SOFT ROBOTICS

Biomedical applications of soft robotics

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Abstract | Soft robotics enables the design of soft machines and devices at different scales. The compliance and mechanical properties of soft robots make them especially interesting for medical applications. Depending on the level of interaction with humans, different levels of biocompatibility and biomimicry are required for soft materials used in robots. In this Review, we investigate soft robots for biomedical applications, including soft tools for surgery, diagnosis and drug delivery, wearable and assistive devices, prostheses, artificial organs and tissue-mimicking active simulators for training and biomechanical studies. We highlight challenges regarding durability and reliability, and examine traditional and novel soft and active materials as well as different actuation strategies. Finally, we discuss future approaches and applications in the field.

The application of robots in the biomedical field dates back a few decades, but recently, the use of soft matter in robotics[1] has enabled new robot abilities[2] that open up possibilities for biomedical applications[3] in which a soft interaction with a patient is preferred. For example, in surgery and endoscopy, robots operate inside a human body, and for rehabilitation and assistance, robots are in physical contact with a patient. Moreover, robotic technologies can be used as prosthetics to replace human limbs or as artificial organs and body-part simulators to mimic human body parts, and finally, robotic devices can be integrated inside or on the skin for drug delivery.

Biocompatibility and biomimicry are key considerations for soft robotics in biomedical engineering (FIG. 1). The materials used in soft robotics need to be compatible to a certain extent with the human body and tissues to guarantee system functionality and body acceptability; however, to what extent depends on the specific biomedical application. For occasional external use, allergies and contact reactions need to be taken into account; for temporary internal use, immediate immune responses need to be considered, and long-term implantation of soft robotic devices affects the long-term immune response and can possibly cause rejection. The materials also need to match the mechanical properties of human tissues to a certain degree. For example, the use of soft robots as prostheses, organs, simulators or implantable replacements requires mimicking of the mechanical properties and function of human tissues.

In this Review, current biomedical applications of soft robotic technologies are discussed from a materials science perspective. We survey applications of soft robots as medical devices for surgery, therapy, drug delivery, rehabilitation and assistance as well as robots that mimic the human body. Scientific challenges related to the identification and integration of available and emerging soft and smart materials, such as biocompatibility, biomimicry, actuation[4] and tuneable stiffness[5], are discussed, and robotic design is examined in the context of orchestrated actuation, control and sensing[6].

Medical devices

Soft robotic devices for surgery. Surgery has undergone a profound revolution in the past 30 years, from open surgery to minimally invasive procedures, which provide advantages such as greater safety and reduction of access trauma, resulting in faster recovery and scar limitation. Especially in abdominal operations, minimally invasive surgery (MIS) has become the gold standard. Normally, MIS is performed by introducing two to three long and rigid tools into the insufflated abdomen through small incisions (about 10–15 mm in diameter) to perform surgical tasks assisted by a rigid laparoendoscope for endoscopic vision. In some procedures (for example, in single-port laparoscopic surgery), surgeons create one larger incision (about 20–40 mm) at the patient's navel, and several semi-flexible instruments are introduced through this incision. This approach reduces the number of necessary abdomen access ports but can lead to the problems of tool encumbrance and triangulation[7]. MIS can also be accompanied by specific procedures to better reach the target organs through natural orifices. For example, a flexible endoscope, endowed with multiple miniature tools on the tip, is introduced through a natural orifice, such as the mouth, vagina or anus, to then perforate the internal wall of an organ. This procedure is called natural orifice transluminal endoscopic surgery (NOTES)[8]. In all traditional MIS procedures, the passage towards the surgical target can be obstructed by the presence of organs or anatomical structures. Thus,

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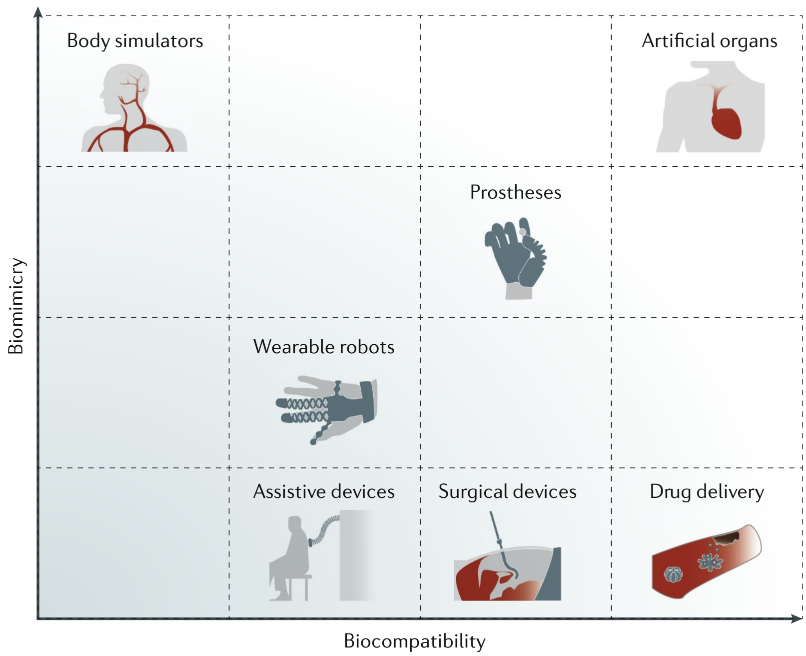

Fig. 1 | **Biomedical soft robots from a materials perspective.** Levels of biomimicry and biocompatibility are compared.

up to five abdominal incisions are often required because of the use of rigid or semi-rigid tools with limited dexterity, flexibility and manoeuvrability. Even in NOTES or single-port surgery, reachability can be a crucial issue, as is instrument clash during the operation, which increases the overall complexity of the procedure[9].

