A novel method for identifying the body's 'noisiest' networks

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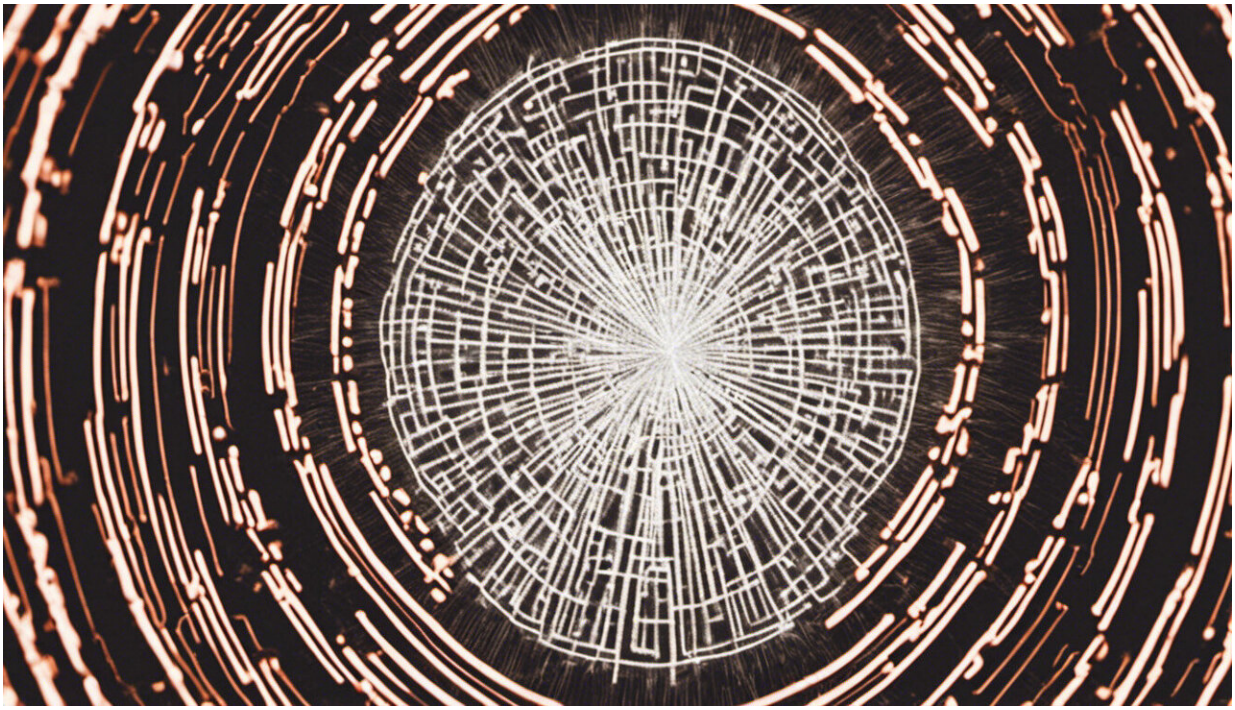

Credit: AI-generated image (disclaimer)

(Phys.org) —A team of scientists led by Yale University systems biologist and biomedical engineer Andre Levchenko has developed a novel method for mapping the biochemical variability, or "noise," in how human cells respond to chemical signals. The research, published Nov. 17 in *Proceedings of the National Academy of Science*, could be

used to tailor drug delivery to a patient's individual cell responses and may have further implications for advances in semiconductor chip design.

Levchenko's method is founded on the recognition that every cell reacts uniquely to the body's chemical signals, even if the cells are all from the same patient and even the same tissue—some cells may react strongly, while other cells may not react at all. A wide diversity of responses is considered a noisy response.

The new method maps noise across multiple branches of complicated biochemical networks. "Knowing how variable the activity is allows us to better target the spectra of activities in those networks," said Levchenko, the John C. Malone Professor of Biomedical Engineering and inaugural director of the Yale Systems Biology Institute.

"For example, if a specific cell network's spectra of response is less noisy, then a comparatively small drug dosage could target the entire spectra. Our mapping technique enables researchers and clinicians to identify those less noisy networks, which could be unique for each patient," he said.

For this research, Levchenko's team—including Alex Rhee and Raymond Cheong of Johns Hopkins University—looked at a signaling system stimulated by cytokine tumor necrosis factor (TNF), which is commonly produced by cells responding to infections. When the body's sentinel cells detect foreign materials, they broadcast the TNF molecule to activate the first line of immune response.

Using a combination of experimental observations and mathematical algorithms, the team measured the effect of TNF input for a small number of target molecules, then inferred how the signal triggers by TNF propagated through the network. Because the TNF signal originated

from the same point, the team could efficiently reconstruct how different branches of the cell communication networks reacted to the signal without measuring the dozens of molecules affected.

"Previous experiments in this field, including our own, would focus on these network responses by looking at the average cell behavior over perhaps millions of cells at a time," said Levchenko. "The new method is unique in that it requires relatively few targets—we observed just three target transcription factors—to reconstruct not only how responsive but also how noisy various branches of the signaling network are. Using this effective methodology, we can now embark on extensive mapping of the sources of noise across signaling networks."

In turn, identifying which networks were noisier enabled Levchenko's team to experimentally confirm that noise tends to increase as the communication chain gets longer, something that could be applicable to research of not only biological networks but even electrical networks.

"Despite the noise in cellular networks," he said, "biology still allows cells and organisms to perform well. Similarly, as today's electronic components become smaller, chip designers more often need to study and circumvent signaling noise. For this reason, the challenges of building effective computational devices and designing effective medical therapeutics are more similar than meets the eye."

More information: Noise decomposition of intracellular biochemical signaling networks using nonequivalent reporters, www.pnas.org/cgi/doi/10.1073/pnas.1411932111

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