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Biohybrid systems: Borrowing from nature to make better machines

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This Editorial highlights the current and future capabilities of biohybrid machines and components over a wide range of topics, from basic research to translation into practice. The blend between biology and engineering for replicating the performance of living machines or for developing machine components with a life-like behavior, better biocompatibility, and better sustainability, is investigated by many research teams, coming from bioengineering, biology, chemistry, and robotics. With seven selected contributions from leading researchers exploring the field of biohybrid machines from different perspectives and for different scientific and application needs, the Special Topic on "Biohybrid Machines" in *APL Bioengineering* will provide the readers with a solid and appealing vision in the field, hopefully stimulating new research avenues.

INTRODUCTION

Biological machines have been evolving over millions of years, and they are now capable of merging different functions ranging from actuation to sensing and powering. Although many artificial machines combining novel materials in a bioinspired design have been proposed and are now commonly used, the exploitation of biological components in artificial machines is still limited to only a few case-studies. On the other hand, traditional actuation and sensing solutions are not adequate yet for building machines at different scales (including micrometric scales), for developing implanted organs, or for developing a controllable motion.

By leveraging the performance of living cells and tissues and directly interfacing them with artificial components, it should be possible to exploit the inherent metabolic efficiency of biological functions within artificial machines and to provide novel solutions to the problems of biocompatibility. For example, controllable and intrinsically biocompatible devices could be realized by designing patient-specific DNA-based molecular machines or integrating patient cardiomyocytes into implantable pumps for drug delivery.

This field has attracted the interest of many researchers, coming from a wide range of backgrounds and motivated by different needs: researchers operating in the tissue engineering domain, who aim to obtain vascularized muscle tissues for myo-related pathologies; scientists exploring biomimetic design principles and technologies for improving machine design; roboticists looking to study self-healing, hierarchical, and scalable actuators with limited biocompatibility problems; and experts in bionics seeking smart solutions for blending artificial and biological components.[1,2]

While the capability to actuate tiny devices by using self-contracting cells was demonstrated more than one decade ago,[3] the scalability of these actuation solutions and their reliability in the long term are not trivial problems. Insect-derived cells[4] can be used in the place of mammalian cells owing to their tolerance of environmental instabilities, which increases their operation time, but up scalability remains an issue. A parallel issue for bringing biohybrid machines to an advanced level of development is related to control.[5] Self-contraction is not the best modality for a biohybrid machine, which should respond to external stimuli or to some external commands. On the other hand, simple electrical stimulation that fails to recapitulate the natural stimulation pathways is not efficient in the long term. Finally, when looking for scalability, the design of a biohybrid machine cannot prescind the manufacturing and assembly processes, which have often been neglected since most efforts focus on one-shot demonstrations.

In this framework, the bioengineering community needs a reference collection of contributions exploring the most recent advances related to biohybrid machines and including modeling of biological actuators, engineering of living muscles or energy scavenging systems, control of biohybrid artifacts at different scales, DNA-based machines, and materials and methods for interfacing biological and artificial components.

SUMMARY OF AREAS COVERED

In the Special Topic "Biohybrid Machines" in *APL Bioengineering*, the grand challenges related to biohybrid machines are approached, ranging from the data-driven modeling of biohybrid bacteria-swarms to the development of biohybrid devices fabricated by using motile bacteria or DNA fragments. The Special Topic also touches problems related to the control of neuromuscular tissues, which is essential for a proper operation of biohybrid devices. Finally, a couple of papers reporting the scaling up of biohybrid components, for larger actuators or for medical simulators, is also included.

Leaman[6] describes a data-driven statistical model for computationally efficient recapitulation of the motility dynamics of two types of *Escherichia coli* bacteria-based biohybrid swarms. *Escherichia coli* bacteria are paradigmatic examples of motile bacteria used in medical microrobotics, for drug-delivery purposes and remote interventions, owing to the possibility to be steered toward a target. The statistical model was combined with a cooperative gene expression model for determining differences in timescales for programmed emergent behavior in two different types of bacteria swarms. The authors identify the parameters regulating the timeframe and the robustness of the emergent behavior in both swarms and they show the relevance of the integration between synthetic biology and predictive modeling for the emergence of robust behaviors, which is essential for the future translation of these bacteria-based technologies.

