Organismal engineering: Toward a robotic taxonomic key for devices using organic materials

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Engineers are often inspired by the behavioral flexibility and robustness seen in nature. Recent advances in tissue engineering now allow the use of organic components in robotic applications. By integrating organic and synthetic components, researchers are moving toward the development of engineered organisms whose structural framework, actuation, sensing, and control are partially or completely organic. This review discusses recent exciting work demonstrating how organic components can be used for all facets of robot development. On the basis of this analysis, we propose a robotic taxonomic key to guide the field toward a unified lexicon for device description.

INTRODUCTION

In robotics, nature has long provided inspiration for device development from abstract structures (1) to detailed systems design (2, 3). Such bioinspiration has contributed greatly to the development of advanced robots, but many capabilities seen in nature have yet to be achieved. Standard materials for robotic fabrication do not exhibit self-healing or have the ability to autonomously generate energy as seen in biological systems. Robotic actuation is also somewhat limited. For example, many existing small-scale traditional robotic actuators lack the compliance, energy efficiency, and power-to-weight ratio observed in musculoskeletal systems. Furthermore, robotic sensing is still limited. For example, there are no affordable, responsive, and reliable chemical sensors that can replace dogs for dog or explosive detection. Finally, the behavioral flexibility, complex control, and advanced learning capabilities observed in animals have not been fully captured by current robotic controllers. As a consequence, organic components provide highly promising alternatives to traditionally engineered systems for the development of complex autonomous robotic systems.

Efforts to integrate organic components with robotic systems require expertise from many different disciplines. Researchers in tissue engineering have sought to develop devices for biomedical applications and pharmacology, whereas those in control engineering have looked to natural nervous systems for insight into neural network algorithms and artificial intelligence development. In robotics, engineers have been drawn to the possibility of using living muscle as a lightweight, compliant actuator for robotic systems.

Researchers are striving to create biohybrid and completely organic robotics—devices with some or all of the components made of organic materials. As a consequence, current components can be divided into three categories: organic, hybrid (combining both organic and synthetic material), and fully synthetic. Despite recent momentum (Fig. 1), there is no comprehensive review of robotic systems using organic components. Several previous reviews on this subject have ranged from discussions of biohybrid devices within the context of biofabrication and biologically inspired design (4) to focused reviews of particular systems, such as the use of biomolecular motors in the development of nanoscale systems (5). The primary focus is typically on organic actuators, either the fabrication strategies (6, 7) or the use of organic material for a particular component or subset of components in robotic design. Several reviews have discussed the use of muscle cells (8–14) or biomolecular motors (5, 11) as organic actuators. Biohybrid actuators are even being included in textbooks on microrobots (15). Other reviews have instead focused on the use of microorganisms and flagellated cells to provide both actuation and basic sensing capabilities for biohybrid devices (12, 13, 16). Discussion of the use of organic components as control systems has been limited, although the need for neuron-based controllers and neuromuscular junctions for muscle-actuated robots has been addressed (14).

A unifying review that analyzes the existing literature would help guide the community that is developing microsystems and next-generation robots. To this end, our review discusses the use of organic components in robotic devices, highlighting the material combinations that make up existing devices. We quantitatively compare current mobile robots incorporating organic components with the performance of animals. Whereas our focus is primarily on non–plant-based devices and applications to enable the development of mobile robotic platforms, it should be noted that the development of biohybrid systems incorporating plants (Flora robotic) (17) is also a growing area of research. Interested readers should refer to Skrzypczak et al. (18) for additional insights into plant-based biohybrid systems. We address the need to formulate a clear and descriptive lexicon for device description that does not currently exist. Finally, we conclude by discussing future avenues of device development.

ROBOTIC TAXONOMIC KEY FOR DEVICE CHARACTERIZATION

A complete, autonomous robotic system requires four elements: structure, actuation, sensors, and control. Each element can comprise organic components, hybrid components, or synthetic components. To better categorize devices that have been previously reported in the literature, we have developed a simple robotic taxonomic key (RTK) (Fig. 2A). Each robotic element is represented by one of the RTK’s four wedges. For each wedge, there is a simple question: Is the component organic (solid), hybrid (striped), or synthetic (open)? By asking these questions, we can categorize all existing devices, whether that device has organic components (Fig. 2B) or is fully synthetic (Fig. 2C), as well as devices yet to come. If a device lacks a particular component, the corresponding wedge can simply be grayed out. This key provides a quick and convenient
visualization for device classification and allows easy categorization by more accurate keywords in the future.

Emerging technologies and applications can be added to the RTK by using additional pattern options. For example, genetic engineering of cells to induce responses to optical stimuli has been used to create optical sensors for robotic devices. Therefore, we can add the question, “Is the organic component genetically engineered?” to the RTK classification process. If the answer is yes, the wedge can be filled with a dot pattern (Fig. 2D). Similarly, the RTK can be updated by future researchers as new, unforeseen technologies are developed. A list of

Fig. 1. Timeline of achievements in biohybrid and organic robots. (Top) Although in its infancy, the field of biohybrid and organic robots is growing quickly, and many papers on organobots, biohybrid robots, and cyborg drones have been published in the past few years. (Bottom) During the past two decades, many exciting devices have been developed, as indicated by the small selection provided here. These devices are color-coded to indicate the organic components as outlined by the RTK (bottom left; see Fig. 2 for RTK details).
selected publications demonstrating the use of the key for classification of the devices is presented in Table 1, along with measures of device performance.

ORGANIC COMPONENTS IN ROBOTICS

Although devices may have multiple categories of organic components, we systematically discuss each category separately: structures, actuators, sensors, and control. We begin by discussing the use of organic structures in robotic platforms. To date, the development of such structures has been limited to the use of collagen or through robotic systems based on existing organisms (organism-based). More research has been focused on the use of organic actuators, sensors, and controllers, wherein the organic components can be cell-based or make use of whole tissues or organs. Furthermore, cyborg drone systems have been developed in which existing organisms are used as a platform on which the robotic control system is built. These devices naturally use organic structures, actuators, sensors, and controllers that are subsequently augmented by synthetic components. To reduce repetition, such organism-based devices are discussed later (see the “Organism-based robots” section).

