SCIENCE ROBOTICS | FOCUS

BIOMATERIALS

Float like a butterfly, swim like a biohybrid neuromuscular robot

Nicole W. Xu*

A butterfly-like robot swims using an electronic device to stimulate human-derived motor neurons and cardiac muscle cells.

Within the broader field of robotics, one direction of thought is to draw inspiration from nature to address long-standing challenges. Animals typically have a higher performance—such as increased energy efficiency, agility, and damage tolerance—compared with their robotic counterparts because of evolutionary pressures driving biological adaptations (*1*). Therefore, bioinspired designs offer promising approaches to enhancing traditional rigid and soft robots.

A relatively nascent and growing subfield of bioinspired robotics is biohybrid robotics, which integrates both artificial and biological materials into an engineered construct. Such biohybrid techniques include microorganism bots, cyborg methods using entire animals, and tissue-engineered robots (*1*–*3*). Tissue-based biohybrid robotics offers additional interdisciplinary insights into human health, medicine, and fundamental research in biology. In their recent article, Tetsuka *et al.* (*4*) debut an untethered biohybrid neuromuscular robot with a spanwise body length of 30 mm (Fig. 1C) that uses butterfly-like flapping motions to swim forward. The robot's average swimming speed is 0.52 ± 0.22 mm s^{-1} and average turning path curvature is 0.11 ± 0.04 mm^{-1}.

Butterfly wings (Fig. 1A) and batoid fish fins (such as those of rays and skates, as shown in Fig. 1B) are models for bioinspiration because they possess oscillatory and/or undulatory motions, which have potential advantages for faster propulsion, decreased power consumption, and enhanced maneuverability (*5*, *6*). Two examples of bioinspired soft robots using entirely engineered materials include a butterfly-shaped construct made from a deformable photoresponsive hydrogel that uses visible light to drive swimming (*7*) and a tethered bistable soft flapping actuator (Fig. 1D). The bistable butterfly bot is composed of a silicone body and two flexible polyester ribbon fin frames and is capable of achieving fast swimming speeds using snapping instabilities, the same principle observed in hair snap clips and jumping popper toys (*5*). These purely engineered actuators offer new methods to design faster and more energy-efficient robots that exhibit similar modes of locomotion to that presented in Tetsuka *et al.* However, artificial actuators still possess some limitations, such as the high driving voltage of select electroactive polymer (EAP) actuators (*2*).

To address these limitations, tissue-based actuators can take advantage of inherent biological systems, such as the greater efficiency at which biological actuators, compared with synthetic actuators, can convert chemical to mechanical energy (*8*). Like the butterfly-inspired swimming robots using engineered materials, previous studies have developed tissue-engineered ray robots for forward propulsion and turning maneuvers in cell culture media. One example is a light-driven biohybrid robotic ray, composed of a monolayer of optogenetic rat-derived cardiomyocytes (CMs) patterned on a flexible scaffold, with a stiff gold skeleton for elastic energy storage (Fig. 1E). This tissue-engineered robot using CMs retained 80% of its initial swimming speed for up to 6 days (*6*), compared with the neuromuscular robot in Tetsuka *et al.*, which maintained signal transduction and retained 82% of its initial angular displacement for up to 5 weeks (*4*). In another manta ray–inspired robot, mouse-derived skeletal muscle tissue was used for actuation. Despite slower swimming speeds compared with other robotic methods, this work showed stable and real-time controllable swimming using a dynamic control method based on circularly distributed multiple electrodes (CDMEs), a method of culturing circular tissues and facilitating cell differentiation (*8*).

A key challenge of tissue-engineered robots is to incorporate upstream neural control into muscle-based biohybrid robots, which prior biohybrid ray robots lacked (*3*). Other previous studies have harvested neuromuscular tissue circuits from sea slugs and incorporated them into biohybrid constructs (*1*), and more recent work demonstrated the successful implementation of neuromuscular units on a light-controlled flagellar construct composed of mouse skeletal muscles and optogenetic motor neurons (MNs). This biohybrid flagellar robot swam at slow speeds, an expected limitation for flagellar motile bots at low Reynolds numbers (*9*).

To design next-generation neuromuscular biohybrid robots with increased controllability and cell responsiveness, Tetsuka *et al.* demonstrate a wirelessly powered bioelectronic robot. Multiple frequencies excite human induced pluripotent stem cell (iPSC)–derived MNs, which then stimulate iPSC-CMs to contract and drive forward swimming (*4*). These authors addressed a previous limitation, that some neuromuscular robots require external control such as a light source, by incorporating an onboard electronic control system to act as an "artificial brain" for selective neural activation. A parallel double-frequency transmitter uses two nonoverlapping modulation signals (6.78 and 13.56 MHz for resonant coils controlling the left and right fins, respectively) to provide electrical stimulations to the neuromuscular robot through magnetic coupling. As illustrated in Fig. 1C, the multilayer robot design includes a wireless circuit, carbon nanotube (CNT)/gelatin thin-film scaffold, and tissue-engineered bilayer of iPSC-MNs–iPSC-CMs.