Robotic technologies can help surgeons to improve their accuracy, predictability and repeatability by restoring the intuitiveness of the procedure and by providing additional dexterity to the tip, which was demonstrated by the success of the da Vinci surgical robot (Intuitive Surgical); however, this procedure still requires rigid and inflexible tools, except for wrist articulation. By contrast, flexible instruments have high intrinsic flexibility and can be used in synergy with MIS procedures, but they are often long and flexible with a swivelling tip, which implies that they also have low dexterity once they reach the surgical site. Moreover, they can apply only limited force and they lack stability[10]. From a medical point of view, precision in surgery is mainly achieved by the use of rigid tools, traditional mechanical coupling and cable-actuated solutions. In endoscopy and catheter-like procedures, flexible tools are required that are less precise but more adequate to navigate through tortuous paths and to avoid obstacles to reach remote organs. In the field of surgical endoscopy, both approaches are combined, making endoscopic procedures as accurate and effective as traditional MIS procedures. Endoscopic and surgical devices are used for acute operations and not for chronic applications. Therefore, tuneable stiffness, organ compliance and overall safety are essential requirements for the device, but long-term immune reaction in response to the soft robotic device does not represent an issue.

Many active soft actuation technologies have been explored to implement flexibility, accuracy, safety and dexterity in soft surgical tools, among which the most promising strategies include new routing approaches to cable-driven flexible mechanisms, smart materials and flexible fluidic actuators (FFAs) (TABLE 1). Cable-driven approaches have the advantage of easy miniaturization (in the case of external positioning of the motors) and light weight, but they are generally expensive and suffer from sterilization problems and mechanical limitations such as fatigue, nonlinear friction, backlash hysteresis and inadequately transmitted forces[11]. Smart materials address some of these issues and thus have been explored not only for traditional endoscopic or surgical procedures but also for catheter-like procedures that require miniaturization. For example, shape memory alloys (SMAs) have been extensively investigated owing to their excellent properties, including high corrosion resistance, biocompatibility and non-magnetic behaviour. Moreover, they possess high energy density, can exert localized forces and can be fabricated in several shapes and dimensions. SMAs enable on-board actuation with direct transmission on a small scale. In addition, owing to their working principle, they perform better and faster when in the configuration of small wires, maximizing heat exchange and minimizing the current required for the Joule effect. Several catheters[12], active endoscopic capsules[13] and one-shot miniature surgical tools (Ovesco) have been developed, aiming to find the best compromise between actuation speed and controllability.

However, SMAs have several severe limitations, including limited strain, low speed (low bandwidth that is heavily dependent on thermal characteristics), control issues (mainly owing to very complex thermomechanical behaviour) and the requirement of high currents to reach the activation temperature[11]. Thus, SMAs, often referred to as 'muscle actuators' because of their bio-like overall performance, have been increasingly used in their superelastic configuration. In this form, the alloy is in the elastic phase at normal working temperature and therefore able to recover its shape once the external load (producing a plastic-induced phase) is removed. The visible behaviour seems superelastic because the material appears to return to its shape after very large bending, which normally produces plastic deformation. Superelastic materials have been applied in cannula-like and continuum robots. These medical devices allow for an increase in working space and improve the reach of small-diameter catheters. They consist of superelastic concentric tubes, which are moved into each other by external motors to produce bent configurations able to reach remote locations. For example, continuum robots, that is, robots without rigid links that continuously bend along their length[14], have better reach than conventional rigid-link robots[15]. However, such robots cannot be considered soft because they contain rigid metals or alloys, the size of which is not altered in response to external forces. Force–contact sensors can be further integrated to control the interaction forces between the medical device and tissue.

FFAs, which are based on soft and shrinkable materials[16], address many of the aforementioned limitations. First used in colonoscopy[17], FFAs made of pneumatic bellows enable self-propelled locomotion, and FFAs made of expanding balloons increase the friction

Table 1 | **Soft robotics actuation technologies**

Technology	Acronym	Subgroups	Working principle
Flexible fluidic actuators	FFAs	McKibben, air muscle, pneumatic artificial muscles, fluidic elastomer actuators, PneuNets and PneuFlex	A flexible inflatable structure operated by a fluid. Modelling or adding of materials to introduce asymmetries enables the design of structures that deform into specific shapes
Shape memory materials	SMMs	Shape memory alloys, shape memory polymers and shape memory composites	Materials with the capability to recover a predetermined (memorized) geometrical shape through heating following plastic deformation. This shape memory effect is based on the specific mechanical properties associated with different stable crystalline phases
Electroactive polymers	EAPs	Dry (electric) and wet (ionic)	Polymers able to undergo deformations in response to electric fields
Tendon-driven actuators	–	–	Although not soft actuators, tendons exhibit very low flexural rigidity if pulled remotely and are often used in continuous soft robots
Material jamming	–	Granular and layer jamming	Systems composed of an external elastomeric membrane and a filler material. Applying a vacuum leads to the collapse of the membrane on the filling material, increasing the density and thus impeding the relative motion of the particles, which results in an increase in rigidity of the whole system
Electrorheological and magnetorheological materials	ERMs and MRMs, respectively	Electrorheological (fluids and elastomers) and magnetorheological (fluids and elastomers)	Materials that incorporate magnetic or electrical particles. In response to an external magnetic or electrical field, the particles are oriented and interact, resulting in greater resistance to deformation

between the device and the intestine walls. Such systems have been integrated in inchworm-like active colonoscopic systems. Current FFAs have many advantages for use in surgical devices. Their elastomeric nature and the fact that they do not need a direct electric source enable applications in the presence of radioactivity and magnetic fields (making them compatible with magnetic resonance imaging)[18]. Moreover, leakages from the chambers that interact with tissues can be minimized because there is no rigid motion[18,19]. FFAs are capable of complex movement using only a small number of parts[20]. Their compliance allows for safe interaction with surrounding organs and tissues and decreases the risk of damage[18,19]; finally, FFAs are made of biocompatible materials. Furthermore, FFAs that use pressurized gas are lightweight and can be inflated by low pressures[21], which makes them safe from an activation point of view. FFAs can be combined with other semi-active actuation technologies that enable rigidity control[5]. Such systems have a soft structure that allows them to reach the surgical site with dexterity, but they can also take advantage of the adjustable rigidity to stabilize the configuration and increase the stability of the robot for force transmission[11].

