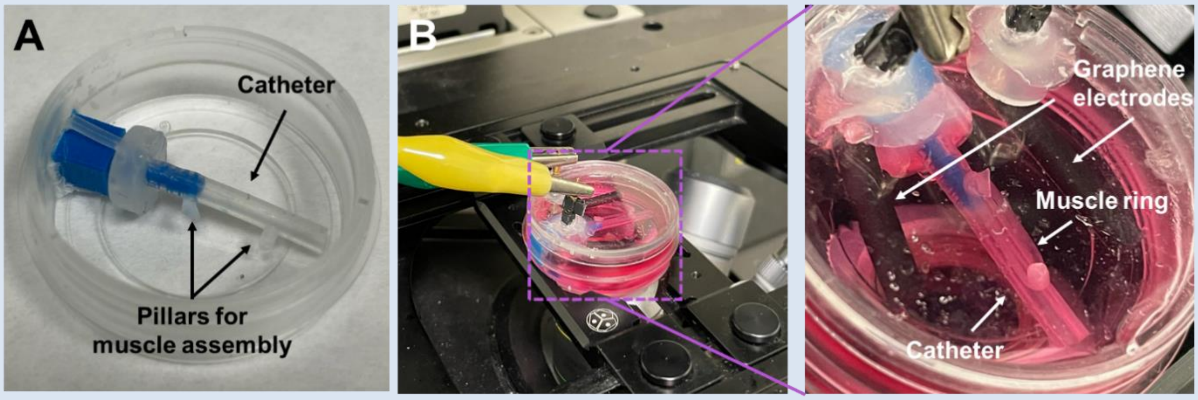


Figure 2. Images of the set up used to test the bending capacity of the catheter with the integrated muscle bioactuator. A) Petri dish containing the glued anchoring structure (blue) with the catheter fixed, which contains the pillars needed for muscle assembly. B) Set up for electrical stimulation. Home-made graphene electrodes are integrated into the petri dish, containing the catheter and the muscle tissue assembled on the pilla.

Università degli Studi di Cagliari
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The activities carried out by UNICA during the last year are related to the development of the feedback control system of the biohybrid machine, i.e. the flexible electronic platform and its electronic control module. These activities have been carried out in strong collaboration with SSSA and IBEC for the definition of geometrical features of the flexible electronic platform to be integrated with the catheter and the biohybrid actuator.

The flexible electronic platform hosts sensing and actuation structures, necessary to stimulate the contraction of the biohybrid actuator, and retrieve information about the actual bending induced on the biohybrid machine. The sensor structure is based on an Organic Field-Effect Transistor (OFET), which was demonstrated suitable for muscle tissue contraction monitoring with programmable sensitivity during the first year of the project. The activity was thus devoted to transferring the fabrication process towards large-area, cost-effective techniques suitable for industrialization of the biohybrid machine, and over ultra-flexible substrates, with a thickness in the range of few microns, allowing the integration of the platform in the soft robot. Thanks to the employment of inkjet printing, all-organic devices have been fabricated and tested with different geometrical features, following the evolution of the biohybrid machine structure during the development of the research activities of the project. Using the same fabrication approaches, graphene electrodes for muscle tissue stimulation were printed on the flexible platform. The device structure, shown in **Figure 1**, has a total area of 120 mm^2, a thickness of about 2 μm that make it suitable for integration on the catheter. Preliminary electromechanical characterization allowed evaluating the actual sensitivity of the device to deformation applied to the catheter tip.

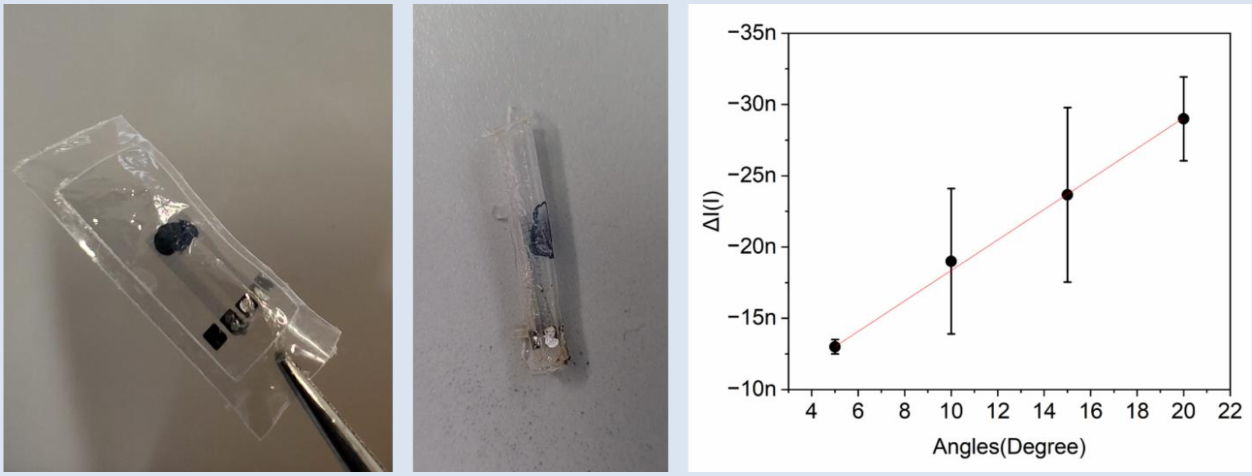

Figure 1. the flexible platform and its integration on a catheter tip. On the far right, the calibration curve of the sensorized catheter showing the current variation deriving from tip bending at different radii.