**Organic structures**

Structural components provide the groundwork upon which robotic devices are built, because the kinematics and the material properties of the structure affect the modes of actuation, sensors, and control architectures that will be incorporated into the device. As the number of biohybrid and organic robots grows, most devices continue to implement hybrid systems in which the organic actuators and sensors interface with inorganic structural components. In such systems, the structures used have been primarily synthetic, biocompatible polymers. However, some exceptions exist through the use of biological polymers or existing organisms (organism-based devices are discussed in detail later).

As a biological polymer, collagen provides an intriguing material for soft robotic structures. Collagen can be readily isolated from a variety of tissues and natively promotes cellular attachment. Takemura et al. (19) used collagen gels, with a stiffness of 270 Pa, as a structure for a cell-powered jellyfish-inspired device. In addition, commercially available collagen sheets have been used in a proof-of-concept system for establishing a cardiomyocyte-driven joint for potential use in legged robots (20). Cells seeded on one side of the collagen were able to bend the joint.
Organic structures can be used not only to promote cellular attachment but also to cause cellular alignment. By using electrocompacted and aligned collagen (ELAC) sheets as a structure for both cardiomyocyte and skeletal muscle cell–seeded robots, Webster et al. (21) fabricated self-assembling devices capable of crawling. The use of ELAC as a structure for completely organic robots has many advantages over synthetic polymers. ELAC is biocompatible and does not require micropatterning to promote cellular attachment or alignment, and the stiffness of the material can be controlled by cross-linking and/or by varying compaction time. The devices reported by Webster et al. had an indentation stiffness of ~640 N/m^2; the stiffness of ELAC can be varied several orders of magnitude with chemical cross-linking. In addition, the collagen causes cellular alignment without micropatterning. Additional devices without synthetic structure components have been developed using bacteria and protists, as will be discussed later.

**Organic actuators**

Organic actuators fall into two categories: cell-powered and tissue-powered. Cell-powered devices are developed by isolating individual cells and culturing them in such a way as to produce coordinated locomotion.

Table 1. Examples of the organic/synthetic makeup and performance of existing devices. Selected papers detailing the synthetic (S) or organic (O) components of devices incorporating biological components in the previously described categories: structure (Str.), actuation (Act.), sensing (Sens.), and control (Con.). Relevant metrics for the devices are reported as available: velocity in body lengths (BL)/s for locomoting device and success rate (S.R.), where success rate is the percentage of total trials in which the devices successfully accomplished the locomotion task tested (e.g., following a line of a certain length). Dash entries indicate a lack of the specified component in the device. Blank entries indicate performance metrics that were not reported for a given device.

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<td>2006</td>
<td>S</td>
<td>O</td>
<td>—</td>
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<td>2007</td>
<td>S</td>
<td>O</td>
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<td>S</td>
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<td>2.5 mm</td>
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<td>2 mm</td>
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<td>S/O</td>
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<td>Hayashi et al. (80)</td>
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<td>Chan et al. (26)*</td>
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<td>S/O</td>
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<td>O</td>
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<td>2 mm</td>
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<td>Zhu et al. (114)*</td>
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<td>S/O</td>
<td>O</td>
<td>O</td>
<td>S/O</td>
<td>380 ± 20 mm</td>
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<td>S</td>
<td>300 μm</td>
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<td>S</td>
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<td>O</td>
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<td>Park et al. (99)</td>
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<td>S/O</td>
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<td>Williams et al. (31)*</td>
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<td>S</td>
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<td>2 mm</td>
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<td>Barroso et al. (100)*</td>
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<td>S/O</td>
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<td>O</td>
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<td>2 μm</td>
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<td>Huang and Krapp (63)</td>
<td>2015</td>
<td>S</td>
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<td>O</td>
<td>S/O</td>
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<td>Sanchez et al. (111)</td>
<td>2015</td>
<td>S/O</td>
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<td>O</td>
<td>S/O</td>
<td></td>
<td></td>
<td>70</td>
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<td>Holley et al. (28)*</td>
<td>2016</td>
<td>S/O</td>
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<td>—</td>
<td>—</td>
<td>9.2 mm</td>
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<td>Li and Zhang (97)</td>
<td>2016</td>
<td>S/O</td>
<td>O</td>
<td>O</td>
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<td>Park et al. (33)*</td>
<td>2016</td>
<td>S</td>
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<td>O</td>
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<td>2016</td>
<td>O</td>
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<td>4 mm</td>
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<td>2016</td>
<td>S/O</td>
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<td>4 cm</td>
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*Inclusion of the reported device in allometric scaling analysis (see the “Allometric scaling in robots with organic components” section).
For such devices, research has focused primarily on cardiomyocytes and skeletal muscle cells. Tissue-powered devices are fabricated by isolating intact tissue, primarily skeletal muscle tissue, from a living organism.

**Cell-based devices**

**Cardiomyocyte.** Cardiomyocytes are a natural choice as actuating cells, because isolated cardiomyocytes spontaneously contract in culture and can be paced with an external electrical field, eliminating the need for complicated onboard circuitry or microfluidics. Early efforts were often inspired by the results of organ-on-a-chip experiments using cantilevers, such as those reported by Park et al. (22, 23), where one side of a microcantilever was seeded with cells. The contraction of the cell layer resulted in bending of the cantilever. By using one or more cantilevers in device body geometries, a wide range of cardiomyocyte-powered devices has been created. For example, in 2005, Xi et al. (24) used this technique to fabricate a two-legged crawling device with a micropatterned silicon backbone to induce attachment and alignment of seeded cardiomyocytes. Contraction of the cardiomyocyte layer resulted in locomotion with a maximum speed of 38 μm/s. Furthermore, Kim et al. (25) demonstrated the possibility of fabricating cell-powered robots that functioned over long periods of time by combining micropatterned polydimethylsiloxane (PDMS) with cardiomyocytes. The resulting asymmetric six-legged robots (Fig. 3A) were capable of functioning for up to 11 days at an estimated speed of 86.8 μm/s. Similarly, Chan et al. (26) have developed a single-legged cantilever-based cell-powered robot with a three-dimensional (3D)–printed polyethylene (glycol) diacrylate substrate. Using a stereolithographic printer, a body was fabricated that consisted of a thick base block with asymmetric cantilever arms on the top. Cells were subsequently seeded on either the top or the bottom of the cantilevers to produce different locomotion gaits.

