Podcast Interview: Josh Bongard

PNAS: Welcome to Science Sessions, the podcast of the Proceedings of the National Academy of Sciences, where we connect you with Academy members, researchers, and policymakers. Join us as we explore the stories behind the science. I'm Paul Gabrielsen and I'm speaking with Josh Bongard of the University of Vermont. In a PNAS article published last year, Bongard and his colleagues described a pipeline for designing and fabricating cell-based organisms that exhibit desired behaviors. They call these organisms Xenobots, after the *Xenopus* frog from which their cells are derived. For making a significant contribution to their field, the study was awarded a 2020 PNAS Cozzarelli Prize in Engineering and Applied Sciences.

Josh, how did you become interested in living synthetic organisms?

Bongard: So, two members of our team, Mike Levin and Douglas Blackiston, are the biologists. They have a particularly notable study, where they grafted an adult frog eye onto a tadpole and not only did it not harm the tadpole, the tadpole grew into a healthy adult frog and, during development, the eye and the spinal cord wired up spontaneously so that the adult frog could actually use the third eye on its back to direct behavior. So my team got together with Mike and Doug, and we showed them some of the work that we do in robotics. In essence, what we do is we teach a supercomputer how to design robots in virtual worlds. When we started this project, Mike and Doug watched our virtual robots in simulation. And Doug, who's a microsurgeon, figured that he could actually build a sculpture of one of our little creatures out of frog cells. And the following week on our research call, he demonstrated a Xenobot structure. It couldn't move, but it was a perfect replica of the virtual robot. And that led to the Xenobots project.

So one of the things that was particularly challenging here was in the year leading up to this work, it took a lot of effort for Sam Kriegman and myself, the two roboticists on the project, to learn the language of Mike and Doug. So it took a lot to understand each other's, you know, methods and challenges, what's easy, what's hard, and really to try and bring those two aspects together to produce the Xenobots, which is sort of more than the sum of their two parts. They're biology, but they're also not biology. And the Xenobots are also robots and also in some ways, not robots, which made this project particularly intellectually challenging, but also intellectually rewarding.

PNAS: Tell me about the AI side of the design process. How can an algorithm determine what functions a cluster of cells can carry out?

Bongard: Yeah, that's a great question. So we took what Mike and Doug could tell us about how frog skin cells and how frog heart muscle cells behave. So in essence, what this means for the AI is it needs to put together what it sees as red and green Lego bricks. Unbeknownst to AI, these are frog heart muscle cells and frog skin cells. But when the AI puts those Lego bricks together, some of the bricks behave in odd manners. So it's sort of trying to build a reliable machine out of unreliable parts. What the AI then

does is to try out billions and billions of combinations of these Lego bricks. And it's looking for particular combinations of biological tissue that will result in a particular desired behavior, which in our case was moving along the bottom of a Petri dish. All of that AI and computational work was carried out by my postdoc, Sam Kriegman.

PNAS: Tell me about the two different cell types you used to create the Xenobots. Why is it important that they have different functions?

Bongard: So when we went into this project, we were viewing what the AI was going to construct, not as a frog, but as a robot. We wanted it to make a useful machine. It's not very useful at the moment. All it does is walk along the bottom of the Petri dish. But when you approach building a robot, obviously you need to enumerate a few basic parts. You need a power source, you need sensors, you need motors, you need structural material, the bones, if you like, of the robot. So we boiled that down to the two simplest parts we can imagine, skin cells, which provide a little bit of passive support for the motor part of the Xenobot, which is the heart muscle tissue.

PNAS: Once you have the design, how do you translate that into a living Xenobot?

Bongard: Yeah, so in this first study we adopted a top-down design approach. So the AI is running on the super computer for a few weeks, searching for a good arrangement of skin and heart muscle tissues. And at the end, it gives us back the winning design. So our microsurgeon took that blueprint and then dissociated cells from a very early frog embryo. And then Doug very carefully pushed these cells together and they spontaneously want to re-adhere. So as they're slowly cohering back into a ball of cells, Doug reaches in with microscalpels and very carefully sculpts or scrapes away unwanted material to produce the shape dictated by the AI. And as you can imagine, we were very excited when Doug's creation was placed in the bottom of a physical Petri dish and the physical Xenobot walked more or less like the AI predicted it would.

PNAS: What are the functions or tasks that the Xenobots are able to do, and which of those functions are you particularly excited about?

Bongard: Yeah, so the very first function, the demonstration that this was possible was just spontaneous movement. So, they can't sense their environment, at least as far as we know, they're almost like a windup toy. So they're able to spontaneously walk or move along the bottom of a Petri dish. We also found that if you create a swarm of them and place them in a dish with particulate matter, they will move around and just unintentionally push material into neat piles. We also managed to make a hollow Xenobot and, we didn't manage to do this in practice, but in theory, the AI showed how this hollow Xenobot could carry a very small piece of cargo inside its body. And that suggested to us, eventually, that there may be some interesting biomedical applications for this technology.

PNAS: There are many directions that this research could go, and many applications for these custom organisms. What directions or applications do you look forward to?

Bongard: This is a brand new technology. We need to be careful in how we handle this technology. So in the short term, one of our goals is a basic science goal. So, can we get the AI to design a Xenobot for us that exposes the secrets of cellular communication? So the Xenobot can be viewed as a new kind of scientific tool to pose and test biological questions about cellular communication, regeneration, and other questions along those lines.

These are Xenobots, again, made from frogs cells. So they're perfectly happy in room temperature fresh water. So assuming that they are safe, in the short-term we could imagine deploying swarms of Xenobots to inspect underwater machines. In the medium term, as we start to scale up this technology, we could imagine exploring larger Xenobot swarms that clean up microplastics in waterways, or remove contaminants from the soil. And then, in the long-term, we could imagine this might be useful for human medicine. It might become possible in the future to make biobots out of human cells. If we could do that, you could imagine deploying biobots into the human body to perform non-invasive surgery or intelligently delivering drugs to various points in the body. And because those biobots would be built out of the human patient's own cells, we might be able to avoid the immune response.

PNAS: How did you feel when you heard that your paper had been awarded a Cozzarelli Prize?

Bongard: Oh gosh. We, the four of us on the team, we were absolutely floored. For my part, I had to read the email a few times for it to actually sink in. It was an incredible honor and amazing surprise. It was particularly inspiring to us to see how much the Academy values this interdisciplinary work between biologists and roboticists. I'm an avid reader of PNAS. There was an amazing crop of articles that were published this past year. So I'm sure it was particularly difficult on the selection committee to pick their winners.

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