On the side of readout electronics, a miniaturized board hosting sensor frontend and current stimulation circuit have been produced and tested. The dimensions of the board are compatible with high portability and cost-effective production of the sensing platform. The platform results effective in the readout of the sensor output current, as well as in inducing the tetanic contraction of the muscle tissue for a stable and prolonged deformation of the catheter tip. A custom software allows programming sensor operating point and stimulation conditions.

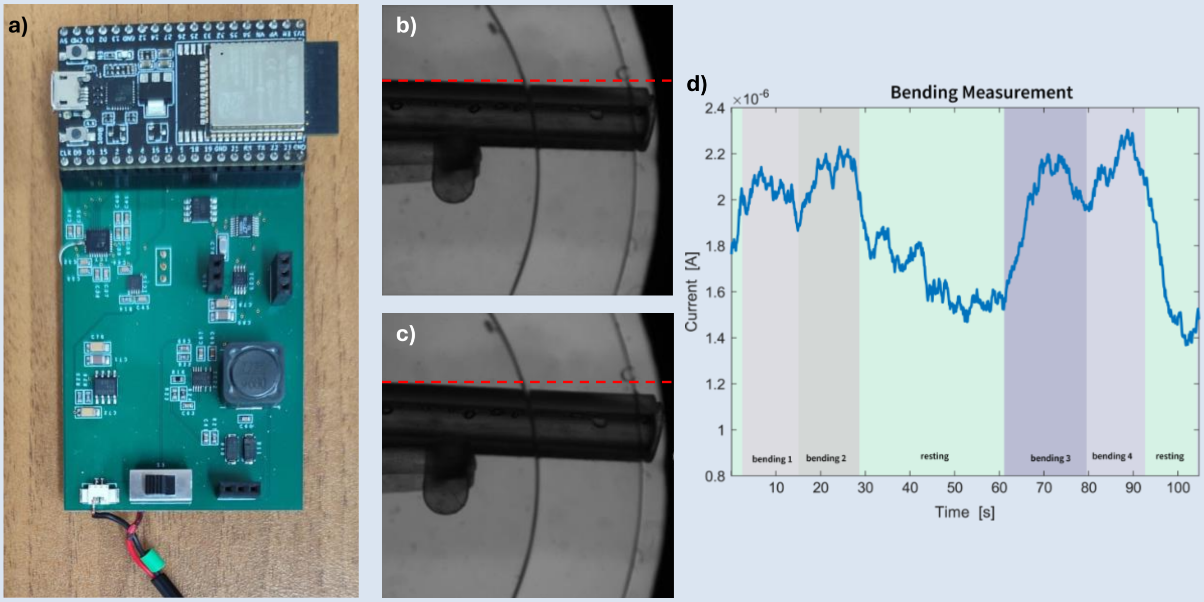

Figure 2. a) the electronic control module; b)-c) the catheter tip in relaxed state and during muscle tissue stimulation by means of the current stimulator on the electronic board, respectively: a sensible deformation of the tip is shown; d) An example of real-time strain sensor readout during bending application

Smart Sensing

The manufacturing process for fabrication and assembly of the bio-hybrid machine consisting of a bio-hybrid flexible catheter has been specified and classified as a case of special product or machine manufacturing, where production activities are characterised by few repeated mostly manually executed processes, very little standardised procedures, and highly specialised operations based on multidisciplinary skills. Though the bio-hybrid catheter production had been initially conceived to occur in a manufacturing cell, during the BioMeld project development the manufacturing cell paradigm has been recognized as inappropriate for bio-hybrid machine production conditions. Hence, the bio-hybrid flexible catheter production has been more suitably designed to take effect in a manufacturing system with the joint characteristics of Integrated Manufacturing, where a group of organisations work together with same industrial goal but specialize in different sectors to realise a highly complex product, and Distributed Manufacturing, where a network of manufacturing units at different physical sites fabricate the product modules that are lastly brought together for final assembly.

The path forward

As we approach the end our project timeline, we are focusing on integration of all components and on bridging the gap between simulation and experimental work. This involves breaking down complex challenges into addressable components: optimizing actuator location, refining pillar configuration, defining biohybrid actuator specifications, designing stimulation patterns, and integrating all components into a functional system.

