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Why many cells are better than one

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Researchers from Johns Hopkins have quantified the number of possible decisions that an individual cell can make after receiving a cue from its environment, and surprisingly, it's only two.

The first-of-its-kind study combines live-cell experiments and math to convert the inner workings of the cell decision-making process into a universal mathematical language, allowing information processing in cells to be compared with the computing power of machines.

The research published on September 15 in *Science* also demonstrates why it's advantageous for cells to cooperate to overcome their meager individual decision-making abilities by forming multicellular organisms.

"Each cell interprets a signal from the environment in a different way, but if many cells join together, forming a common response, the result can eliminate the differences in the signal interpretation while emphasizing the common response features," says Andre Levchenko, Ph.D., associate professor of biomedical engineering and member of the Institute for Cell Engineering. "If a single blood vessel cell gets a signal to contract, it is meaningless since all the surrounding cells in the blood vessel need to get the message to narrow the blood vessel. Cell collaboration does wonders in terms of their ability to transfer information and convert it into decision-making."

One bit of information represents two choices: yes or no, on or off, or one or zero in binary code, used by computer programmers. Two bits doubles the amount of choices to four and so on for each bit added.

To determine how many bits of information a cell has for each decision, the researchers had to measure a real biological decision in progress. They decided to look at a well-known cell stimulant, a protein called tumor necrosis factor (TNF), responsible for turning on the inflammation response in the body. When cells detect TNF on their surface, they transmit a message that sends a messenger protein into the nucleus to turn on inflammation genes.

The researchers administered different amounts of TNF to mouse cells in dishes, and then they determined whether the messenger went to the nucleus. They bound the messenger with a glowing tag; the more messenger present in the nucleus, the brighter the nucleus would appear under a microscope. The researchers used a computer program to quantify the brightness of the nucleus after the addition of TNF. From this, they calculated a single cell's response to be 0.92 bits of information, allowing for two possible decisions.

"What we get from this information is that the cell can only reliably detect the presence of the signal or not, nothing more precise," says Levchenko. "This was a little bit dissatisfying because we were hoping that the cells could recognize many more levels of the input and use that to make more decisions than just two."

The researchers tested other scenarios to see if cells could respond in more ways. They looked at decision outputs other than inflammation, like development and cell survival. They also looked to see if the cell's response to a certain stimulus changed over time, as well as explored whether receiving different input signals that led to the same outcome could boost decision-making potential. None of these different situations drove cells to show greater decision-making ability. Cells seem to have distinct limits to the amount of information they intake that confines the number of decisions they can make, says Levchenko.

Finally, the researchers investigated the idea that cells could collectively respond to input to make decisions together. They went back to quantifying the brightness of the nucleus in response to TNF, but this time they examined clusters of cells and compiled this data into their equation. They found that clusters of as few as 14 cells could produce 1.8 bits of information, corresponding to somewhere from 3 to 4 different potential decisions for the cluster.

The fact that combinations of cells can make more decisions suggests why being multicellular is such a good thing in the animal world and why cells can sometimes achieve so much more if they are working together than separately, says Levchenko.

"We've learned that there is a clear limit on what can happen in a cell, and we are actually quantifying for the first time what the cells can and can't do," says Levchenko. "A lot of people were surprised that this was even possible. This framework we've laid will allow us to test what kind of tricks cells use, other than being multicellular, to expand their decision repertoire."

Provided by Johns Hopkins Medical Institutions

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