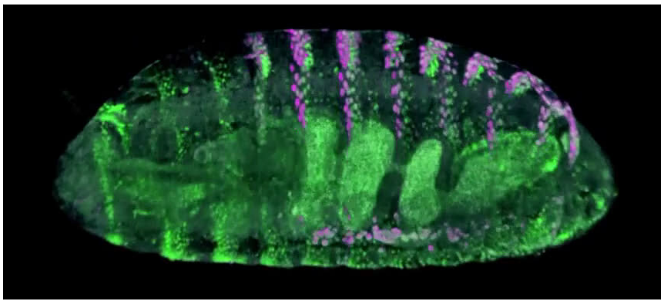
Robots are helping to advance developmental biology

14 October 2020



The study of developmental biology is getting a robotic helping hand.

Scientists are using a custom robot to survey how mutations in regulatory regions of the genome affect animal development. These regions aren't genes, but rather stretches of DNA called enhancers that determine how genes are turned on and off during development. The team describes the findings—and the robot itself—on October 14 in the journal *Nature*.

"The real star is this robot," says David Stern, a group leader at HHMI's Janelia Research Campus. "It was extremely creative engineering."

The project was led by a former postdoc in Stern's lab, Justin Crocker, now a group leader at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany. In the past, to study the role of regulatory regions in development, scientists have examined the effects of just a few mutations at a time. But Crocker and Stern wanted to study hundreds of mutations—to determine the role of every position in a regulatory region. These experiments required a complex preparation protocol to be repeated in exactly the same way across thousands of fruit fly embryos. Even slight inconsistencies in the preparation of samples could change the results.

So the pair worked with the Janelia Experimental Technology team, jET, to design and build a robot that could do the finicky work of preparing samples.

"The timing of many of these steps is critical," Crocker says. "For us, the goal was to be able to remove the human as much as we could from the equation, to make things very standardized."

jET engineers followed Crocker around the lab, watching him carry out each step of the complex protocol, and even tried their hand at the process themselves. Then they developed creative solutions for each step, ultimately designing a robot that could translate the manual movements into automated steps. It took several years and two failed prototypes before the team landed on a winning design: a toaster-sized contraption that can consistently preserve and stain hundreds of fly embryos in different stages of development.

Crocker and his colleagues used the Hybridizer robot to study the effects of mutations in one enhancer that the Stern lab had studied for decades. Past research had suggested that there's a lot of flexibility in the exact genetic sequence of this enhancer—lots of room for mutations to change the sequence without having big effects on function. But with the help of the Hybridizer, the new comprehensive survey presented a different picture.

Crocker's team created many variants of this enhancer, each with a handful of random mutations. Then they created 800 different fly strains, each carrying a different enhancer variant. Stern's lab had made one-off modifications to this enhancer in the past. But without the technological assist from the Hybridizer, it hadn't been possible to analyze the outcomes of hundreds of different possible changes.

Crocker and Stern initially thought that this experiment would highlight the few small regions critical for the enhancer's function. But surprisingly, they found that most of the mutations altered gene expression in some way. And it didn't matter where those mutations were made: almost all areas of the enhancer seemed to encode valuable information.

"The regulatory regions of genes encode information much more densely than previously appreciated," Stern says. Also, single mutations often had several different effects—for example, reducing gene expression in some parts of the fly while increasing expression elsewhere. "Both of these facts may constrain how regulatory regions can evolve," says Stern.

The scientists aren't yet sure why that's the case or how their findings square with the fact that enhancers often evolve very quickly. "We hope it will lead people to start thinking about these regions differently and designing new kinds of experiments to explore this problem more deeply," Stern says.

Crocker is now collaborating with engineers at EMBL to improve the Hybridizer and design new robotic tools, which he hopes will make it possible for others in his field to automate similar experiments. "It's allowing us to do entirely new types of experiments and answer questions that people haven't been able to touch before," Crocker says.

More information: Dense and pleiotropic regulatory information in a developmental enhancer, *Nature* (2020). DOI: 10.1038/s41586-020-2816-5

Provided by Howard Hughes Medical Institute