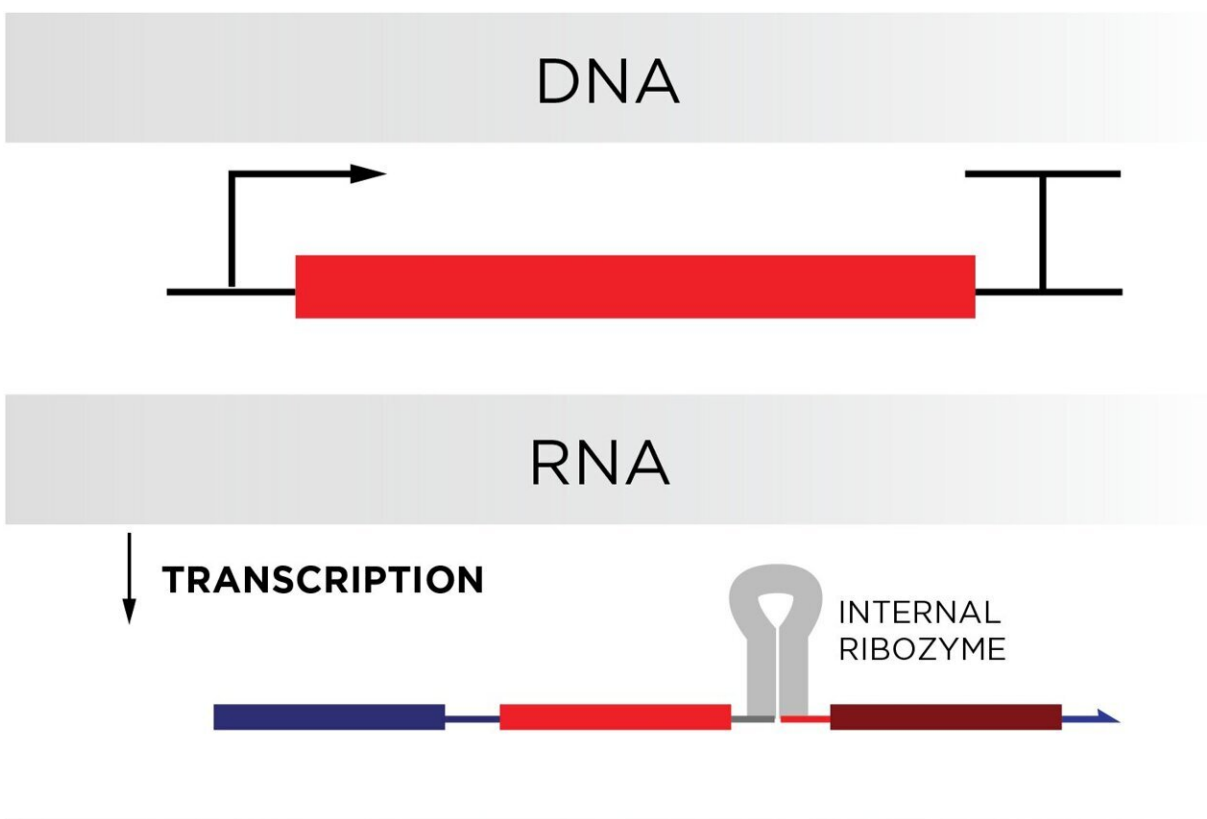


Revamped design could take powerful biological computers from the test tube to the cell

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NIST researchers aim to turn the cell into a biological computer factory by designing and inserting DNA into a cell's genome. Cell proteins would produce RNA based on the DNA through transcription. The RNA strand would then fold, binding to itself, and split in two, thanks to a special self-cleaving sequence of RNA called a ribozyme. The resulting structure, an RNA circuit gate, would only come undone and trigger further chemical reactions under certain conditions.

Credit: N. Hanacek/NIST

Tiny biological computers made of DNA could revolutionize the way we diagnose and treat a slew of diseases, once the technology is fully fleshed out. However, a major stumbling block for these DNA-based devices, which can operate in both cells and liquid solutions, has been how short-lived they are. Just one use and the computers are spent.

Now, researchers at the National Institute of Standards and Technology (NIST) may have developed long-lived biological computers that could potentially persist inside [cells](#). In a paper published in the journal *Science Advances*, the authors forgo the traditional DNA-based approach, opting instead to use the nucleic acid RNA to build computers. The results demonstrate that the RNA circuits are as dependable and versatile as their DNA-based counterparts. What's more, living cells may be able to create these RNA circuits continuously, something that is not readily possible with DNA circuits, further positioning RNA as a promising candidate for powerful, long-lasting biological computers.

Much like the computer or smart device you are likely reading this on, biological computers can be programmed to carry out different kinds of tasks.

"The difference is, instead of coding with ones and zeroes, you write strings of A, T, C and G, which are the four chemical bases that make up DNA," said Samuel Schaffter, NIST postdoctoral researcher and lead author of the study.

