Biochemical cell signals quantified for first time

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Just as cell phones and computers transmit data through electronic networks, the cells of your body send and receive chemical messages through molecular pathways. The term "cell signaling" was coined more than 30 years ago to describe this process.

Now, for the first time, scientists have quantified the data capacity of a biochemical signaling pathway and found a surprise – it's way lower than even an old-fashioned, dial-up modem.

"This key biochemical pathway is involved in complex functions but can transmit less than one bit – the smallest unit of information in computing," says Ilya Nemenman, an associate professor of physics and biology at Emory University. "It's a simple result, but it changes our view of how cells access chemical data."

The journal *Science* is publishing the discovery by Nemenman and colleagues from Johns Hopkins University, including Andre Levchenko, Raymond Cheong, Alex Rhee and Chiaochun Joanne Wang.

During the 1980s, cell biologists began identifying key signaling pathways such as nuclear factor kappa B (NF-kB), known to control the expression of genes in response to everything from invading pathogens to cancer. But the amount of information carried by chemical messengers along these pathways has remained a mystery.

"Without quantifying the signal, using math and computer analysis to

attach a number to how much information is getting transmitted, you have a drastically incomplete picture of what's going on," says Nemenman, a theoretical biophysicist.

He and Levchenko, a biomedical engineer, began discussing the problem back in 2007 after they met at a conference.

Levchenko developed microfluidic and measurement techniques to conduct experiments on bio-chemical signaling of the NF-kB pathway, and measure the transmissions occurring on the pathway in many thousands of cells at one time. Nemenman formulated the theoretical framework to analyze and quantify the results of the experiments.

"It was a shock to learn that the amount of information getting sent through this pathway is less than one bit, or binary digit," Nemenman says. "That's only enough information to make one binary decision, a simple yes or no."

And yet NF-kB is regulating all kinds of complex decisions made by cells, in response to stimuli ranging from stress, free radicals, bacterial and viral pathogens and more. "Our result showed that it would be impossible for cells to make these decisions based just on that pathway because they are not getting enough information," Nemenman says. "It would be like trying to send a movie that requires one megabit per second through an old-style modem that only transmits 28 kilobits per second."

They analyzed the signals of several other biochemical pathways besides NF-kB and got a similar result, suggesting that a data capacity of less than one bit could be common. So if cells are not getting all the information through signaling pathways, where is it coming from?

"We're proposing that cells somehow talk with each other outside of

these known pathways," Nemenman says. "A single cell doesn't have enough information to consider all the variables and decide whether to repair some tissue. But when groups of cells talk to each other, and each one adds just a bit of knowledge, they can make a collective decision about what actions to take."

He compares it to a bunch of people at a cocktail party, with cell phones that have weak signals pressed to their ears. Each person is receiving simple messages via their phones that provide a tiny piece to a puzzle that needs to be solved. When the people chatter together and share their individual messages, they are able to collectively arrive at a reliable solution to the puzzle.

A similar phenomenon, called population coding, had been identified for the electrical activity of neural networks, but Nemenman and his colleagues are now applying the idea to bio-chemical pathways.

They hope to build on this research by zeroing in on the role of cell signaling in specific diseases.

In particular, Nemenman wants to analyze and compare the signaling capacities of a cancerous cell versus a normal cell.

"Cancerous cells divide when they shouldn't, which means they are making bad decisions," he says. "I would like to quantify that decision-making process and determine if cancer cells have reduced information transduction capacities, or if they have the same capacities as healthy cells and are simply making wrong decisions."

Nemenman uses a malfunctioning computer as an example. "If you push the 'a' key on your computer and a 'd' always shows up, that means the computer is misprogrammed but the information from your keystroke gets through just fine," he says. "But if you keep pressing the letter 'a'

and different, random letters show up, that indicates a problem with the way the information is being transmitted."

Provided by Emory University