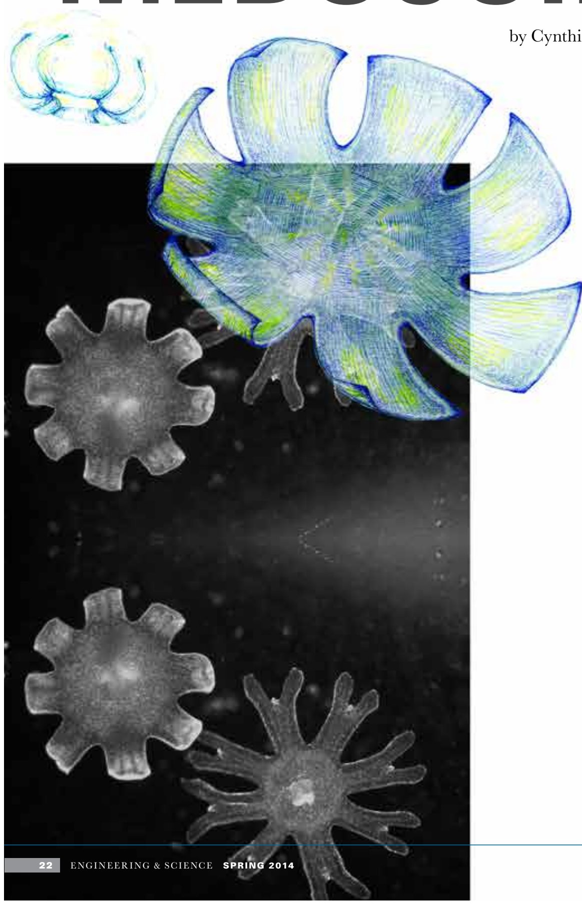
MEDUSOID IN MOTION

by Cynthia Eller



Call it a medusoid—that's what its makers have dubbed it. Or, if you prefer, call it a ratfish, since it was constructed by layering rat muscle tissue atop a silicone substrate. Or perhaps you'd prefer cniborg (rhymes with cyborg, which is what it is, from the phylum Cnidaria); or robojelly, since this star-shaped creature, constructed in the lab of Caltech bioengineer John Dabiri, is both robot and jellyfish.

Whatever you call it, this one-centimeter-diameter creature is worthy of your attention. Although the medusoid is not the first nor the only attempt to culture cells in the lab and attach them to an inorganic substrate, it does something no other such invention has yet been able to accomplish, something truly extraordinary: it swims.

This may not seem amazing to you. Perhaps you yourself can swim. Even a paramecium can swim, with only one cell to its credit. But for the medusoid—which lacks a heart, a brain, or even a central nervous system—it's quite a feat. According to Dabiri, who came up with the idea of bioengineering a cyborg jellyfish, and biologist Janna Nawroth, who designed the creature, making a medusoid that could swim was a three-and-a-half-year labor of love and science.

The medusoid is the product of a collaboration across disciplines, marrying biology to engineering, electrophysiology to fluid dynamics. This description suits Dabiri himself, whose work with jellyfish comes not simply from an interest in marine life, but out of an appreciation for the jellyfish's simple but effective form of propulsion.

"As a kid I was fascinated with rockets and helicopters and airplanes," Dabiri remembers. This enthusiasm for moving and flying things grew into an interest in fluid dynamics, a field of engineering that, in spite of the term *fluid*, applies to both water and air. For Dabiri, fluid mechanics is "a challenging topic but also a really beautiful one. You see these water motions that a jellyfish creates, and it's neat to think that you could describe them with a few equations."

Those motions, or vortices, are the result of the jellyfish's repeated cycles of body contraction and relaxation. What makes jellyfish propulsion fascinating is that the creature continues to propel itself through the water during its relaxation phase (though not quite as far as during its contraction phase). In most animals, this is not the case. Propulsion occurs when the muscles contract, but when they release, propulsion slows down, or even reverses.

In the spring of 2008, after Dabiri had given a lecture at Harvard on the intricacies of jellyfish propulsion, Harvard bioengineer Kit Parker introduced himself to Dabiri, commenting that the videos of juvenile jellyfish propelling themselves through the water had brought to his mind the muscular contraction and relaxation of the heart tissue he was working with in his lab. Parker had by then pioneered a technique through which muscle cells would attach themselves in an organized fashion to fine lines of protein laid down on silicone. This work marked the first time that researchers had been able to grow muscle cells that would not only contract and relax individually, but would act as actual muscle *tissue*, the cells working in concert with one another. Dabiri and Parker realized that Parker's "functionalized" laboratory muscle tissues meant that it was now theoretically possible to build from biological materials, in the lab, something that could potentially swim as a jellyfish does.