FFAs have been used as actuators for needle insertion and driving cannula robots[22], and in surgical instruments and manipulators[21]. Small catheters and manipulators can be realized by combining multiple chambers that can be pressurized differently. For example, the flexible micro-actuator (FMA), introduced in 1991, is based on a cylinder composed of silicone rubber reinforced with nylon fibres, which are circularly deposited, forming three internal chambers that can be individually inflated[23,24]. Alternatively, the chambers can be designed to act antagonistically in respect to a central floating flexible spine, which creates a neutral axis for the bending moment of the chambers[18]. A surgical manipulator with omnidirectional bending and elongation capabilities can be designed based on a similar concept. In this system, three fluidic chambers, but no internal spines, are embedded in a cylindrical silicone body. Thus, the simultaneous inflation of all three chambers results in a length increase. The system can be contained by a bellows-shaped sleeve[25] or inextensible threads placed around the individual chambers[26]. Alternative to differential pressurization, the device can be based on an anisotropic material composition. For example, pneumatic balloon actuators (PBAs)[27] are made of two flexible films; the upper film is made of silicone rubber and acts as membrane, and the lower rigid (but still flexible) polyimide film acts as the substrate. The two films are glued together to create a cavity that can be inflated. When pressurized, the polyimide film bends owing to the bending moment generated by the tensile forces of the silicone membrane. This behaviour results in a large out-of-plane vertical displacement. Bending is the most investigated actuation mode for fluidic-driven systems. However, fluidic pressure can also be exploited for surgical micromanipulators to induce rotatory motion, owing to the presence of radially and vertically arranged fibres[28], and torsion, owing to the combination of two FFAs with a rotational joint[29]. FFAs can also be used for the development of soft and effective tools, such as grippers. For example, FFA-based grippers can be composed of a plate that is placed along the trajectory of a bending FMA[30], of multiple bending actuators connected at their base[31] or of a linear fluidic soft actuator to actuate a traditional metallic claw[32]. The bending motion of FFAs has also been used to support task devices, such as retractors[33] and forceps[34].

Despite the ideal properties of FFAs, issues related to miniaturization and control have hampered their wider use in surgery thus far. Miniaturization involves the scaling down of the flexible fluidic actuator, which is challenging not only in terms of fabrication but also in

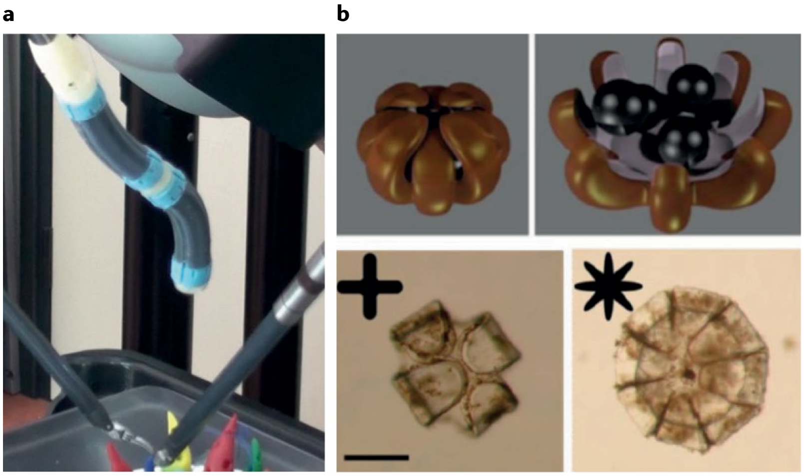

Fig. 2 | **Soft robots for surgery and drug delivery. a** | Stiffness controllable flexible and learnable manipulator for surgical operations (STIFF-FLOP) is a robotic manipulator for minimally invasive surgery. **b** | Concept (top) and photographs (bottom) of a soft device for drug delivery (scale bar = 100 μm). Panel **b** is adapted with permission from REF.[44], John Wiley and Sons.

terms of redimensioning. The fluid source can be placed outside the device, and thus its size does not have to be changed, but the rest of the fluidic system has to be redimensioned. Moreover, internally located valves are often customized because only a few suitable micropumps are commercially available (The Lee Company). Such valves often require a complex fluid distribution system[35]. Examples of approaches to miniaturize customized valves include classic spool valve design[36], which is composed of a series of membranes that are controlled electro–thermo–pneumatically as well as by a driving fluid[37], featuring actuated valves with freely suspended resistive heaters[38]. Alternatively, the pipes and their routing can be designed to achieve an off-board solution. However, such thin pipes are difficult to fabricate, and higher pressures are required to compensate pressure drops. Finally, manufacturing of miniaturized devices is problematic not only in terms of chamber fabrication but also if multiple materials and structures are combined to realize specific system behaviours, for example, containment fibres to obtain elongation or bending[39] or inextensible materials to create anisotropic rigidities. A simple solution is the introduction of geometrical asymmetries by using non-concentric moulds[40]. Elastomers also have highly nonlinear behaviour, making their precise modelling difficult and thus reducing possible control strategies.