Micropatterning can be used to orient cells at any angle to the base substrate. Feinberg et al. (27) demonstrated this concept by using angled patterning to fabricate a wide variety of actuators, including radial coiled actuators, cylindrical actuators with displacement along the long axis, and microgrippers. In the same study, the effect of anisotropic versus isotropic cell orientations was demonstrated through the fabrication of triangular-shaped swimming cell-powered robots.

More complex swimming devices have also been developed, including a PDMS-based self-stabilizing swimming robot powered by cardiomyocytes (28–30). The device consisted of three layers: a PDMS-nickel composite layer, a PDMS cantilever layer, and a PDMS-microballoon composite layer. The cantilever layer served as an actuating tail sandwiched between the nickel-composite ballast and the microballoon composite top. By varying the ratios of nickel to microballoon PDMS, the stability of the device could be tuned. Furthermore, the nickel layer was magnetic, allowing for control of the device’s position during cell seeding.

Animals also provide a source for body morphology inspiration, leading to biologically inspired cell-powered devices. Taking bioinspiration from spermatozoa, Williams et al. (31) developed a synthetic flagellar swimmer. Cardiomyocytes were localized at the junction between a broad head and filament tail (Fig. 3B). Contraction of the cells subsequently deflected the tail, propelling the robot forward. In 2010, Takemura et al. (19) developed a hemispherical jellyfish-inspired, cell-powered swimming robot using gel-encapsulated cardiomyocytes.

![Fig. 3. Examples of cardiomyocyte-powered devices.](http://robotics.sciencemag.org/)
Cells were seeded in a thin cylindrical collagen gel. Because of the thickness of the gel, cells within the bulk of the material were starved of nutrients and died off, leaving only an external layer of living cells. The passive and active stresses of this layer caused the cylinder to deform, resulting in a dome with living cardiomyocytes on the concave bottom surface. Active contraction of the gel resulted in pulsating displacement that served to propel the device at a speed of 6.25 mm/s. Using inspiration from another species of jellyfish, Nawroth et al. (32) reverse-engineered a body and musculature pattern mimicking that of the animal. By patterning an approximate musculature on a PDMS film with radially oriented arms, the device was capable of locomotion between 0.8 and 1.4 mm/s (Fig. 3C).

Optogenetically modified actuating cells have also been used to control biohybrid devices. In 2016, Park et al. (33) used optogenetics to create a steerable cell-powered robot inspired by the stingray. Cells were seeded on an engineered body with spatially varying geometric and mechanical properties (Fig. 3D). The cells on each side of the body were genetically modified to respond to light at different wavelengths. When the matching wavelength is focused on the front of the body, the cells contract and signal proximal cells via electrical gap junctions. This results in a contractile wave propagating along the body of the device, moving it forward. By adjusting the strength of light on the two sides of the device, the contraction force on opposite sides of the body can be varied, thereby steering the robot.

Many other interesting cardiomyocyte-powered devices have been developed. For example, cardiomyocytes have been used to actuate micropumps (34). In addition, cantilevers can be used for “heart-on-a-chip” applications, which may allow testing of the effects of pharmaceuticals on cellular contraction (35, 36).

Skeletal muscle. Development of skeletal muscle cell-powered devices has, in many ways, mirrored that of cardiomyocyte-powered devices, with early efforts making use of skeletal myotubes cultured on cantilevers (37–40). Although most research efforts have focused on mammalian or avian cell sources, contractile cells have also been isolated from insects (41, 42). Similar to cardiomyocytes, skeletal muscle cells can be optogenetically modified to contract in response to light stimuli. Using such techniques, Sakar et al. (43) developed optically controllable skeletal muscle actuators on tissue gauges (Fig. 4A). Similarly, Neal and Asada (44) have demonstrated the ability to use optogenetically modified cells to control the position and rotation of suspended PDMS blocks (Fig. 4B).

In mobile device applications, skeletal muscle cells have been shown to produce faster locomotion as compared with cardiomyocytes when both are seeded on the same type of device (21). In 2014, Cvetkovic et al. (45) developed a 3D-printed device powered by skeletal muscle cells. The device was printed with a long body and two T-shaped legs. A cell/gel mixture was then seeded around the legs while the device was upside down. During culture, the passive stresses of the cells tightened the gel around the legs, forming a tissue construct. When the device was flipped over, slight asymmetries in the structure allowed the cell-powered robot to move forward (Fig. 4C). Furthermore, Webster et al. (21) created completely organic multilegged devices powered by skeletal muscle cells using electrocompacted collagen structures. During fabrication, the collagen molecules were compacted into a robust sheet and aligned along the leg axis of the device. This method aligns the cells so that their contraction is coordinated. The devices were capable of crawling in response to an external electrical field (Fig. 4D).

**Tissue- or organ-based devices**

Several devices have used muscle tissue to directly power devices. Because the structure of the muscle is maintained, overall contractile force is improved as compared to monolayer cultured muscle-based actuators. However, removal of the muscle from the supporting vasculature results in rapid deterioration. As a consequence, devices have limited lifetimes. In 2004, Herr and Dennis (46) developed a swimming robot actuated by tissue from the semitendinosus muscle of a frog. In this device, the muscle was sutured to the synthetic body consisting of a rigid forebody and compliant tail. The muscle was subsequently stimulated, using onboard circuitry, via electrodes wrapped around the tissue. The device swam for 4 hours over a 42-hour lifetime when stimulated with a 10% duty cycle. This lifetime is much shorter than that of devices using cultured cell layers, likely due to the inability of nutrients to diffuse throughout the thick muscle tissue.

Recently, invertebrate muscle has found use in biohybrid systems. Many invertebrates are capable of surviving in a wide range of environmental conditions and, as a consequence, have developed robust tissues. Insect dorsal vessel tissue has been demonstrated to be a suitable actuator for microrobots. Akiyama et al. (47) combined excised dorsal vessel tissue with a molded PDMS frame to create a stepping robot capable of locomotion at 66 mm/s with a locomotion efficiency of 17%. Furthermore, the velocity of the device can be increased eightfold by addition of crustacean cardioactive peptide to the surrounding medium. In addition, the marine mollusk *Aplysia californica* has been investigated as a source of muscle tissue (48). *Aplysia*’s open circulatory system allows thin muscles to function without specific vasculature, which may simplify the design of larger robots. Using the thin 12 muscle from the animal’s feeding apparatus, Webster et al. (48) fabricated a crawling robot with a 3D-printed body capable of locomotion speeds of about 0.08 mm/s. Muscle tissue from earthworms has also been used to drive a biomicropump (49). In this pump, a section of earthworm muscle was isolated and flattened to drive the displacement of a diaphragm.

