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Conjugated-Polymer Micro- and Milliactuators for Biological Applications

C. Immerstrand, K. Holmgren-Peterson, K.-E. Magnusson, E. Jager, M. Krogh, M. Skoglund, A. Selbing, and O. Inganäs

Abstract

The development of new conjugated-polymer tools for the study of the biological realm, and for use in a clinical setting, is reviewed in this article. Conjugated-polymer actuators, based on the changes of volume of the active conjugated polymer during redox transformation, can be used in electrolytes employed in cell-culture media and in biological fluids such as blood, plasma, and urine. Actuators ranging in size from 10 μm to 100 μm suitable for building structures to manipulate single cells are produced with photolithographic techniques. Larger actuators may be used for the manipulation of blood vessels and biological tissue.

Keywords: artificial muscles, electroactive organic materials, biomaterials, conjugated polymers.

Introduction

Conjugated polymers have added a new dimension to the field of polymer materials; electronic and photonic processes typical of semiconductors and metals can be implemented in soft and fusible polymers. This electronic structure is crucial for inducing charge on the polymer chain, whether by chemical, electrochemical, optical, or electrical methods. By the appropriate combination of the electrochemical properties of conjugated polymers with the structural properties of polymers, new material hybrids appear that can be made stiff or soft by electrochemical oxidation and reduction processes; they may also be induced to swell or to shrink. Redox processes in conjugated polymers lead to geometrical changes in the polymer chain; the introduction of charge on the polymer chain leads to polaron (radical cation) formation with concomitant changes of bond lengths

and chain conformation. This realization led to the suggestion, in the early 1990s, that conjugated polymers may be used as mechanical actuators.^{1,2} Several groups have pursued this goal,^{3–13} leading to numerous studies of redox-induced volume change in conjugated polymers, to a large degree related to ion and solvent insertion/deinsertion in the polymer.¹⁴ More recently, the development of carbon nanotube actuators has been pursued, where the higher elastic moduli of nanotubes is a feature that could lead to strong charge-induced actuation in the tubes.¹⁵

As ion transport from an ion-storage medium (an electrolyte) to a solid material is common for both types of electroactive actuators, whether based on nanotubes or polymers, the rate of ion transport is crucial to the scalability of the actuators. With solid polymers like polypyrrole, which

can easily be combined with aqueous electrolytes, ion diffusion is slow. This rewards thinner layers of polymer in which the mechanical changes may be more rapid due to shorter diffusion lengths. It is therefore attractive to use thin layers of polypyrrole in making artificial micromuscles, in order to reduce the length of ion transport. These thin actuators will, however, be weak, suggesting that they should be made in a small format.

We are currently pursuing the development of polymeric actuators for biological and biomedical applications, a field that is still in its infancy. The present genomic and proteomic* revolution in the biosciences relies to an increasing degree on data generation from genes or proteins on biochips using small oligomers of DNA, RNA, or polypeptides as probes. These microarrays all utilize microtechnology. Microarrays have been crucial in sequencing the human genome; we expect microactuators to play an important part as more and more detector functions are miniaturized to allow massive data extraction from minuscule sample volumes.

Most samples coming from the biological realm are based on aqueous solutions. Microfluidics in aqueous environments will therefore be essential to the operation of micromachined biological sensors. Therefore, microactuators operating in aqueous environments should enable this technology. This is where our polymer actuators come in.

The possibility of deploying polymer actuators in biological fluids is an interesting opportunity. On much larger dimensions, medical practice is being transformed through the application of minimally invasive surgery. Tools for this purpose will eventually be available from a broader range of technologies than is offered by the classical small-sized mechanical tools operated by hand. This is a field of medical technology where polymer actuators may offer advantages.

The Actuators

The actuators we use are all based on the doping-induced volume change in a conjugated polymer, a volume change that is controlled by the applied potential on a polymer electrode in an electrochemical cell. The rather moderate volume change in this layer, typically a 2–5% linear change,^{3,14} is converted into larger geometrical changes by building bilayer assemblies in which an active polymer layer is laminated to an inactive supporting layer.

*Relating to the science of protein synthesis and protein-protein interaction within the cell.

The volume change is now converted to a bending of the bilayer, discernible by means of simple measurements.

We have built simple and more elaborate micromuscles and millimuscles with lateral dimensions from 10 μm to 5000 μm . The bilayers used are sometimes Au/polypyrrole¹⁶ ($\approx 0.5\text{--}2\ \mu\text{m}$ thick) or polymer/Au/polypyrrole ($\approx 15\ \mu\text{m}$ thick). The lateral geometries are defined by photolithographically controlled materials deposition on top of a silicon or glass chip, which acts as our carrier substrate. The polymer is generated by electrochemical polymerization on top of a gold surface. The silicon wafer with gold/polymer multilayer structures is then immersed in an aqueous electrolyte and actuated by electrochemical reduction and oxidation to set the muscle free from the substrate and then to drive the movement of the assembly. The assembly may be simple bilayers of gold and polypyrrole, which give rise to curling and uncurling "fingers," much longer than they are wide. The thickness of the micromachined structures is small; they are therefore exceedingly slender and may be bent to a very large degree. The curling and uncurling of these fingers may be used to hold objects. They may also be inserted in cylindrical structures such as blood vessels inside the body.

The Applications

Sizewise, these millimuscles match structures inside the body and may therefore be used as tools that are carried on a catheter to the point of operation or insertion and then activated. In most medical applications, these will only be used temporarily; in others, the structure will be permanently integrated in the tissue.