By assembling a specific sequence of bases into a strand of nucleic acid, researchers can dictate what it binds to. A strand could be engineered to attach to specific bits of DNA, RNA or some proteins associated with a

disease, then trigger [chemical reactions](#) with other strands in the same circuit to process chemical information and eventually produce some sort of useful output.

That output might be a detectable signal that could aid medical diagnostics, or it could be a therapeutic drug to treat a disease.

However, DNA is not the sturdiest material and can quickly come apart in certain conditions. Cells can be hostile environments, since they often contain proteins that chop up nucleic acids. And even if DNA sequences stick around long enough to detect their target, the chemical bonds they form render them useless afterward.

"They can't do things like continuously monitor patterns in gene expression. They are one use, which means they just give you a snapshot," Schaffter said.

Being a nucleic acid as well, RNA shares many of DNA's woes when it comes to being a biological computer building block. It is susceptible to rapid degradation, and after a strand chemically binds to a target molecule, that strand is finished. But unlike DNA, RNA could be a renewable resource in the right conditions. To leverage that advantage, Schaffter and his colleagues first needed to show that RNA circuits, which cells would theoretically be able to produce, could function just as well as the DNA-based kind.

RNA's edge over DNA stems from a natural cellular process called transcription, wherein proteins produce RNA on a continuous basis using a cell's DNA as a template. If the DNA in a cell's genome coded for the circuit components in a biological computer, then the cell would produce the computer components continually.

In the biological computing process, single strands of nucleic acids in a

circuit can easily end up bound to other strands in the same circuit, an undesired effect that prevents circuit components from binding to their intended targets. The design of these circuits often means that different components will be natural fits for each other.

To prevent undesired binding, DNA sequences that are part of computers known as strand displacement circuits are usually synthesized (in machines rather than cells) separately and in a double-stranded form. With every chemical base on each strand bound to a base on the other, this double strand acts as a locked gate that would only unlock if the target sequence came along and took the place of one of the strands.

Schaffter and Elizabeth Strychalski, leader of NIST's Cellular Engineering Group and co-author of the study, sought to mimic this "locked gate" function in their RNA circuit, keeping in mind that, ultimately, cells would have to produce these locked gates themselves. To set cells up for success, the researchers wrote the sequences so that one half of the strands could bind flush with the other half. Binding this way, RNA sequences would fold on themselves like a hotdog bun, ensuring they are in a locked state.

But to work properly, the gates would need to be two chemically bound but distinct strands, more like a hamburger bun or sandwich than a hotdog bun. The team obtained the double-stranded design in their gates by coding in a stretch of RNA called a ribozyme near the folding point of the gates. This particular ribozyme—taken from the genome of a hepatitis virus—would sever itself after the RNA strand it was embedded in folded, creating two separate strands.

The authors tested whether their circuits could perform basic logical operations, like only unlocking their gates under specific scenarios, such as if one of two specific RNA sequences was present or only if both were at the same time. They also built and examined circuits made of

several gates that performed different logical operations in series. Only when these circuits encountered the right combination of sequences, their gates would unlock one by one like dominoes.

The experiments involved exposing different circuits to pieces of RNA—some of which, the circuits were designed to attach to—and measuring the output of the circuits. In this case, the output at the end of each circuit was a fluorescent reporter molecule that would light up once the final gate was unlocked.

The researchers also tracked the rate at which the gates unlocked as the circuits processed inputs and compared their measurements to the predictions of [computer](#) models.

"For me, these needed to work in a test tube as predictively as DNA computing. The nice thing with DNA circuits is most of the time, you can just write out a sequence on a piece of paper, and it'll work the way you want," Schaffter said. "The key thing here is that we did find the RNA circuits were very predictable and programmable, much more so than I thought they would be, actually."

The similarities in performance between DNA and RNA circuits could indicate that it may be beneficial to switch to the latter, since RNA can be transcribed to replenish a circuit's components. And many existing DNA circuits that researchers have already developed to accomplish various tasks could theoretically be swapped out for RNA versions and behave the same way. To be sure, though, the authors of the study need to push the technology further.

In this study, the authors demonstrated that transcribable circuits work, but they have not produced them using the real cellular machinery of transcription yet. Instead, machines synthesized the [nucleic acids](#) through a process similar to that used to produce DNA for research. Taking the

next step would require inserting DNA into the genome of an organism, where it would serve as a blueprint for RNA circuit components.

"We're interested in putting these in bacteria next. We want to know: Can we package circuit designs into genetic material using our strategy? Can we get the same sort of performance and behavior when the circuits are inside cells?" Schaffter said. "We have the potential to."

More information: Samuel Schaffter, Co-transcriptionally encoded RNA strand displacement circuits, *Science Advances* (2022). [DOI: 10.1126/sciadv.abl4354](https://doi.org/10.1126/sciadv.abl4354). www.science.org/doi/10.1126/sciadv.abl4354

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