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Making this robo-jellyfish, Dabiri knew, "would require a broad range of skills—tissue engineering, electrophysiology, fluid dynamics. But what it required first of all is someone who is persistent."

With those requirements in mind, Dabiri assigned the creation of the medusoid to Nawroth as her doctoral thesis project. Nawroth had originally come to Caltech to study neuroscience, but when her mentor moved to Germany, she started looking for other opportunities. Having been intrigued by the work in Dabiri's lab during an earlier research rotation, Nawroth returned, looking for a meatier project. Dabiri handed her the medusoid challenge.

Over the next several years, Nawroth would move back and forth between Parker's lab at Harvard and Dabiri's lab at Caltech. At Harvard, Nawroth worked on tissue cultures, learning Parker's methods for attaching cells to substrates; at Caltech, she turned to questions of what the appropriate architecture might be for a medusoid. This back-and-forth was helpful, Nawroth says, because Harvard's biologists were, like herself, "much more used to dissecting organisms and analyzing their internal structure." The engineers in Dabiri's lab, on the other hand, were more interested in examining the shape, movement, and fluid interactions of intact jellyfish so as to find the best possible design for an engineered creature that could swim.

From the outset, Dabiri's focus was on function rather than form. "For centuries, there's been an interest in biomimicry," Dabiri explains, "in building something that looks like a biological system. If you're trying to build an airplane and you see a bird, for example, you might start by mimicking its flapping wing design. But the history of aviation shows us that until we decided to use a fixed wing and stick an engine on the back of it, that plane wouldn't go anywhere. So we're realizing that directly copying animals isn't the way to success. Instead, we have to figure out the underlying physical principles and then bring engineering materials and control systems to bear on them.” Which is why Dabiri tasked Nawroth with designing a creature that *moved* efficiently like a jellyfish; what it looked like, he said, didn’t matter.

With this broad mandate, Nawroth initially came up with some very *un*-jellyfish-like prototypes, each of which took about a year to design and construct, and each of which, in turn, failed. Ultimately, the design that worked—the medusoid—had a star shape reminiscent of a juvenile jellyfish. But that, says Dabiri, was just coincidence: they were replicating jellyfish propulsion, not jellyfish physiology.

In her first research rotation in Dabiri’s lab, Nawroth had experimented on the effects of water temperature on the shape of adult jellyfish. Juvenile jellyfish have star-shaped bodies with gaps between each petal or lobe. As they grow, webbing fills in between the lobes to form the bell, or body, of the jellyfish. According to Nawroth’s observations in Dabiri’s lab, jellyfish that grow in colder water—which is more viscous—develop webbing more slowly, using “sticky” layers of viscous fluid between the lobes to give them greater traction on the fluid through which they must move.

Below: The bottom strip of images shows a juvenile jellyfish as it contracts and releases its muscles; above those are illustrations of the same process as performed by the medusoid.

Jellyfish in warmer waters grow tissue between the lobes more rapidly, to compensate for traction lost by contact with the less viscous warm water.

Because Dabiri was planning to use mammalian (rat) muscle to power the medusoid, a warmer fluid environment—close to human body temperature—would be needed, and this suggested that the medusoid would require smaller gaps between its lobes. “People always talk about DNA, DNA, DNA,” he says. “But in reality, the environment plays a big role in determining the shapes and sizes of organisms. Knowing the environment in advance helps us think more constructively about design.”

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The next step in making a medusoid was to determine whether or not rat heart muscle—the key component in Parker’s tissue experiments—shared more than a superficial similarity with the muscles of a juvenile jellyfish. Nawroth began directly examining the propagation of electrical signals through rat muscle tissue using a procedure called optical mapping, in which cells are stained with a dye that is voltage sensitive. As an electrical stimulus passes through the muscle tissue, the color of the dye changes, making it possible to directly visualize the tempo and movement of the electrical charge. Nawroth then attempted similar experiments on jellyfish, a tricky business, she reports, since a jellyfish “is evolutionarily so far away from a rat, and many dyes and experimental techniques developed for rodents don’t work in jellyfish.” Nevertheless, these optical maps confirmed for Nawroth that the wave pattern along the muscles in the lobes of a juvenile jellyfish and those in the heart muscle of a rat were similar enough that the latter cells could indeed stand in for the former.