For soft robots to replace traditional tools in endoscopic or surgical operations, extraordinary flexibility is required to enable the robots to perform simple tasks and to reach remote areas of the human body, and additionally, the robots have to be capable of exerting high forces for precise surgical operations[10] (for example, 2–6 N are required to make a suture). These features can be realized by implementing stiffness tunability or by designing hybrid solutions. For example, integrating soft-bodied robots made of silicones and braided sleeves into the da Vinci surgical system allows for the combination of the extraordinary ergonomic and intuitive control performance of the da Vinci system with the flexibility of the soft robot[41] (FIG. 2a).

Soft materials for drug delivery. If the target area for a therapy is very remote, as is the case for the inner parts of the brain, liver or pancreas, or if the therapy is based on the chronic release of a drug by implantable devices, endoscopic and surgical tools cannot be used. Navigating through the vasculature to reach small target areas and delivering drugs with a precise administration profile cannot be realized with wired surgical tools. Many soft materials used in soft robotics for drug delivery are based on hydrogels and biocompatible and biodegradable materials, which degrade over time to release their cargo. The release profile is only partially tuneable, and the reach often relies on systemic administration, with limited effectiveness. Such soft robots can be guided to a specific location, and the drug can be passively or actively released, for example, by using external stimuli, such as magnetic fields, ultrasound or temperature.

Micelles, nanoparticles, microcarriers and thin films can be used as drug delivery systems[42]. Thin-film technology was first introduced in the 1970s, with the aim of overcoming difficulties in ingesting tablets and capsules[43]. Thin films are made of conformable material layers, with thicknesses ranging from a few nanometres to hundreds of micrometres. Thin films have a unique combination of properties, including high flexibility, non-covalent adhesiveness, molecular permeability, large surface area, high aspect ratio and large drug-loading capacity. The inclusion of nanofillers, such as magnetically or optically responsive particles, within the thin films further improves the properties of the materials in terms of implementing material responses and endows the material with new functionalities, turning a rather inert polymeric material into a responsive matrix that can be remotely controlled. Traditional (passive) release usually employs the monotonic delivery of a drug, which can lead to adverse tissue reactions because of excessive drug concentrations. By contrast, active drug release through external stimuli allows for the temporal and spatial control of drug release and dosage, which enables long-term treatment, for example, for chronic diseases.

In the past 4–5 years, the field of soft microrobotics has explored microscale carriers made of hydrogels that incorporate magnetic particles for drug delivery. Such responsive nanomaterials can be applied for therapy or diagnosis, and the use of a soft shell reduces the immune response of the body. For example, an untethered, self-folding, soft microrobotic platform integrating different functionalities can be used for the targeted, on-demand delivery of biological agents[44]. This device contains magnetic alginate microbeads that are encapsulated in a bilayer hydrogel structure that is responsive to near-infrared light. The hydrogel structure is designed to seal and protect the beads and to open and release them once the surrounding temperature reaches 40 °C (FIG. 2b). A similar approach has been used for the development of soft microgrippers that can self-fold and possess thermomagnetic responsiveness[45]. To improve their grasping capability, a stiff segmented polymer (polypropylene fumarate) is added to the photo-crosslinked soft hydrogel, and iron oxide nanoparticles are embedded to enable remote magnetic guidance. Such approaches have been explored for many years and have only recently been collected under the umbrella of soft microrobotics because different scientific communities are exploring links with soft robotics, for example, regarding scalable biohybrid actuators[46]. Moreover, traditional lithography has been partially replaced by fabrication technologies that are based on soft materials, including silicones and a variety of other polymers as well as hydrogels, enabling the fabrication of various shapes of soft devices at the microscale.

Rehabilitation and assistance

Assistive robots represent a viable solution to the needs of an ageing society. Rigid-component robots can help in assisting a person in daily activities; however, a soft approach to robotics expands the possibilities for safe interaction and cooperation. In rehabilitation, robotic assistance is beneficial for delivering therapy and for restoring motor functionality[47]. The importance of active adaptable systems for assisting or replacing lower limbs rather than passive approaches was realized in the 1970s[48], and the beneficial use of adaptive systems for upper limbs was exploited in 1958 by Dr Joseph McKibben, who developed an assistive device based on fluidic actuators (which took his name) to restore the motion of the polio-paralysed hand of his young daughter. Assistive and rehabilitation systems share the same challenges: to guide limb mass displacements by providing the necessary force. Additionally, systems that operate in intimate contact with the user have to be effective and safe, and they have to apply force (often higher than the user force) without hurting the patient.

Wearable soft robots. Active adaptability can be achieved either by using compliance and impedance control on robots that are based on rigid links or by using soft robots made of materials that have intrinsic adaptive characteristics. Biomimetic approaches, such as muscle-like active technologies, including electroactive polymers (EAPs), SMAs and FFAs, have been employed with the aim of exploiting their intrinsic variable stiffness. With the emergence of reliable and effective soft mechatronic devices, robotic systems for rehabilitation and assistance gradually developed from rigid interfaces connected through bioinspired actuators to entirely soft wearable systems, with the active adaptable parts designed to stay in close contact with the user.

Simple assistive devices for lower limbs are based on rigid interfaces and rotary joints, which are attached to the body of the patient and driven by soft actuators, such as McKibben-like actuators, to support ankle[49] and hip[50] rehabilitation for ambulation. The same interfacing approach can be used with different types of soft actuators, for example, FFAs, whose restraining method is based on straight, inextensible fibres[51]. SMAs can also be implemented in assistive devices (for example, SHADE and Leia) to promote ankle dorsiflexion[52,53], with the drawbacks that the device components have substantial inertia, which interferes with the natural motion of humans, and that the joints have to be carefully aligned to the joints of the user to prevent unphysiological loads that can damage cartilage. These issues can be addressed by using soft and lightweight actuators that are in close contact with the skin of the user and that directly exploit human joints, without the need for external rigid structures[54]. However, in contact with the human body, SMA actuators have the disadvantage of thermal activation and thus need to be insulated. Moreover, additional interfaces and devices are often necessary to improve the response speed and working frequency.