Notably, this biohybrid robot uses artificial electrical synapses, or gap junctions, between the two different cell types for more robust cell signaling, including faster bidirectional signaling and longer sustained muscle contractions up to 150 s. In comparison, this

---

Paul M. Rady Department of Mechanical Engineering and Robotics Program, University of Colorado Boulder, Boulder, CO 80309, USA.
*Corresponding author. Email: nicole.xu@colorado.edu

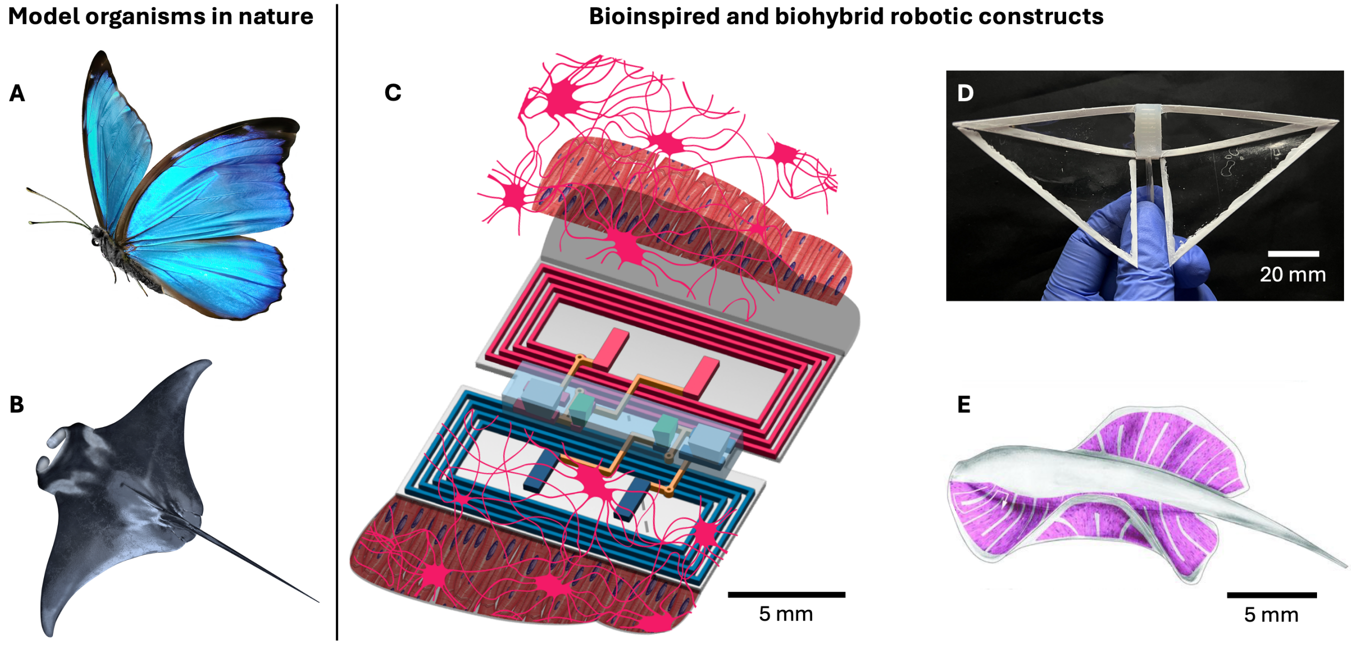

Fig. 1. Bioinspired thin-film robotic constructs based on flapping animals. Model organisms for bioinspired and tissue-based biohybrid robots include (**A**) butterflies and (**B**) ray fishes. (**C**) A notable example of a biohybrid robot is a bioelectronic neuromuscular construct that uses frequency multiplexing. As shown in the schematic, a wireless circuit comprising cell stimulation electrodes, coils, diodes, and capacitors uses two frequencies (6.78 and 13.56 MHz) to activate a layer of human-derived MNs, which then stimulate CMs, embedded on a thin film of CNT fiber/gelatin and encased in polydimethylsiloxane (PDMS). The MNs stimulate cardiac muscle contractions to incite forward swimming (*4*). Other examples of flapping fin robots include (**D**) butterfly-like soft robots that use bistable flexible actuators (*5*) and (**E**) ray-like tissue-engineered robots that use rat CMs (*6*).

is 7.5 times longer than neuromuscular robots that use chemical synapses, which exhibit muscle fatigue after 20 s because of the depletion of neurotransmitter vesicles at the neuromuscular junction (*9*). By independently modulating the left and right fins, Tetsuka *et al.* trigger synchronized flapping using interdigital signal multiplexing and alternate flapping using time-differential multiplexing; alternating fin flapping resulted in maximum straight swimming speeds. Another substantial result of this work is the decreased threshold voltage to excite the cardiomyocytes through neurons, rather than directly stimulating the muscle cells. This finding suggests that neuromuscular robots can reduce power costs compared with cardiomyocyte-only–based robots (*4*).