**Organic sensors**

Although many recent research efforts in the biohybrid and organic robotics field have focused on developing organic actuators, the use of organic materials as robotic sensors is not new. It might be said that the first “Biorobot” was a device using organ-based sensors (see below) (50). Organic sensors have been developed for a wide variety of sensory modes using cell-, tissue-, or organ-based systems.

**Cell-based devices**

Mammalian cell–based systems have been used for olfactory, visual, and tactile sensing. In 2013, Du et al. (51) developed a cell-based olfactory sensor using genetically engineered olfactory sensory neurons. To target a specific olfactory ligand, diacetyl, the cells were modified by transfection with the *Caenorhabditis elegans* gene for the ODR-10 olfactory receptor. The sensor demonstrated the ability to distinguish between odorants with and without diacetyl. Furthermore, the position of olfactory cells relative to the recording array can be modified with DNA-directed immobilization (52). This enables precise placement of cells on electrode pads, thereby improving recording sensitivity. Organic components have also been used as optical and visual sensors. As mentioned above, muscle cells have been optogenetically modified to contract in response to specific light cues, allowing local position control of small PDMS blocks (43, 44) and steering of a stingray-inspired robot (33). Furthermore, the walking robot initially presented by Cvetkovic et al. (45) has been further developed to include optogenetically modified cells for stimulation (53), demonstrating similar locomotion capabilities between electrically stimulated and optogenetically stimulated devices. The slime mold *Physarum polycephalum* can also be used as an optical sensor (54).
Physarum exhibits phototaxis behavior, and regular oscillations in the cell’s surface potential are measurable via external electrodes. Adamatzky (54) has demonstrated that a slime mold cultured across two electrodes displays unique changes in surface potential in response to red, blue, and green light but did not exhibit discrimination between green and white light. This phenomenon could be used for the future development of slime mold circuits and robots.

Biohybrid systems can also be used to create tactile sensors. In such platforms, mechanical stimulation of the biological components results in changes in membrane potentials of the cells that are monitored via electrodes. This technique has been previously used with fibroblasts, and even with slime mold, serving as the biological components. In 2011, Buselli et al. (55) developed a stretchable skin-like sensor in which a cell monolayer was seeded on a PDMS substrate in a 100-µm gap between two Au/Ti electrodes. Stretching the PDMS substrate applied mechanical loads to the cells, resulting in the activation of ion channels and subsequent changes in intracellular ion concentrations. Using similar concepts, Cheneler et al. (56, 57) proposed a fibroblast-based sensor in which the cells were encapsulated in alginate between a PDMS cover and a conductivity sensor. Microfluidic channels were incorporated into the base of the device to provide nutrients to the cells. Rather than sensing the lateral stretch of the cell culture substrate, the sensor responds to pressure to the PDMS cover above the cell-laden alginate. Such pressure sensors can be developed with a variety of cells. Using Madin-Darby canine kidney cells, Salgarella et al. (58) developed a biohybrid tactile sensor and investigated the effect of including a hydrogel layer over the cells as compared with only growth media, finding an improvement in sensor performance in the growth media alone.

Because the fundamental principle behind using living cells in biohybrid tactile sensors is the mechanochemical properties of cell
membranes and ion channels, the concept is not limited to mammalian cells. Adamatzky (59) has previously presented a tactile sensor using P. polycephalum as the living component in a biohybrid sensor. Physarum exhibits natural periodic oscillation in surface electrical potential with amplitudes ranging from 0.1 to 5 mV. To use Physarum in a biohybrid tactile sensor, Adamatzky cultivated a single Physarum cell between two electrode pads. Pressure to the protoplasmic tube that formed between the pads resulted in measurable spikes in membrane potential and alterations in the overall oscillation. Similarly, bristles can be attached to the electrodes, and the Physarum will grow around the base of the bristles (60). Deflection of the bristle then resulted in a measurable voltage change across the electrodes. A more detailed review of biohybrid and bioinspired tactile sensors can be found in the study of Lucarotti et al. (61).

**Tissue- or organ-based devices**

Whole-organ sensors in robotic systems have primarily used insect tissues as visual or olfactory sensors. The visual system of the blowfly, specifically the H1 cells, has been used to provide visual input to a robotic system (62, 63). The H1 cells are excited by back-to-front visual motion. The blowfly was mounted on a wheeled robotic platform, and extracellular electrodes were used to record from the cells of interest (Fig. 5B). The robot was preprogrammed to move in a sinusoidal pattern to provide back-to-front visual motion with a front-facing blowfly. Sensory input then served to modify the trajectory of the robot so that it could follow a wall down a corridor.

Early biohybrid olfactory sensors used insect antennae to provide sensing capabilities. In 1995, Kuwana et al. (50) built a robotic platform that read sensory input from the isolated antennae of silk moths. This robot consisted of a simple synthetic motor-driven platform. Two isolated antennae were attached to an amplifier that provided input to a microprocessor. When pheromones were sprayed on the right sensor, the robot turned to the right, and when sprayed on the left sensor, the robot turned to the left. Using insect-based electroantennograms, Myrick et al. (64) demonstrated the ability to discriminate odors in real time using four to eight antennae to provide electrical inputs to a classifier. However, the longevity of the isolated antennae was low (30 to 90 min). Therefore, Myrick and Baker (65) modified their four-channel electroantennogram to hold four live moths, thus reducing the problems of longevity. With this platform, they were able to locate a distant odor source, although the system was not mounted on a robotic platform.

More recently, Martinez et al. (66) have developed a mobile platform using a synthetic base and controller with organic sensors. As with Myrick et al.’s live moth electroantennogram, Martinez et al. have developed a device in which an intact moth is mounted on a robotic platform (Fig. 5A). Electroantennograms are then recorded from the animal. This resulted in a longer operating time for the sensors than those observed for Kuwana et al.’s mobile platform. Whereas isolated antennae showed an exponential decay in output over a few hours, the use of the intact animals showed no such decrease over an 8-hour trial period.

