Training cells to perform boolean functions? It's logical

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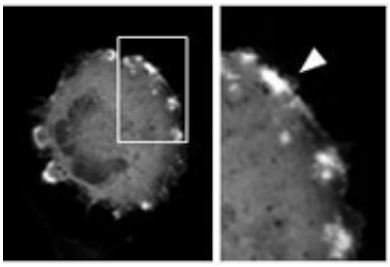

When either FRB and FKBP or GID1 and GAI linked up, the cell's membrane developed ruffles easily visible under a microscope. Credit: Inoue lab

(Phys.org) -- Johns Hopkins scientists have engineered cells that behave like AND and OR Boolean logic gates, producing an output based on one or more unique inputs. This feat, published in the May issue of Nature Chemical Biology, could eventually help researchers create computers that use cells as tiny circuits.

Study leader Takanari Inoue, Ph.D., an assistant professor in the Department of Cell Biology and member of the Institute of Basic Biomedical Sciences' Center for Cell Dynamics at the Johns Hopkins University School of Medicine, explains that many researchers are striving to mimic devices in everyday use by engineering new qualities into biological materials, including biomolecules and cells. Several of those engaged in this relatively new field, known as synthetic biology, have tried to create biological computers.

At the heart of both the biological and the more everyday silicon-based variety of computers are Boolean logic gates, which produce responses that vary depending on what type and how many inputs they receive. For example, AND gates need two unique inputs to generate an output. In contrast, OR gates generate an output based on whether they receive one input, or another, or both.

Inoue says that previous research has shown some success in generating logic gates based on biomolecules in test tubes or petri dishes. However, he adds, developing logic gates using whole cells has proven significantly trickier. Most previous efforts have taken advantage of cells' transcriptional machinery — the cellular processes that read genes to create proteins — to generate an output signal. But transcription can be a slow process, taking from minutes to days to produce the desired response.

"People like to have speedy computation," Inoue says. "We were hoping to achieve computation in cells on the order of seconds, which is significantly faster than what people have achieved thus far."

To accomplish their goal, the researchers used a technique called chemically inducible dimerization, or CID. This tool takes advantage of natural biological mechanisms that bring together two proteins into a complex in the presence of a chemical.

Since AND and OR gates generate a response based on two different inputs, either together or separately, the researchers needed two different CID systems that didn't compete or overlap with each other. They relied on one system that's been studied for years, which brings two proteins, called FRB and FKBP, together in the presence of a drug called rapamycin. Rapamycin comes from bacteria, and FRB and FKBP come from animals.

In addition, they used a second CID system that brings together two other proteins, known as GID1 and GAI, in the presence of a plant hormone called gibberellin. Since this system is native to plants, the gibberellin-based system doesn't compete with the rapamycin-based one, Inoue explains.

The researchers engineered mammalian cells that produce all four of the requisite proteins, as well as a response when the right two proteins came together. When either FRB and FKBP or GID1 and GAI linked up, the cell's membrane developed ruffles easily visible under a microscope.

To create the OR gate, FRB and GAI were bound together at the cell membrane, while FKBP and GID1 were bound together floating freely in the cell. Adding either rapamycin, gibberellin, or both to cells brought the freely floating complex to the one at the cellular membrane, linking up the matching proteins and triggering the output signal.

To create the AND gate, the researchers placed just GAI at the cell membrane, with just FRB and complexes of FKBP and GID1 free-floating in the cell. This system required all four proteins to link up to produce membrane ruffling, which wouldn't occur without both input chemicals.

Tests showed that each of the engineered cellular logic gates produced the desired response reliably, in a matter of seconds. Additionally, as a second proof of principle, the researchers generated similar logic gates that used fluorescence as an output, which worked just as well and quickly.

Eventually, Inoue notes, researchers might use similar cellular logic gates to build larger, more complex circuits that could form the basis for computers that use cells as basic units. In the meantime, these individual cellular circuits could be engineered to produce specific outputs in the

presence of chemicals, making them useful detectors or diagnostic agents. He adds that researchers might also use synthetic logic gate systems like this one to study how cells naturally produce outputs to keep bodily functions running smoothly.

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