The advent of this bioelectronic neuromuscular robotic swimmer suggests the potential to build autonomous biohybrid robotic systems that can achieve adaptive motor control, sensing, and learning. New tissue-based biohybrid robots could have promising biomedical applications for studying neuromuscular diseases, such as organoids-on-a-chip for drug evaluation (*10*). Using electrical synapses and localized neural stimulation to enhance cell signaling and robust muscle stimulation, as demonstrated in this new study (*4*), future work can focus on other challenges, such as continued progress on scalability, fabrication, predictive modeling, and ethical considerations of tissue-engineered biohybrid robots.

REFERENCES

1. V. A. Webster-Wood, M. Guix, N. W. Xu, B. Behkam, H. Sato, D. Sarkar, S. Sanchez, M. Shimizu, K. K. Parker, Biohybrid robots: Recent progress, challenges, and perspectives. *Bioinspir. Biomim.* **18**, 015001 (2023).
2. L. Ricotti, B. Trimmer, A. W. Feinberg, R. Raman, K. K. Parker, R. Bashir, M. Sitti, S. Martel, P. Dario, A. Menciassi, Biohybrid actuators for robotics: A review of devices actuated by living cells. *Sci. Robot.* **2**, eaaq0495 (2017).
3. R. Raman, Biofabrication of living actuators. *Annu. Rev. Biomed. Eng.* **26**, 223–245 (2024).
4. H. Tetsuka, S. Gobbi, T. Hatanaka, L. Pirrami, S. R. Shin, Wirelessly steerable bioelectronic neuromuscular robots adapting neurocardiac junctions. *Sci. Robot.* **8**, eado0051 (2024).
5. Y. Chi, Y. Hong, Y. Zhao, Y. Li, J. Yin, Snapping for high-speed and high-efficient butterfly stroke–like soft swimmer. *Sci. Adv.* **8**, eadd3788 (2022).
6. S.-J. Park, M. Gazzola, K. S. Park, S. Park, V. Di Santo, E. L. Blevins, J. U. Lind, P. H. Campbell, S. Dauth, A. K. Capulli, F. S. Pasqualini, S. Ahn, A. Cho, H. Yuan, B. M. Maoz, R. Vijaykumar, J.-W. Choi, K. Deisseroth, G. V. Lauder, L. Mahadevan, K. K. Parker, Phototactic guidance of a tissue-engineered soft-robotic ray. *Science* **353**, 158–162 (2016).
7. Q. Guo, W. Yang, H. Liu, W. Wang, Z. Ge, Z. Yuan, An aquatic biomimetic butterfly soft robot driven by deformable photo-responsive hydrogel. *Soft Matter* **19**, 7370–7378 (2023).
8. C. Zhang, Y. Zhang, W. Wang, N. Xi, L. Liu, A manta ray-inspired biosyncretic robot with stable controllability by dynamic electric stimulation. *Cyborg Bionic Syst.* **2022**, 9891380 (2022).
9. O. Aydin, X. Zhang, S. Nuethong, G. J. Pagan-Diaz, R. Bashir, M. Gazzola, M. T. A. Saif, Neuromuscular actuation of biohybrid motile bots. *Proc. Natl. Acad. Sci. U.S.A.* **116**, 19841–19847 (2019).
10. M. Shin, T. Ha, J. Lim, J. An, G. Beak, J. Choi, A. A. Melvin, J. Yoon, J. Choi, Human motor system-based biohybrid robot-on-a-chip for drug evaluation of neurodegenerative disease. *Adv. Sci.* **11**, 2305371 (2024).

10.1126/scirobotics.ads4127

CREDIT: (A) MEDIAPRODUCTION/ISTOCKPHOTO, (B) LARYSA PASHKEVICH/ISTOCKPHOTO, (C) (4), (D) (5), AND (E) (6)

Science Robotics

Float like a butterfly, swim like a biohybrid neuromuscular robot

Nicole W. Xu

Sci. Robot. **9** (94), eads4127. DOI: 10.1126/scirobotics.ads4127

Science Robotics (ISSN 2470-9476) is published by the American Association for the Advancement of Science. 1200 New York Avenue NW, Washington, DC 20005. The title *Science Robotics* is a registered trademark of AAAS.