Olfactory sensors have also been developed using intact mammalian tissues. In 2010, Liu et al. (67) developed a “bioelectronic nose” by recording extracellular potentials from intact olfactory epithelium isolated from rats. By isolating intact tissue, Liu et al. maintained the functional structure of the organ, including the support cells and the receptor neurons, along with any spatial structure associated with each neuron’s unique odorant response. Using power spectrum analysis, this sensor could discriminate between two different odorants. Using this platform, Liu et al. (68) subsequently developed a system capable of distinguishing between four odors presented in real time. As with the intact moth electroantennograms previously discussed, mammalian tissues do not necessarily need to be isolated to be used as olfactory sensors. In 2013, Dong et al. (69) used in vivo recording from a single site within the olfactory bulb of rats via a brain–computer interface (BCI) to achieve odor sensing accuracies of up to 95%. Although the system demonstrated high sensitivity to odor stimuli, the neural activity was not analyzed to distinguish between different odors.

**Organic controllers**

The vast majority of research into onboard organic controllers for mobile robots to date has focused on the development of cell-based
devices. These systems used dissociated neurons with electrodes or multielectrode arrays to record from and stimulate cultured neural circuits. Furthermore, recent research has begun to investigate the use of whole ganglia, intact clusters of neurons, as simple onboard controllers for muscle-actuated robots. In addition, off-board organic control can be achieved using BCIs. Two overarching categories of BCIs exist: those in which the interface is used to externally control an organism (i.e., cyborg drones) and those in which the organism controls mobile elements or external devices via the interface (e.g., functional electrical stimulation of leg muscles to bypass spinal cord injuries). This distinction is based on the locus of the goal setting for the biohybrid device. In the case of cyborg drones, an external user dictates the goals of the organism, whereas in most rehabilitation applications, the patient’s goals dictate changes in their body or external systems (internal goal BCI). For the purposes of our review, we classify cyborg drones as organism-based devices (see the “Organism-based robots” section), whereas we will discuss internal goal BCIs in the context of organ-based control. Because BCIs are a prevalent tool in neurorehabilitation research and have been extensively reviewed elsewhere, we will only briefly discuss such systems in the context of mobile robots. Interested readers are encouraged to refer to the recent BCI reviews by Lebedev and Nicolelis (70) and Pohlmeyer et al. (71).

**Cell-based devices**

To develop organic controllers, researchers have often used neurons cultured on electrode arrays so that they may record from and stimulate the neurons. In early efforts to use living neurons to control an artificial system, DeMarse et al. (72) demonstrated the ability of cortical neurons cultured on a multielectrode array to control a simulated animal. Although the simulation received input from the living culture and, in turn, provided sensory feedback in the form of stimulation to the cells, the simulation was not trained to perform any particular task. Similar neural cultures have been used to control external mobile robots for more specific goals (73). For example, using a Khepera robot, Novellino et al. (74) developed a bidirectional neural interface that allowed the small wheeled robot to perform obstacle avoidance in an arena while under the control of cultured neurons. In 2010, De Santos et al. (75) developed a system using neuroblastoma cells, in which cell activity was recorded and processed (Fig. 6A). Control signals were subsequently transmitted to a remote mobile robot system. Similarly, Warwick et al. (76, 77) developed a robot using a synthetic wheeled platform. To control the robot, about 100,000 cortical neurons were cultured on a multielectrode array. The neural activity served as input to the platform’s actuators, and the cultured cells were stimulated based on signals from onboard ultrasonic sensors to provide feedback. Although the device would turn in response to the presence of a wall, demonstrating closed-loop capabilities using neural control, it also generated spontaneous turns, in which no stimuli were present, at a higher frequency than meaningful turns. In fact, 54% of turns were spontaneous.

Neural cultures have also been used to control robotic drawing arms, bringing together biology, art, and robotics (78, 79). As with neuron-controlled mobile robots, this system used multielectrode arrays to record from and stimulate living cells. The neural culture was used to control two robotic arms, each grasping a pen. The activity of the neurons was transmitted remotely to the arms, which subsequently drew using the pens. A camera mounted above the drawing then transmitted sensory information back to be input to the neural culture. In this way, the platform could be installed in art galleries around the world (78).

Cultured neurons are often combined with artificial intelligence techniques to serve as controllers. For example, in 2011, Hayashi et al. (80) presented a neuron-controlled mobile robot in which they used fuzzy logic to have the device follow a line (Fig. 6B). Signals from the neuron culture were represented as fuzzy If-Then rules, and activity...
in the culture controlled motor speed. Using this system on a commercially available Khepera robot platform, the device could follow a line while avoiding wall collisions with an 80% success rate.

Furthermore, the potential learning capabilities of cultured neuron controllers have also been investigated. Building on the Khepera platform developed by Novellino et al. (74) discussed earlier, Novellino et al. (81) subsequently incorporated a learning phase to enforce obstacle avoidance as the robot navigated an arena. Conditional stimuli were provided as a pairing of tetanic bursts with low-frequency stimuli when the robot struck an obstacle (82). Following this training protocol, the robots exhibited a 30% decrease in the number of obstacles struck. In 2016, Li et al. (83) developed a robotic system in which cultured neurons controlled the robot’s heading by stimulating turns based on received inputs such that the robot would move toward an object. Li et al. showed that providing high-frequency training stimuli when the robot turned the wrong way significantly improved the robot’s correct turning ratio. Human neurons differentiated from human fetal neural stem cells (obtained from donated miscarried fetuses) have also been used to investigate learning and operate a small mobile robot. Pizzi et al. (84) developed a control architecture using these human neurons cultured on a microelectrode array as a pattern classifier. Patterned stimuli were provided to the culture, and subsequent responses were recorded using the electrode array. An artificial neural network (ANN) was then used to process the output and provide information to the robotic platform.

**Tissue- or organ-based devices**

Incorporating the natural neural architectures can enhance the effectiveness of organic controllers. Researchers have primarily used cultured cells rather than intact isolated tissues as controllers for mobile robots in vitro. However, in 2017, Webster et al. (85) developed a mobile biohybrid robot using the natural neural circuitry and neuromuscular junctions from *A. californica*. This robot used an intact muscle [the I2 protractor muscle (86)] from the animal’s feeding apparatus as an actuator. Native innervation from the buccal ganglia (motor control) and the cerebral ganglion (higher-level control) was kept intact. The muscle and associated ganglia were then mounted in a 3D-printed, inchworm-inspired body that isolated the cerebral ganglion from the rest of the circuit, allowing chemical stimulation to be applied to it, without directly stimulating the muscle. The application of carbachol, which is known to induce biting patterns in semi-intact in vivo preparations (87), resulted in cyclic contraction of the muscle, without the use of external electrical stimulation. In this way, the ganglia acted as a motor controller for the muscle, thereby producing locomotion.