Alternatively, pneumatic actuators can be employed for the development of more conformable and wearable robotic devices for ankle and foot rehabilitation[55]. Based on this concept, using cable-driven mechanisms, a whole-body soft exosuit has been designed for gait assistance[56] (FIG. 3a), exploring innovative textile materials that transmit assistive torques without the need for rigid external structures[57,58]. These garments passively generate assistive forces for particular tasks owing to their natural movement and can extend in response to movement of the user, thus not restricting the wearer. Different sensors can be embedded in wearable devices for force and deformation sensing, for example, elastomer-based sensors have been successfully mounted and tested on a soft exosuit[59]. These sensors are made of a liquid metal that is embedded in an elastomeric chamber. Elongation of the chamber produces a variation in the cross section that leads to changes in the longitudinal electrical resistance of the sensor.

Incorporating soft actuators into platforms based on rigid links has also been explored for upper limbs[60]. Such systems can be actuated by pneumatic artificial muscles and have the advantage of controllable compliance, providing a wide range of functionalities, as well as safety and light weight. Soft systems have also been developed for specific body parts, for example, the wrist[61], elbow[62], shoulders[63,64] and single fingers[65,66]; however, most efforts have been devoted to restoring hand functionality. To exploit the joints of the patient, hand devices are often shaped as gloves. This approach enables the patient to bend their fingers with enough torque to execute rehabilitation exercises or assistive tasks. However, such technologies, for example, the use of EAP[67], require high voltages, which can be dangerous to the user. Therefore, pneumatic actuators and tendon-driven solutions are being explored as alternatives.

Gloves can also serve as exomusculature by using an integrated cable system to open and close the hand of the patient[68]. A Bowden system is used to deliver tensile forces generated by servomotors (placed in a backpack) to the fingers, thus aiding extension and flexion. Each cable is passed through specific types of guides to maximize comfort. To maintain design flexibility, each finger is individually actuated, with a total of five servomotors driving ten tendons (extension and flexion are provided by the same motor). A less complete yet more optimized system is the Exo-Glove[69], which is based on the same concept but with a reduced number of required tendons, achieved by the coupling of the motion of two a b c d

Fig. 3 | **Wearable soft robots. a** | Cable-driven soft exosuit. **b** | Exo-Glove Poly. **c** | Soft robotic glove. **d** | I-SUPPORT soft arm to support bathing tasks. Panel **a** courtesy of Conor Walsh, Harvard University, US. Panel **b** courtesy of Kyu-Jin Cho, Seoul National University, South Korea. Panel **c** is adapted with permission from REF.[73], Elsevier.

fingers through an infra-interdigital under-actuated mechanism. A single tendon runs along the index and middle fingers passing through U-shaped tubes, acting as pulleys. Shortening and tension of the tendon are distributed to both fingers because they share the same path. The mechanism enables adaptation between the phalanxes on the same finger and between the two fingers when the glove is in contact with uneven surfaces. In combination with the thumb, the use of two fingers provides more stable grasping. This concept has been extended to an improved version, called Exo-Glove Poly, in which the textile parts are completely substituted by elastomers[70] for easy sanitization (FIG. 3b).

Similar to surgical tools, the main drawback of systems based on cables is the difficulty to effectively transmit the force generated by the servomotors to the end of the kinematic chain (that is, the fingers in this case) because of friction and interference with the body of the wearer. Pneumatic actuators offer an alternative to minimize routing. The main transducer (the air compressor) also operates remotely, but the arrangement of tubes is flexible as long as they transport compressed air to the fluidic chambers. For example, Pneuglove[71] is based on five polyurethane chambers placed along the fingers on the palmar side of an elastomeric glove. The device is designed for patients with residual control of finger flexion, and chamber expansion is used to support digit extension. Flexible fibre-reinforced actuators have also been proposed as 'wearable actuators' (REF.[72]) to restore flexion. Strings embedded in the silicone material are used to constrain the expansion of the fluidic actuators so that the deformation is directed along the fingers, thus causing finger flexion, similar to what is used in soft robotic gloves[73]. In the first PneuNets prototype[74], flexion is obtained with elastomeric pneumatic actuators based on internal patterning, limiting radial expansion. Improved systems use fibre-reinforced fluidic actuators (FIG. 3c).

The incorporation of soft sensors in the glove for upper limb systems should not affect the overall system performance. For example, an integrated solution for hand rehabilitation can be achieved by using embedded sensorized actuators composed of soft pneumatic actuators and stretchable strain sensors[75] to detect bending through electric resistance variation. These actuators are based on a thin layer of screen-printed silver nanoparticles on an elastomeric substrate, enabling stretchability and flexibility while maintaining excellent conductance (~8 Ω^{-1}).

Other soft assistive robots. Rehabilitation devices can also exploit soft robotic technologies and their intrinsic advantages in standalone systems. For example, a haptic device[76] for hand neuromuscular rehabilitation has been designed to offer adjustable stiffness in both clinical and home settings. This handle is based on a pneumatic soft structure made of highly compliant materials that act as actuators of the haptic interface. The stiffness can be tuned through pressure increase (in an open or closed loop) and by using interchangeable sleeves that can be customized to include materials of varying stiffness. Soft robotic technologies can also be used for tremor suppression. For example, the dynamically responsive intervention for tremor suppression (DRIFTS) project aims to develop a dynamically responsive wearable orthosis to suppress upper limb tremor without affecting natural movement. Using materials that can change their viscoelastic properties through the application of magnetic fields (magnetorheological fluids)[77], the tremor energy can be selectively attenuated.

