Math discovery provides new method to study cell activity, aging

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New mathematical tools revealing how quickly cell proteins break down are poised to uncover deeper insights into how we age, according to a recently published paper co-authored by a Mississippi State researcher and his colleagues from Harvard Medical School and the University of Cambridge.

Galen Collins, assistant professor in MSU's Department of Biochemistry, Molecular Biology, Entomology and Plant Pathology, co-authored the paper published in the *Proceedings of the National Academy of Sciences* in April.

"We already understand how quickly proteins are made, which can happen in a matter of minutes," said Collins, who is also a scientist in the Mississippi Agricultural and Forestry Experiment Station. "Until now, we've had a very poor understanding of how much time it takes them to break down."

The paper in applied mathematics, "Maximum entropy determination of mammalian proteome dynamics," presents the new tools that quantify the degradation rates of cell proteins—how quickly they break down—helping us understand how cells grow and die and how we age. Proteins—complex molecules made from various combinations of amino acids—carry the bulk of the workload within a cell, providing its structure, responding to messages from outside the cell and removing waste.

The results proved that not all proteins degrade at the same pace but instead fall into one of three categories, breaking down over the course of minutes, hours or days. While previous research has examined cell protein breakdown, this study was the first to quantify mathematically the degradation rates of all cell protein molecules, using a technique called maximum entropy.

"For certain kinds of scientific questions, experiments can often reveal infinitely many possible answers; however, they are not all equally plausible," said lead author Alexander Dear, research fellow in applied mathematics at Harvard University.

"The principle of maximum entropy is a mathematical law that shows us

how to precisely calculate the plausibility of each answer—its 'entropy'—so that we can choose the one that is the most likely."

"This kind of math is sort of like a camera that zooms in on your license plate from far away and figures out what the numbers should be," Collins said. "Maximum entropy gives us a clear and precise picture of how protein degradation occurs in cells."

In addition, the team used these tools to study some specific implications of protein degradation for humans and animals. For one, they examined how those rates change as muscles develop and adapt to starvation.

"We found that starvation had the greatest impact on the intermediate group of proteins in muscular cells, which have a half-life of a few hours, causing the breakdown to shift and accelerate," Collins said. "This discovery could have implications for cancer patients who experience cachexia, or muscle wasting due to the disease and its treatments."

They also explored how a shift in the breakdown of certain cell proteins contributes to neurodegenerative disease.

"These diseases occur when waste proteins, which usually break down quickly, live longer than they should," Collins said. "The brain becomes like a teenager's bedroom, accumulating trash, and when you don't clean it up, it becomes uninhabitable."

Dear affirmed the study's value lies not only in what it revealed about cell protein degeneration, but also in giving scientists a new method to investigate cell activity with precision.

"Our work provides a powerful new experimental method for quantifying protein metabolism in cells," he said. "Its simplicity and rapidity make it particularly well-suited for studying metabolic changes."

More information: Alexander J. Dear et al, Maximum entropy determination of mammalian proteome dynamics, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2313107121

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