The reconnection of two ends of a divided small blood vessel is a challenging task in surgery of the hand, heart, brain, and spine, as well as in transplantation surgery. In other areas of the body, it is usually not necessary to repair damaged small blood vessels. Long operation times, clotting, anastomosis patency (obtaining a functioning connection), vascular stenosis (constriction of the blood vessel), and foreign-body reactions are common problems.^{17–19} We envisage that polymer actuators may be applicable here. By forming a tube from a polymer bilayer, of a greater width than length, it is possible to control the outer diameter of the tube by applying a potential to contract the active polymer (see Figure 1). In this state of tube contraction, induced by the voltage, the vessel ends to be joined are pulled over the slowly expanding connector, which is simultaneously disconnected from the voltage delivered via the catheter carrying the millistructure.

Figure 1. Schematic illustration of an expanding connector used in cylindrical polymer-bilayer tubes. (a) The connector is contracted during insertion (caused by the application of -1 V) and (b) slowly expands after placement (application of 0 V).

A tight connection of the adapted vessel walls will be formed. The connector has walls so thin that it will not restrict the lumen channel of the blood vessel. To further secure the vessel ends, tissue glue can be used without increasing the risk of thrombosis. The connector will thus be incorporated in the vessel wall. Figure 2 shows an *in vitro* insertion of such a connector to join placental blood vessels.

Polypyrrole has been studied in cell cultivation and implantation into mammals.²⁰ Most studies demonstrate polypyrrole to be non-cytotoxic,²¹ and *in vivo* studies show only minimal tissue response.²⁰ The polypyrrole layer will be facing the vessel wall, and the underlying material will be in direct contact with blood. A number of different materials can be used as a substrate and still give the component the same functional properties. To improve the blood compatibility, the connector can be coated with heparin. Preliminary tests have shown good blood compatibility and preserved micromuscle function after heparin treatment. Further testing is necessary.

Micromuscles

The flexible micromuscles may be combined with stiffer elements, such as plates or beams, to build more elaborate structures. A first example is that of microboxes, which can be assembled by actuation of a number of flexible muscles/actuators joining hard plates that form the surface of the box. Here, all muscles are simultaneously actuated.²² Moreover, if we do sequential activation, we use a first muscle to move the base of the next muscle, thus making possible more elaborate movements.²³

A more complex structure is that of a microrobot capable of gripping and moving small objects in an electrolyte.²⁴ Here, we use up to five individually controlled

Figure 2. In vitro insertion of a polymer/gold multilayer connector (length, $\sim 5\text{ mm}$) to unite a divided placental blood vessel. (a) The catheter is placed inside one end of a divided 1.2-mm-wide blood vessel. (b) The connector is delivered in one of the vessel ends. (c) The connector is manually pushed back to enter the other end of the divided blood vessel, and a tight connection is formed. Another catheter with a contracted connector is shown below the repaired blood vessel for comparison.

micromuscles to control the movement of the imitation hand, where three fingers are simultaneously activated to hold the object, and two joints (mimicking the elbow and the wrist) are used to bring about the larger movement. So far, we have used this device to move synthetic objects, such as the glass bead shown in Figure 3; we plan to use this microrobot to manipulate cells and tissues.

Figure 3. (a)–(d) A microrobot arm capable of gripping and moving small objects in an electrolyte is shown grasping and lifting a 100- μm glass bead. (e) Schematic illustrations of the motion in (a)–(d). In this case, the arm has three fingers, oriented 120° from each other. The bead is actually lifted from the surface before it is placed at the base of the robot arm (illustrated in gray in the second diagram). (See videos at www.ifm.liu.se/biorgel/.)

Figure 4. An array of (a) opened and (b) closed cell clinics. The contours of the second microvial from the left in (a) are marked with a black outline. Each microvial ($100\ \mu\text{m} \times 100\ \mu\text{m} \times 20\ \mu\text{m}$) is equipped with two electrodes.

We are currently incorporating sensors into micromachined structures equipped with these actuators in order to be able to interrogate the state of cells confined within a small volume, something we call the “cell clinic” (see Figure 4).²⁵ An example of this kind of study is shown in Figure 5, where the impedance between two micro-machined gold electrodes is measured in the presence of biological cells. Here, we have chosen cells from the frog *Xenopus laevis* that also act as chromophores. Aggregation and dispersion of pigments within the cell can be induced by chemical stimuli and observed in optical microscopy (see Figure 6). We correlate the state of aggregation of the pigment to the impedance signal from a few cells confined on the microelectrode within a cell clinic. So far, we are not using a closed cell clinic, but are attempting to establish an experimental protocol that will allow us to study individual cells confined in clinics. Mechanical stimulation of a single cell will affect many internal transport sys-

Figure 5. Impedance signal from a cell clinic containing frog (*Xenopus laevis*) cells during stimulation with the marine toxin latrunculin, which interacts with the actin polymerization and causes pigment aggregation, as observed in Figure 6. R is the resistive part of the impedance, and X is the capacitive part of the impedance.

Figure 6. Representative images of *Xenopus laevis* chromatophores in a $100\ \mu\text{m} \times 100\ \mu\text{m} \times 20\ \mu\text{m}$ cell clinic (a) shortly after addition of cells; (b) after the cells have attached to the clinic surfaces and the pigment granules are dispersed; and (c) after stimulation with latrunculin, which causes aggregation of pigment granules.

tems and is therefore an interesting option for study.

Summary

We are pursuing the development of polymer actuators compatible with biological fluids, with dimensions comparable to the cell or structure to be interrogated.²⁶ These novel tools may find application in massive cell screening, as valves in microfluidic systems, or for the mechanical stimulation of cells. They may also offer interesting alternatives as surgical tools inside the body.

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