Assistive devices can also aid in personal hygiene. Soft robots can get in contact with the user and effectively cooperate with him or her. For example, a robotic shower can support users in bathing tasks[78]. A soft robot arm (I-SUPPORT soft arm) is built with three cylindrical modules in series, capable of omnidirectional bending.

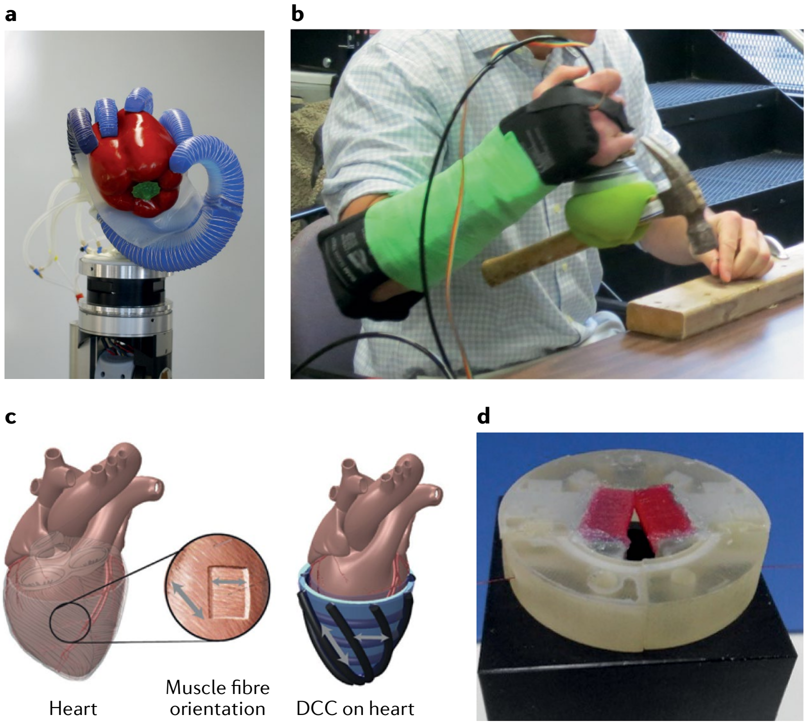

Fig. 4 | **Soft robots as prostheses. a** | Artificial soft hand with high adaptability and stability to grasp unfamiliar objects. **b** | Soft grasper based on granular jamming. **c** | Elastomeric sleeve to restore the functionality of a failing heart. **d** | Physical simulator of human vocal folds. DCC, direct cardiac compression. Panel **a** courtesy of Raphael Deimel, Berlin University of Technology, Germany. Panel **b** courtesy of Nadia Cheng, Empire Robotics, US. Panel **c** is adapted with permission from REF.[88], AAAS.

Each module is based on three tube-shaped pneumatic chambers in a polymeric material covered by a plastic braided structure that guides the deformation to maximize elongation. The overall structure is shaped by transverse plastic discs, which also distribute the deformations of the three chambers along the longitudinal axis (FIG. 3d). Three cables per module enable shortening, contribute to omnidirectional bending and allow for tuning of the arm stiffness through antagonistic action on the pneumatic chambers. The material that interfaces with the user is removable, washable and changeable, and can be fabricated according to the preferences of the user.

Soft robots mimicking the human body

Prostheses. Soft robotic technologies can greatly improve the functionality and acceptability of limb prostheses. For example, upper limb prostheses can provide remarkable dexterity by using grippers or hands that are adaptable and effective, with a low number of control variables. In general, soft robotics has improved robotic manipulation performance. For example, compliance can implement forms of mechanical intelligence[79] to refine grasping capabilities[80] (FIG. 4a). The main challenge is to exploit soft mechatronic technologies to distribute the necessary amount of compliance. A variety of artificial hands have been developed based on soft robotic technologies, but only a few of them have been intended for prosthetics. The implementation of delicate yet effective grasping of objects, provided by soft robots, is also interesting for non-biomedical fields, such as the food industry (Soft Robotics) and underwater exploration[81].

The development of soft robotic prosthetics requires the portability and controllability of the system, similar to assistive and rehabilitation devices. Thus, similar technological solutions have been investigated for prosthetic devices. For example, cable-driven approaches can be used to provide finger flexion of prosthetic hands made of soft or flexible materials. Elastomeric fingers can be 3D printed, which is a low-cost and reproducible fabrication method, and finite element method (FEM) simulations can be used for their design to optimize material properties. Using this approach, it has been determined that a non-symmetric elliptical flexure hinge is the most suitable geometrical shape of a flexural hinge for a soft and monolithic robotic finger[82]. However, in this case, only a single material with a predetermined elastic modulus has been investigated owing to the restricted amount of available printable materials. Moulding is slower and less reproducible than 3D printing but enables the fabrication of a variety of elastomers. A study comparing different materials and fabrication methods was carried out to optimize the design of pneumatically driven fingers, taking into account both material properties and geometrical features[83]. First, a real human hand was scanned to define the segments representing phalanges and material sections. The optimal material for each section was then determined by a genetic algorithm-based optimization, using finite element analysis. The accurate definition of the geometries and material properties enables a simple approach (there is only one free parameter, either pressure or cable displacement) to design a finger with human-like motion.