Another way to incorporate natural neural architectures is to use BCIs. Most BCI research is geared toward functional restoration after stroke or spinal cord injury through the use of implanted electrodes. Using implanted electrodes enables direct mapping of neural signals for controlling robotic arms and prosthetics, as well as driving wheelchairs. In 2000, Wessberg et al. (88) demonstrated the ability to train owl monkeys to control a robotic arm in real time via implanted microwire arrays in the cortical areas of the frontal and parietal lobes. The ability of primates not only to control robotic arms but also to provide whole-body movement via a BCI-controlled wheelchair has also been demonstrated using implanted electrodes (89). Monkeys were placed in a chair mounted on a wheelchair base and were trained to control the wheelchair to move toward a food reward station. Initially, the wheelchair was driven externally so that the monkeys observed that motion to the feeding station resulted in a reward. Subsequently, both monkeys learned to navigate to the reward station using the interface. Over the 3- to 6-week experimental period, both monkeys achieved significant reductions in travel time, indicating improved control abilities (89). Implanted electrodes have also been used in humans with tetraplegia to control reaching and grasping with a robotic arm (90). Using 96-channel microelectrode arrays implanted in the motor cortex of each participant, Hochberg et al. (90) decoded spiking signals to use as control inputs for a robotic arm. Success rates in reaching and grasping trials ranged from 47.9 to 95.6%.

The natural neural architecture may generate noninvasive signals that can also be used for control. Although many patients with severe motor disabilities would be willing to accept implanted electrodes (91), noninvasive solutions are needed for many applications, particularly remote control of robotic systems by healthy individuals. Noninvasive BCI systems have been developed that use external sensors to monitor brain activity and translate the signals to control commands. Examples of such systems include electroencephalographic (EEG) control of wheelchairs (92–94), humanoid robots (95), and telepresence platforms (96). With EEG control, users are instructed to execute mental tasks that correspond to higher-level control concepts. For example, the wheelchair control system developed by Galán et al. (93) required users to execute three mental tasks, including imagined left-hand movement, word association, or mental rest, that corresponded to the wheelchair turning left, turning right, or going forward, respectively. To control a humanoid robot, the system developed by Bell et al. (95) used EEG signals corresponding to patient focus on higher-level concepts, such as objects and locations in the testing arena, to provide goals and behaviors to the robot, which then autonomously completed the commanded task. EEG-based BCIs have even been used to control cyborg drone cockroaches (97), as described in the next section.

**Organism-based robots**

More traditional engineered components have also been used to “hijack” living systems. Such “hijacked” systems have been developed with bacteria, spermatozoa, protists, and insects. Several devices have used bacteria or protists to provide actuation, sensing, and control by attaching single-celled organisms to a synthetic structure. In 2012, Kim et al. (98) demonstrated that bacteria could be attached to the surface of polystyrene microbeads. The hybrid system would subsequently locomote toward a chemoattractant without outside input. In this case, the attached bacteria were sensing the chemoattractant and actuating their flagella to propel the microbeads. In 2014, Park et al. (99) demonstrated similar chemical gradient navigation with bacteria. In contrast to the device developed by Kim et al. (98), Park et al. (99) used selectively patterned microbeads that resulted in bacteria attaching to a specific hemisphere of the bead. This served to coordinate the actuation of the bacteria such that the flagella pointed in a more uniform direction. Similarly, in 2015, Barroso et al. (100) developed an optical assembly technique that allowed a bacterium to be attached to individual zeolite L crystals. The assembled devices could locomote in response to a chemical gradient.

Rather than using chemical gradients to direct bacteria, some devices make use of magnetism. A single bacterium can be captured in a magnetic microtube. The swimming bacterium becomes a bioengine to drive the microtube, which can be steered externally via a magnetic field (Fig. 7A) (101). In addition, by using MC-1 magnetotactic bacteria, the swimming direction of the bacteria can be influenced directly by application of a magnetic field that applies a torque to a single chain of membrane-bound magnetic crystals (102). Using this mechanism, swarms of bacteria can be formed, which could be used to manipulate
small blocks. When using nonpathogenic, magnetotactic bacteria, such as MC-1 or MSR-1, these devices have demonstrated applicability in targeted drug delivery (103, 104).

Similarly, swarms of protists have been used to manipulate objects. In 2008, Itoh and Tamura (105) used the phototaxis capabilities of *Euglena* to form swarms of organisms (Fig. 7B) capable of transporting particles requiring up to 70 nN to move. Swarms could be guided at speeds of 1 to 5 μm/s. Negative inhibition of actuating bacteria can be used to control object manipulation. In 2013, Wong et al. (106) developed microrobots by attaching bacteria to the surface of polymer (SU8) objects. By applying ultraviolet light to certain regions of the object, bacteria at those locations could be immobilized, allowing control over rotational motion.

Whereas bacteria and protists have been used to steer microparticles, flagellated animal cells have also been used to provide actuation. Rather than using an organism to drive a synthetic structure, Magdanz *et al.* (107) developed a technique for steering spermatozoa. Spermatozoa were confined in magnetic microtubes, and the orientation of the microtubes was controlled by application of an external electric field. Therefore, the flagellar action of the spermatozoa provided forward thrust, whereas the microtubes provided heading control.