The project has identified six key exploitable outcomes that hold promise for future medical innovations: the biohybrid catheter itself, novel integration technologies, flexible electronics with specialized sensors, biohybrid 3D printing, powerful AI design tools, and manufacturing system planning frameworks.

The future of medical technology lies at the intersection of biology and engineering. Through our continued collaboration and innovation, BioMeld is helping to define this emerging frontier, creating technologies that harness the unique capabilities of living systems for improved medical care.

Exploitable outcomes

UNSPF and UWE Bristol

Bridging the digital-physical gap with advanced simulations and AI

1. Physics-informed neural networks for complex biological interface design:

Our multi-scale simulation approach, which links component-level behaviors to system performance, when coupled with AI, could create a powerful tool for designing soft-robotics systems. The technology would be particularly valuable in designing soft robots for delicate operations like agricultural harvesting or food processing where traditional rigid robots fail.

2. Indirect representation of architectures for more efficient optimization

The integration of Compositional Pattern Producing Networks provide an effective indirect representation method for optimizing architectural designs tailored to specific applications. Their ability to generate complex, regular patterns through mathematical functions enables the creation of structures that align well with additive manufacturing processes. This approach not only enhances performance of possible solutions but also simplifies manufacturing by accommodating changes in architectural dimensionality without necessitating a complete re-evaluation from scratch.

3. Digital Manufacturing Decision Support Systems

The integration of parametric analysis with AI-driven optimization could be further developed to create a powerful decision support system applicable to advanced manufacturing across industries. This approach could transform production planning for complex mechanical components by predicting how manufacturing variations might affect performance, enabling real-time adjustments to manufacturing parameters based on simulation insights. Such systems would be particularly valuable for components with tight tolerances and multi-material interfaces where trial-and-error approaches are prohibitively expensive.

IBEC-SSSA

Skeletal muscle-based biohybrid systems hold promise across a broad spectrum of applications, including reverse engineering, the development of living machines, and implantable biomedical devices. Among these, untethered skeletal muscle bioactuators stand out for their potential to emulate the sophisticated functions of living organisms, paving the way for the next generation of biohybrid soft robotics. The use of biological muscle actuation also supports miniaturization, a key factor in enabling micro-scale biohybrid robots that can interact more precisely with biological systems, operate more efficiently, and integrate seamlessly into delicate or complex environments. In parallel, tethered systems serve as valuable platforms for investigating muscle development, modeling diseases, conducting drug screening. The biohybrid catheter developed in the framework of Biomeld has potential that extends beyond its conventional use, working as a directional drug delivery system where drug release can be precisely controlled. Its design features a soft, flexible tubular structure, enabling straightforward scalability for both micro- and macro-scale applications and facilitating the easy integration of the muscle tissue. When multiple biohybrid catheters are combined, they can form a gripper-like mechanism capable of manipulating or gripping objects at the milli- and microscale. In addition to soft robotics applications, these simple yet high-performing systems can also serve as reliable platforms for muscle development studies and drug testing, as the bending motion of the catheter directly correlates with the actuation and performance of the muscle tissue.

UNICA

The feedback electronic system developed in the framework of BioMeld has several potential applications beyond the scope of the project. First, the flexible electronic platform approach has a prompt extension in the development of wearable devices for biomedical monitoring. Indeed, thanks to its high flexibility and conformability to any surface, it can be employed as sensing platform directly integrated on skin or on garments, paving the way for next generation on-body sensor. The OFET-based strain sensor hosted in the current version of the flexible electronic platform can be adapted, among others, to gesture and movement monitoring, with applications in sport and occupational medicine. Moreover, the same fabrication approach can be employed for the integration of biochemical sensors, thus allowing the real-time, non-invasive monitoring of biomarkers directly on skin, for the management of diseases such as diabetes and other metabolic conditions. Second, the electronic control platform, configured as a portable module capable for sensor readout and stimulation, can be extended itself to other applications in the field of bioengineering. The current stimulator, in particular, can be used for peripheral nervous system stimulation capable of inducing distinguishable feelings, thus being suitable for being integrated in next generation prosthetic systems.

Smart Sensing

Exploitable outcomes for the manufacturing system framework

As regards the framework of manufacturing system design and development, the technologies emerging from BioMeld activities are related to the implementation of the concept of bio-intelligent manufacturing as defined by Byrne et al., 2021, where the manufacturing system for special product or machine manufacturing, such as the bio-hybrid machine consisting of a bio-hybrid flexible catheter, is established based on an integrated and distributed manufacturing model, merging AI and simulation with bio-inspired and bio-integrated manufacturing solutions. The lessons learnt from project activities can allow for the future development of innovative technological solutions, also beyond the scope of the ‘BioMeld’ project, in the expanding field of bio-hybrid machine production devised as special product or machine manufacturing cases.

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