Designing a prosthetic hand with fingers and a palm is extremely important from an aesthetic viewpoint, but other effective systems have also been proposed to restore grasping capabilities; for example, a prosthetic terminal device based on jamming transition[84] (FIG. 4b). Granular jamming is a physical phenomenon that relies on the interaction between granules embedded in an elastomeric membrane. Applying a vacuum leads to the collapse of the membrane on the granular material, arresting the relative motion of the granules, which leads to fixation of the shape of the system associated with an increase in stiffness. In-hand manipulation is not possible, but objects can be very well grasped and handled. However, pumps are needed for vacuum generation, and the object needs to be pushed to be grasped, limiting this system in terms of portability and acceptability by the patient.

Comfortable wearing of prostheses is related to the design and fabrication of the prosthesis and the attitude and use of the patient. Research efforts are devoted to developing more comfortable prostheses. Soft robotic technologies can improve the conformability of traditional prostheses, such as artificial limbs based on rigid materials, by actively or passively supporting the adaptability to body changes. A major problem in wearing lower limb prostheses is related to the poor adaptability of the socket between the stump and the artificial limb. A rigid socket surrounding the stump can lead to lesions or humidity problems, and a soft socket can cause stability problems, making gait unstable. Moreover, the volume of the stump usually changes from the time of amputation and during the day, constituting a major challenge for the design of an adaptive socket. Active interfaces with variable stiffness can be used to address this issue. For example, magnetorheological fluids allow for the control of both interface stiffness and volume[85]. However, this approach is limited by the bulkiness of the control and power supplies. Granular jamming may offer an alternative technology that is able to solve both the issue of high interfacial stresses and volume fluctuations, providing higher stiffness with increasing limb volume, which usually occurs at softer tissue regions. Alternatively, for lower limbs, inflatable actuators can be inserted at specific sensitive locations within the socket wall. The actuators can be filled with gas (light) or liquid (heavier but easier to control) and can be operated in an open loop (externally or manually adjusted) or in a closed loop (through wearable sensors)[86].

Artificial organs. Active materials are mandatory to replicate physiological functions in artificial organs. Artificial organs or supporting devices for natural organs have the same demands as endoscopic or surgical soft devices, but they are implanted, which requires the materials and manufacturing technologies to be designed in a way that limits the fibrotic response of the human body.

The heart has been at the centre of soft robotics research efforts owing to its ‘simple’ function (a pump), its softness and the severe impact of organ dysfunction on human health. Artificial supporting devices can be used to restore the mechanical function of the heart. For example, an elastomeric sleeve containing a series of McKibben actuators can be implanted around a failing heart to restore its ejection capability[87]. Physiological apical twist and overall contraction (that is, volume reduction) can be restored, but neither the number nor orientation of actuators was analysed in this study. In a more biomimetic approach, the individual contracting elements are oriented in a layered helical and circumferential fashion[88], mimicking the outer two muscle layers of the mammalian heart (FIG. 4c). A more simplified extracardiac device[89] contains a series of McKibben actuators that are connected by coupling bands. This device was used to investigate its temporal synchronization with the native heart, the adhesion of actuators to the ventricles and the contraction–relaxation ratio of the actuators required to generate optimal cardiac output. As a more invasive approach, an implantable linear pneumatic artificial muscle was proposed as an intracardiac device to restore ventricle ejection in right heart failure cases[90].

Entire soft artificial hearts have also been explored to completely replace the natural organ. The shape and function of the heart can be replicated with 3D-printed devices[91]. The soft design allows for the recreation of the physiological movement of the human heart during pumping and to reproduce physiological blood flow. The design is based on three separate elastomeric chambers: two ventricles (left and right) and an expansion chamber. Inflation of the expansion chamber by an external pump leads to squeezing of the two ventricles and the consequent displacement of blood, resulting in a pulsatile flow. In terms of implantation, the main limitations are the durability (3,000 beats) and the simultaneous compression of the two ventricle-like chambers. The two chambers cannot simultaneously pump blood in a closed loop circuit unless atriums are provided. This issue can be addressed by decoupling the chambers. Alternatively, a polydimethylsiloxane (PDMS)-based heart can be designed that exploits gas combustion for actuation[92]. Monoblock structures can be used to guarantee long-term stability, as has been assessed by testing the power density and number of cycles. However, this system might face challenges for clinical application in terms of heat generation and exhaust gas expulsion. Open-celled foams, such as poroelastic foams, can be combined with inextensible materials to direct deformation inwards and thus enable volume reduction, mimicking ventricle contraction. Although not developed for implantation, such an approach allows for the simple fabrication of complex soft robots with similar functionalities as an artificial heart[93].

Most studies aimed at developing artificial hearts and based on soft robotic technologies have focused on the mechanical requirements (achievable pressure, frequency and sometimes working cycles). However, to engineer a durable implantable device, biocompatibility and a sustainable continuous energy source also have to be considered, which is reflected in a recent European project aimed at integrating soft mechatronic components, tissue engineering and wireless energy transfer (HybridHeart).

Soft robotic solutions have also been explored for other body parts with mainly mechanical functions. Sphincters are muscles that control the openings and closings of body passages and orifices, and the malfunctioning of, for example, urethral sphincters affects more than 300 million people worldwide[94]. Continence can be restored by implanting an annular balloon system around the duct. The opening of the urethra can be manually controlled, or a shape change of the system can be triggered by four SMA plates connected with bias springs to open the urethra[95]. However, the system generates heat and operates slowly. Alternatively, EAP[96] (with limitations related to the high operating voltage) or hydraulic systems, such as inflatable balloons[97], can be used with a certain degree of self-controlled occlusion force, minimizing the risk of atrophy or erosion[98].