Engineered control systems have also been used to hijack much more complicated organic systems. Because the goals of such devices are set externally, we refer to these as “cyborg drones.” Insects have been the primary focus for the development of autonomous cyborg drones, as has been reviewed previously (108). We will provide a brief overview of previous work and discuss more recent devices. In such devices, the sensory-neural system of the insect is stimulated in response to external input to control the locomotion of the insect. In 2009, Sato *et al.* (109, 110) demonstrated the ability to remotely control insects in free flight via an implantable neural stimulation system. Flying beetles were equipped with onboard stimulation systems that allowed initiation and cessation of flight, as well as elevation control, to be elicited via neural stimulation of the brain, whereas turning was controlled via direct stimulation of the basilar muscles. More recently, Sanchez *et al.* (111) demonstrated locomotion control of a cockroach via stimulation of the prothoracic ganglion (Fig. 7C). They found that the turning radius could be controlled by varying either the frequency or voltage of the stimulation. Such cyborg drone insects can also be controlled via sensory organs. In 2012, Latif and Bozkurt (112) modified a cockroach so that it was capable of line following when the appropriate antenna was stimulated. Using such techniques, cockroaches have been modified so that they can be controlled by human subjects via a BCI (97). Although the success rates were low (20%), this demonstrates the ability of human operators to potentially control other organisms. Furthermore, insects provide a possible power source for the onboard electronics needed for control. Schwefel *et al.* (113) have demonstrated that by using a biofuel cell implanted in a cockroach’s thorax, energy available in the animal’s hemolymph can power onboard electronics for wireless communication.
The use of organisms for biorobot fabrication is not limited to insects. In 2012, Zhu et al. (114) developed an intestinal biorobot using the mud eel as a source of locomotion for a potential endoscopy system. The mud eel was encapsulated in an outer shell, and locomotion was controlled by stimulating the eel via a surface-mount microelectrode (Fig. 7D). The encapsulated eel was capable of navigating a simulated intestinal tract, as well as sections of isolated intestine, at rates of 12 to 24 mm/s.

**ALLOMETRIC SCALING IN ROBOTS WITH ORGANIC COMPONENTS**

Can general principles be derived for robots that incorporate organic elements? To achieve this goal, there should be more consistency in robotic metrics reported for each device, making device-to-device comparisons, and the development of design guidelines, possible. In our efforts to investigate scaling laws in such devices, we assessed 28 research articles that reported mobile devices and performance metrics (indicated by asterisks in Table 1), excluding cyborg drones. These articles provide a sample of the field, including a range of size scales, actuators, and materials. Cyborg drones were not included in this analysis, because they are fundamentally animals upon which an electronic control system is built. Most cyborg drones use the animal’s natural locomotion abilities and only apply turning or locomotion initiation cues. As a consequence, their allometric length-velocity scaling would coincide with the animal systems on which they are constructed.

Typical robotic metrics were reported as follows: mass (6/28), speed (21/28), dimensions (23/28), actuator force (7/28), device success rate (10/28), and cost of transport (0/28). Some of these metrics, such as cost of transport, may be difficult to determine because of the nature of the robotic systems. However, metabolic assays may report robot parameters and metrics, as is common in traditional robotics. Such metrics include mass, speed, actuator metrics, device success rate, and cost of transport. In addition, current biohybrid and robotic devices exhibit substantially lower speeds than similarly sized animals moving in similar environments. The robots with the highest Reynolds numbers made use of intact or native muscle rather than dissociated cells. Future research should either seek to maintain or better mimic the natural structure of muscle or focus on locomotion modes appropriate for the Reynolds number regimes in which the robots are expected to function.

**A NOMENCLATURE FOR DESCRIBING ROBOTS WITH ORGANIC COMPONENTS**

As with the performance metrics currently reported for robots with organic components, there is inconsistency in the language used to describe such devices. It is important to understand how the language of the field is developing and to ensure uniformity in linguistic designations across research groups. Robots with only organic components, robots with both synthetic and organic components, and robots using traditional materials (i.e., “nuts-and-bolts” robots) whose designs are inspired by biology all incorporate biology and robotics. As a consequence, the terms describing such devices have overlapped so that literature searches inevitably turn up results for all three kinds of devices.

To better understand how organic, hybrid, and synthetic bio-inspired robotic systems are described, we have analyzed 51 articles, including 3 reviews on biologically inspired robots. From each article, we have identified key terms used to describe the devices. Such an analysis reveals that a wide range of terms is used to describe these devices, ranging from highly specific terms such as Flora robotica (17) to vague terms that fail to convey the presence of organic components (e.g., robot). Furthermore, “biohybrid,” “robot,” and “machine” are used most commonly to describe the analyzed systems with organic components (used in 12, 11, and 8 papers, respectively). However, with the most commonly used word appearing in less than 25% of the papers analyzed, the inconsistency in keywords is apparent. A consistent vocabulary is needed to enable researchers to readily locate research of interest. To propose a unifying lexicon, we first turn to the RTK presented earlier. Fundamentally, the key first asks a simple question: Is the device completely synthetic? If the answer is “yes,” the language is simple. The device is a synthetic robot. Because organic components are introduced, the vocabulary is no longer so straightforward. Although the term biohybrid is commonly used in existing literature and accurately describes devices combining organic and synthetic components, it fails to fully describe all devices in the field, because there is growing interest in completely organic devices. We propose that the term biohybrid be used categorically for devices with both synthetic and organic components. The RTK can also guide the choice of additional keywords to provide further clarification about the device, such as specifying which components are organic (e.g., cardiomyocyte actuation). In cases where the device relies on an existing living organism, details about the organism should be clarified, such as using the term “cyborg drone” for devices that rely on steering a living multicellular animal, and organism-specific terms, such as
“Bacteriobot,” for devices that use single-celled organisms. In addition, we propose a novel term, “Organobot,” to describe robotic devices consisting of solely organic components. To aid in choosing consistent keywords and terminology, we have developed a dichotomous key (fig. S1) and taxonomy (fig. S2). Both tools can grow to include future technologies. In addition, table S1 demonstrates how these terms would apply to devices previously reported in the literature.

CONCLUSIONS

Structure, actuation, sensing, and control make up the fundamental building blocks of robots. To date, devices have been developed with organic structures, organic actuators, organic sensors, and organic controllers separately, but a true complete organobot has yet to be produced with all four components. Although we have presented a range of exciting devices, considerable work remains to be done. Current biohybrid devices and preliminary organobots are very simple when compared with more traditional robotic systems. They are often only able to perform one function and lack the sensorimotor control system needed to perform complex tasks. However, recent developments in both tissue engineering and organic controllers suggest exciting possibilities for such devices in the near future.