The use of bacteria-based machines for medical application is also presented by Buss,[7] who developed microswimmers for autonomous cargo delivery to a target. Although this is one of the most richly studied applications for biohybrid machines, important problems related to immunogenicity and motility performance remain unsolved. In this work, genetically modified *Escherichia coli* bacteria have been integrated with nanoliposomes from red blood cells, thus demonstrating the possibility to fabricate personalized biohybrid motile machines that are intrinsically biocompatible, being obtained from the patient's own cells. The optimization of the cell extrusion technique for developing biohybrid microswimmers is a key feature of this paper, enabling a robust fabrication modality for clinical use.

The use of much smaller biological components in comparison with bacteria for fabricating biohybrid machines is reported by Kasahara.[8] DNA-based hydrogels have been developed in various configurations for realizing tiny movable devices relying on DNA hybridization.[9] The efficiency of these tiny machines mainly depends on the shape control of DNA hydrogels. A novel photo-lithographic method for DNA hydrogel shape control, based on photo-activated sled-assembly of Y-shaped DNA nanostructures, is the object of the Kasahara work. The definition of the DNA hydrogel shape is triggered by UV illumination acting on a photo-active linker, which provides a superb controllability in constructing the biohybrid artifact, when compared to state-of-the-art fabrication technology.

One of the main challenges in controlling and activating biohybrid muscle construct is related to the replication of functional neuromuscular junctions. Kaufman[10] demonstrates that an intact segment of lumbar rat spinal cord forms functional neuromuscular junctions with engineered, 3D muscle tissue, grown on 3D-printed polyethylene glycol (PEG). The final construct forms, in 7 days, the *in vitro* model of the *in vivo* peripheral nervous system and the innervated muscles exhibit spontaneous contractions as measured by the displacement of pillars on the PEG skeleton, thus resembling a natural central pattern generator.

Neural control of skeletal muscle actuators in different configurations is also approached by Aydin.[11] They have developed a platform for 3D neuron-muscle co-culture, which can test and compare neuromuscular biohybrid actuators. The platform is used for electrophysiology studies by microelectrode arrays capable of unveiling the interactions behind the co-development between neural and muscle tissues. The possibility to grow up to four target muscle actuators and then measure contraction forces enables, for the first time, studies on the role of long-range interactions in neuronal pattern development.

Bringing biohybrid machines from the Petri dish to the real world is hampered by the robustness of biohybrid devices when working in air. For this reason, many researchers are working on smart encapsulating technologies for integrating biohybrid artifacts in totally artificial machines. In the "Biohybrid Machines" Special Topic, Morimoto[12] proposes a novel encapsulation method for skeletal muscle tissues where a collagen structure maintains the required humidity when the system is operated in air. The authors demonstrate the robust operation of this construct by using the biohybrid actuator as a robotic end-effector for object manipulation.

Scaling up from the DNA to the cell and to the biohybrid muscles, Horvath[13] demonstrates a particular application of biohybrid constructs for biological apparatus simulation (i.e., the respiratory system). More specifically, they insert organic lungs into a biomimetic thoracic cavity designed starting from physiological specifications and integrating a functional artificial diaphragm. By tailoring the input pressures and timing in the hybrid simulator, they can represent different breathing motions and disease states for elucidating some pathological phenomena and for teaching or training younger clinicians. In addition, this hybrid simulator can be used as a test bench for lung sealant materials or assistive breathing devices, thus reducing the need for animal trials and increasing the likelihood of success in the final application.

CONCLUSIONS

Without claiming to be exhaustive, the "Biohybrid Machines" Special Topic presents different enabling technologies for developing reliable biohybrid machines by starting from different biological elements at different scales (e.g., DNA fragments, bacteria, cells, and entire organs). The Special Topic also highlights several applications of these biohybrid devices, ranging from scientific tools for understanding basic biological behaviors, to biomimetic actuators and robots, to small shuttles for repairing the human body, and finally to medical simulators. We hope that this set of papers will be enjoyed by the community of APL Bioengineering readers and will stimulate their creativity and curiosity.

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