Bio Focus

Multiphoton lithography creates conducting polymer-based biomaterials

Electronic devices that can signal directly to living cells have a variety of medical applications, from targeted drug delivery to artificial eyes and ears. Pacemakers, which use electrical impulses to keep the heart beating steadily, are one example of such technology already in use. But getting rigid traditional electronics to interface well with soft tissue can be challenging. Now, an international team of researchers has used multiphoton lithography to create bioelectrodes from conducting polymers. Their results, published recently in the *Journal of Materials Chemistry B* (DOI: 10.1039/c5tb00104h), open the door for more customizable and precise bioelectronic devices.

"The tunable properties of conducting polymers make them attractive components of electroactive biomaterials such as drug delivery devices, electrodes, or tissue scaffolds," writes John Hardy, a postdoctoral associate at the University of Florida and the first author on the article.

According to Hardy, conducting polymers are "softer than the inorganic conductors commonly used—for instance, metals—which diminishes mechanical mismatch with the tissues surrounding the implant."

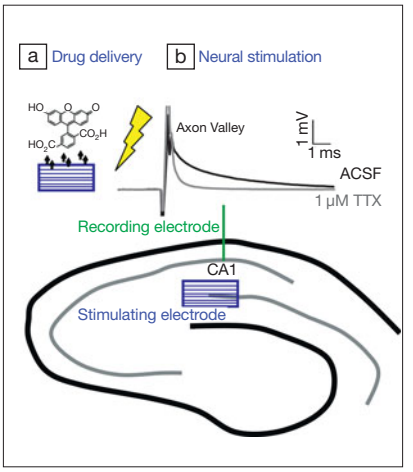
The researchers used a printing technique called multiphoton lithography to produce arrays of wires out of polypyrrole, a conducting polymer, on glass. Multiphoton lithography allows for precise design on the micrometer scale, the size scale of living cells, making the technique ideal for fabrication of biologically relevant structures.

The team tested the drug delivery capabilities of the array by loading a fluorescent dye and then applying a voltage to the wires. As hoped, the stimulation (0.6 volts applied over 30 seconds) caused release of the dye into a buffered saline solution.

The researchers also wanted to explore whether the conducting polymer structures could potentially be used as implantable neural interfaces. They used the conducting polymer array as an electrode to stimulate cells in an *ex vivo* slice of mouse brain. Again, when electrical current was applied to the wires, the targeted cells in the mouse brain showed activity, demonstrating that the conductive polymers could interface successfully with the nervous system.

The conducting polymer arrays will certainly require fine-tuning before being used clinically—passive leakage of the dye was one problem—and the amount of dye actively transported under electrical stimulation was fairly modest. However, once optimized, the technique can be used in a wide variety of medical applications.

"Conceptually, it should be possible to print de *novo* designed 3D [three-dimensional] structures to make patient-specific implants," says Hardy, where this is a direction the research group plans to explore in the future. "In the long term, we can foresee prospects for such materials as drug delivery devices or long-term biointerfaces with bodily tissues."



Polypyrrole (Ppy) electrode arrays could be used for (a) drug delivery or (b) neural stimulation. Credit: John George Hardy, University of Florida.

"Being able to precisely design stimulation and recording traces at micron resolution could bring unprecedented control to neural interfacing *in vitro* and *in vivo*," says Jonathan Rivnay, a researcher at École des Mines de Saint-Étienne in France, who was not involved in the research.

Rivnay sees applications to both basic and applied research. "Their ability to deliver minute amounts of [a] drug on cue, and in a highly localized manner—potentially at sub-cellular resolution—could pave the way for both novel fundamental studies of controlled networks of neurons, as well as for clinical therapies based on combined chemical and electrical stimulation," he says.

Laurel Hamers

Nano Focus

3D superlattice of nanoparticles and DNA assembled through directionality of interactions

A research group led by Oleg Gang from Brookhaven National Laboratory has assembled a complete three-dimensional (3D) superlattice from nanosized cubes and spheres, using complementary DNA matching and shape-related directional interactions. Significantly, the researchers are able to change the type of the lattice by using octahedra instead of cubes and have shown that the final structure is a function of DNA flexibility and the relative cube-to-sphere sizes. Such controlled organization of nanoparticles is a highly sought-after goal in the field of emergent materials, where it promises tantalizing applications in areas such as metamaterials, photonics, and catalysis. The researchers reported their results in the April issue of *Nature Communications* (DOI: 10.1038/ncomms7912).

DNA has previously been used to assemble nanoparticles into 3D structures. These are usually chemically synthesized, single-stranded DNA, containing anywhere from ten to a few hundred bases. When complementary bases from two such strands meet, they form a duplex and therefore a bond. Assembly of DNA-functionalized spherical nanoparticles only yields one type of crystal lattice as the structure is determined by packing considerations alone. This is similar to how metals form structures—most metallic

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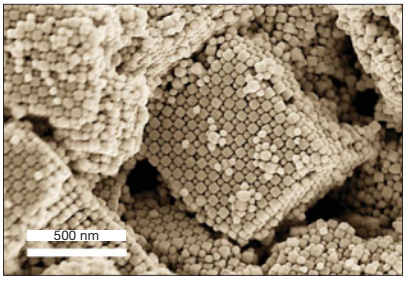
lattices are cubic. The rich diversity of crystal structures found in nature comes from the inherent directionality of covalent bonds. Gang and his team member Fang Lu reasoned that attaching DNA to a polyhedron such as a cube would cause the bonds to be perpendicular to the faces, such that they would form directional bonds.

A binary system of spherical (SNP) and cubic (CB) gold nanoparticles, each with 46 nm in size, were coated with complementary DNA and allowed to mix. Mixing in a 6:1 ratio generated clusters, while a 1:1 ratio formed lattices. The resulting 3D spatial arrangement of clusters was determined by tomography in a transmission electron microscope. Each CB was decorated at the center of each face by an SNP, which corresponds to a coordination number of six.



High magnification scanning electron microscope image of cubic-spherical nanoparticles 3D superlattice. Credit: Oleg Gang.

As expected, the use of octahedra instead of cubes resulted in eightfold coordination as the octahedron has eight faces. Annealing the 1:1 mixture at 39°C created an extended 3D lattice (see Figure) that was determined by small-angle x-ray scattering to be a NaCl type cubic lattice of unit cell size ≈100 nm. The superlattice based on the octahedron, in contrast, was found to be a CsCl type lattice. Thus, the shape symmetry of the polyhedra is found to translate predictably to the global superlattice structure.

"Directionality of interactions provided by the polyhedron is crucial for defining the lattice type. At the same time, DNA structure and SNP size control the morphology. Flexible DNA motifs are required for achieving crystalline organization," Gang says; "However, excessively flexible DNA results only in short range order."

Also interesting is the effect of size mismatch between the SNP and CB. Smaller SNPs of 27-nm edge length did not form extended global lattices. This can be understood by considering the local geometry of the interaction. The adhesive energy between the SNP and CB is correlated to the projected area of the SNP on the square face of the CB. If the SNPs are smaller than the cube, the projected area need not fall around the center of a face, making the position of the SNP and hence the bond direction ambiguous. An intermediate SNP of 38-nm diameter did form good crystals, but with a reduced lattice parameter, which implies that the DNA must be in a moderate state of compression.

"There has been a lot of work using DNA to crystallize spherical nanoparticles and to get directional interaction, but this research combines these two ideas for the first time," says John Crocker of the University of Pennsylvania, who was not involved in the study.

Vineet Venugopal

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