Soft robots as body-part simulators. The combination of soft materials, contractile actuators and flexible sensors in soft robotics also opens opportunities for the generation of body-part simulators. With the objective of reducing animal or patient tests and motivated by the need for standardized medical procedures, realistic body-part simulators have been developed for the training of specialists in high-fidelity health-care simulation scenarios and for the investigation of the physiology of the body. For example, surgical training requires simulators with a realistic response to external stimuli, which can be realized using software simulators. Thereby, operators drive virtual tools by operating a master console that is acting on virtual environments, which have been designed to specifically react to forces, torques and displacements. However, haptic feedback is often missing or limited, and thus running simulations on actual body mimics is more effective for training. For example, the endovascular evaluator (EVE) simulator (BR Biomedical Pvt Ltd) mimics body parts by embedding active materials with different mechanical properties, which can be used for practising endovascular procedures. In an EVE simulator, vessels have realistic properties, and actuators simulate a pumping heart. Another example is a preterm baby lung simulator, in which the stiffness can be finely tuned to simulate different stages of development or pathologies[99]. Other various stiffness systems employ a wide range of soft materials, such as magnetorheological fluids that can be produced in sponges to replicate the realistic sensation of natural organs[100].

Soft sensors can be embedded in the simulator to detect the contact and measure the force produced by the operator during endoscopy or intubation. The Bionic Humanoid is an ambitious Japanese project aimed at developing a human model equipped with sensors and actuators to serve as a substitute for animal tests. In the course of this project, a realistic eye surgery simulator (Bionic-EyE) has been developed based on a chemically crosslinked poly(vinyl alcohol) (PVA) hydrogel to practice the peeling of the superficial layer of the retina[101].

For the creation of physical models to investigate human physiology, the materials need to have similar mechanical properties as biological tissues. For example, a simulator of human vocal cords can be designed based on three layers of tissues with different compliance[102] (FIG. 4d). By properly tuning the chemistry of commercial silicones, three-layer vocal cords can vibrate in the same frequency range as human vocal cords. This simulator is able to replicate physiological conditions, but it is envisioned to also recreate pathological conditions, such as polyps and hypertonic vocal cords, in the future. Dysphagia is a swallowing disorder that can be studied using a bioinspired swallowing robot. The soft-bodied robot is made of silicone rubber with layers of inflatable chambers and contains an embedded stretchable deformation sensor matrix to replicate the human swallowing process. A central pattern generator model is used to generate peristaltic wave signals[103]. The movement of the tongue and its interaction with the surroundings can also be investigated using a soft robot that mimics the motion of the human tongue[104]. This robotic tongue is simpler than a human tongue but can recreate a realistic and flexible tongue model. It is made of a soft material, such as silicone rubber, which forms an extensible layer, and PDMS as a less extensible layer, with a series of embedded chambers. The robotic tongue deforms under pressure owing to the difference in the strain of the two layers.

Conclusions and perspective

Biomedical soft robots face different challenges regarding the choice or development of materials depending on the applications and the associated requirements for biocompatibility and biomimicry. Medical devices for surgery, endoscopy and drug delivery require an acute or semi-chronic safe interaction with the human body. Assistive robots and wearable soft robots need to provide smooth and effective contact and coupling with human limbs and body parts. Finally, artificial organs and body-part simulators need to mimic human tissues in terms of mechanical properties, motion and function.

The controllability and tunability of the mechanical properties, a controllable response to external stimuli and morphological adaptability to physiological environments are key features of materials for biomedical soft robots to be able to meet biomedical needs that cannot be fully addressed by traditional rigid-link robots. Thus, progress in the design of smart soft materials plays a key role in the future development of biomedical soft robots.

Fluidic actuation has been well investigated and is the most commonly used actuation technology in soft robotics. In the past 10 years, fluidic actuation has been combined with elastomeric chambers for the development of soft actuators. These FFAs are versatile and easy to fabricate and thus became the gold standard for soft robotic actuation for most applications. The combination of elastomers and fluids with different configurations and elastomeric chamber modifications simulates natural muscle properties very well, thus representing an important milestone towards biomimicry, which is important for surgical devices, assistive and rehabilitation robots and realistic simulators; however, prosthetics, artificial organs and drug delivery systems need to be portable or implantable. The portability of such systems is still limited owing to the need for a source of compressed air. Some portable solutions have already been developed[105] but they do not yet represent a universal solution.

Most other emerging actuation technologies (TABLE 1) are incompatible with biomedical applications. High temperature, strong electric fields and high currents are common issues hampering clinical translation. A futuristic approach could be the use of the human energy source ATP to sustain the functionality of wearable devices or prostheses. Electrical signals are already being exploited in artificial and natural systems for the sensing and control of prostheses; alternatively, a chemical power source could be provided by the user[106]. A joint effort of biology, materials science, chemistry and engineering will be necessary to realize such alternative power sources.

Biocompatibility aspects are currently addressed mainly by the use of inert materials that do not induce an immune response, such as silicones or hydrogels. However, to implement biocompatibility, biomimicry, portability and functionality, improved active materials and novel actuation and sensing principles are required. A real step forward would be the combination of materials science for implants and surgical tools with tissue engineering approaches. Moreover, the global trend towards personalized medicine and patient-specific medical solutions requires a substantial revolution in instrumentation design. For example, controllable and intrinsically biocompatible tools could be realized by designing actuators hosting biological cells of the patient or DNA-based molecular machines[107]. This approach would allow the design of tools that are not transparent to but accepted by the immune system, thus paving the way for biohybrid soft robots for surgery.

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Author contributions
C.L. and M.C. conceived the topic of the Review. M.C. analysed aspects related to prostheses, wearable devices and artificial organs. C.L. and M.C. analysed aspects related to assistive robots and body-part simulators. A.M. and P.D. analysed aspects related to surgery and drug delivery. All authors equally contributed to the writing and revising of the paper. All authors contributed to the discussion to draw conclusions and perspectives.

Competing interests
The authors declare no competing interests.

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