But what to attach them to? Dabiri and Nawroth knew that whatever they laid the muscle cells on would need to be able to recoil—or flap—with each released contraction of the muscles, just as the mesoglea (the middle, jellylike layer of tissue) in a jellyfish does. They already knew from Parker’s work that muscle cells could adhere to silicone if it was properly prepared with lines of protein; fortunately a thin piece of silicone is also suitably elastic for an efficient recoil. And so silicone it was.

With such a lightweight material to control, the researchers knew that they could apply their muscle cells very sparingly. In the end, they needed only a one-cell-thick layer of muscle cells to be able to flap the silicone substrate.

Two challenges remained, both fairly easily solved once Nawroth had put silicone and cells together into a workable design. First, Nawroth needed to figure out how to protect the medusoid’s muscle cells—after all, the cells came from rats, where they are ordinarily covered by layers of more muscle, bone, fat, and skin—and how to keep the cells fed. She determined that placing the medusoids in a tank of carbohydrate-rich cell-growth medium would protect the cells, and that the sugar in the growth medium would easily be taken up as food—and thus energy—by the muscle tissue.

“Muscle tissue is more efficient in storing energy than, say, trying to attach a battery to the medusoid,” says Dabiri, who explains that this is one of the key advantages of using a biological rather than a synthetic material to mimic jellyfish propulsion. “The medusoid doesn’t require a big backpack with a battery on top, because the energy is taken from the solution.”

Nawroth’s second challenge was to figure out how best to stimulate the medusoid’s muscle cells to contract in unison, in a productive pattern. Nawroth provided her medusoid a pacemaker by attaching two U-shaped electrodes to the side of the tank and using them to deliver a pulse of electricity through the water every second. Like the coxswain in a boat commanding the rowers to stroke in unison, the electrodes commanded the medusoid’s muscle cells to contract, relax, contract, relax—and thus propel the medusoid through the water.

Set loose in their tank, the 20 or so medusoids Nawroth ultimately created did in fact look strikingly like juvenile jellyfish pulsing through the water. Sadly, within an hour, and as expected, their response to the electric pulsing slowed and eventually stopped; this was due, says Nawroth, “to the physiological stresses and toxic electrochemical products generated by the stimulation over time.” Following their successful experiments, Dabiri, Nawroth, and Parker coauthored a paper reporting their findings, titled “A tissue-engineered jellyfish with biomimetic propulsion.” It was published in *Nature Biotechnology* in August 2012.

A tiny swimming disk of silicone and rat muscle is exciting all on its own. But that excitement ratchets up a notch or three when you consider that something like a medusoid—a bioengineered, self-sustaining contractor—could one day be used to address human heart malfunctions.

“If you’re thinking about building an artificial heart or a valve or an active stent,” Dabiri explains, “you want materials that are biocompatible and relatively gentle in handling blood cells. Biologically inspired systems that can deform and generate a gentle flow, as the medusoid does, are things that I think have an interesting future. A heart is an amazing system,” says Dabiri, “but there’s no reason not to ask how we could improve upon what nature has refined over millions of years.”

Nawroth is especially excited about the possibility of using medusoids for testing new drugs. As she explains, “Currently the options for testing drug efficacy and biosafety are pretty limited. To test biosafety, you have a cell culture, and you just put the drug on it and see if the cells survive. If the drug passes that test, you go to an animal model to test efficacy. But this is very costly and not always informative about the effect the drug will have in humans. So one idea is to build medusoids from human-derived cardiac muscle and then test the effect of cardiac drugs on the swimming of these specialized medusoids. This would serve as a proxy for cardiac muscle health and contractile strength.”

The work on medusoids also contributes to basic science and engineering. “By getting closer to these engineered systems that incorporate both muscle tissue and biological control, we’re able to ask more precise questions about the evolution of design,” Dabiri says. “It helps us better understand the biology, and it also helps us to build better technologies.” E&S

John Dabiri is a professor of aeronautics and bioengineering; Janna Nawroth, who received her PhD in biology from Caltech in 2013, is now a postdoctoral fellow with the Disease Biophysics Group at Harvard’s School of Engineering and Applied Sciences. *Their work on the medusoid was funded by the National Science Foundation, the National Institutes of Health, and the Office of Naval Research. Jellyfish were provided by the New England Aquarium and the Cabrillo Marine Aquarium.*

To see a video of the medusoid in motion, visit http://goo.gl/wB8ETa.