Developing a consistent nomenclature is critical for unifying any field. For example, the use of genetic sequencing in the identification of ion channel genes has led to consistent naming conventions that better allow study and classification of new excitable tissues (134). A consistent naming scheme enables classification, facilitates concise communication of key concepts, and reveals gaps in the field that can lead to the development of novel devices. The RTK presented here will be of value for all of these reasons. Similarly, developing consistent metrics for these robots will make comparisons possible and lead to general design principles for such robots.
Current limitations in the use of organic components in robotics

Despite recent developments in the field of biohybrid and organic robotics, there are still many limits on the use of organic components as structures, actuators, sensors, and controllers that will need to be addressed in the future. Many of these limitations stem from the effect of the structure on actuators, sensors, and control, particularly when working with cell-based components. For example, actuators made from cells seeded on an isotropic structure lack the organization of native muscle. To compensate for this lack of organization, micropatterning or aligned structures can be used to induce cellular organization. However, such devices have largely involved 2D structures or used a single extracellular matrix component. As a consequence, the cultured tissue lacked the full 3D organization and robustness of native muscle. Similarly, maintenance systems will need to be built into the structure of these devices to support long-term performance. Existing devices lack the vasculature needed to support long-term maintenance of cultured cells or to provide nutrients to muscle tissue-based actuators. In addition, current devices have been engineered without regard to the protective mechanisms (e.g., immune system and skin) needed to allow devices to function outside of research laboratories. Finally, in animals, muscles interact with complex supporting structures in many ways (e.g., musculoskeletal systems, muscular hydrostats, and hydrostatic skeletons) (135, 136). These organizational structures allow animals to perform complex behaviors and can provide inspiration for future organic robots (137). Advances in bioprinting and biofabrication are likely to allow future devices to better replicate the supporting structures needed for robust robotic systems.

However, current limitations are not restricted to the structural components. Biological systems are highly interdependent, and to consider any component alone is to eliminate some supporting mechanisms. For example, removal of the nervous system from actuating cells or tissues may eliminate the modulatory effects observed when muscle is natively stimulated by motor neurons. Similarly, isolating a nervous system from sensory and actuating units essentially eliminates the feedback system through which native nervous systems function. Although organic controllers have been developed for synthetic mobile robotic platforms, such controllers have yet to be used for higher-level control of organic actuators. In addition, in such cases, the neurons have been used to perform input-output transformations rather than make complex decisions. Therefore, it is possible that the neurons could be replaced with more traditional computing techniques such as ANNs. In the future, it will be important to demonstrate that cultured neural controllers have advantages over ANNs—for example, in their robustness to damage or unexpected inputs—to convincingly justify their use. It may be possible to exploit natural neural architectures that are capable of performing complex processing and decision-making (e.g., the cerebellum) to control future devices.

Challenges

Clearly, many exciting robotic devices have been developed using organic components, but many challenges exist before such devices are deployed in the field. Currently, there are no field-specific software tools to aid researchers in the design and prototyping of robots with organic components. As a consequence, in the immediate future, there is a need to create engineering tools and computational frameworks for the design and simulation of novel biohybrid and organic systems. This necessitates multidisciplinary collaboration to bring together simulation techniques from neurobiology, dynamics, and soft body modeling to build a toolbox akin to those that exist for traditional robotic simulation and development. Efforts toward this goal are beginning. For example, Raman et al. (138) have developed a modular protocol for designing and fabricating legged muscle-powered biohybrid robots, which is an important step toward the development of future design platforms.

In addition, as researchers move toward the use of neurons as organic controllers, they will be adding additional layers of complexity to the devices, with substantial unknowns. To advance the field, there is a need to better understand animal nervous systems either to grow our own organized cell-based control architectures or to exploit and retrain existing nervous systems to obtain complex autonomous control. This will likely require new mathematical frameworks, such as the Dynome (139), allowing for growth patterns or training protocols to be tested computationally before the biological implementation. Along with fundamental biological research to better understand the nervous system, further efforts are needed to ensure that muscle activation is efficient to limit device fatigue.

Furthermore, the nature of the organic components means that a continuous source of nutrition or power must be integrated into biohybrid and organic robots, especially for long-term operation. For shorter missions, nutrients may be provided by a fluid bladder and perfusion system. However, for longer missions, systems will need to be developed to extract nutrients from the environment. For biohybrid devices with synthetic electronics, a power source will be needed. In the case of insect-based cyborg drones, researchers have demonstrated the potential for the insect’s own hemolymph to serve as a biofuel cell to power onboard electronics (113, 140, 141). In the future, power systems will be needed to support not only cyborg drones but also cell-based devices. To this end, it may be possible to develop supporting media inspired by hemolymph to build in such fuel cells or to incorporate external microbial fuel cells to provide power (142). Alternatively, contractile cells themselves can be used to generate power for synthetic components via deflection of piezoelectric microcantilevers (143). Larger biohybrid robots and organobots may use more traditional robotic power supplies such as batteries or solar panels. In addition, the presence of organic material makes such devices targets for bacteria and other contaminants. This also presents a major challenge for researchers seeking to create devices for long-term operation.

Last, in any research involving tissue or cells, there are many ethical concerns that must be considered. The development of biohybrid robots and organobots is subject to many of the same concerns facing more traditional tissue engineering, such as the ethical procurement of cells or tissue as well as proper animal treatment for research using primary cells or tissue explants. In general, the costs of using animals should be weighed against the benefits of the potential robots made from animal components if doing so will induce pain or take the life of the animal. Such device development also presents unique questions and challenges, especially as the field progresses. With the development of more autonomous devices with advanced peripheries, concerns begin to arise over the possibility that the device may experience pain or stress or may even begin to exist as a living organism unto itself. Autonomy may also imply that the device pursues its own goals, rather than those of its original fabricator, and these goals may have problematic consequences. These concerns will need to be addressed as the field progresses.
Future directions
Beyond the challenges facing the field, there are several additional promising avenues for the development of future organobots. To improve actuation, devices should attempt to replicate the 3D environment of muscle tissue to make use of structural cues from the extracellular matrix. Three-dimensional bioprinting offers one exciting avenue for such developments (144). For organic actuators in large-scale robots and bioprosthetics, a vascular system providing nutrient-rich fluid will be necessary for long-term operation. Recent advances in tissue engineering point to many approaches that can be integrated into future organobots (145). With further development, biohybrid devices, organobots, and cyborg drones have a bright future in many fields: from microscale devices capable of navigating the human vascular system and performing maintenance and diagnostic tasks to the development of vascularized mobile platforms for environmental monitoring and bioprosthetics. The development of robots with organic components is a growing and exciting area of research.

SUPPLEMENTARY MATERIALS
robotics.sciencemag.org/cgi/content/full/2/12/eaap9281/DC1
Fig. 51. Dichotomous key.
Fig. S2. Taxonomy.
Table S1. Example of dichotomous key usage.

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Organismal engineering: Toward a robotic taxonomic key for devices using organic materials
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