3D Cellular Maps: DNA Microscopy Reveals Life's Inner Structure

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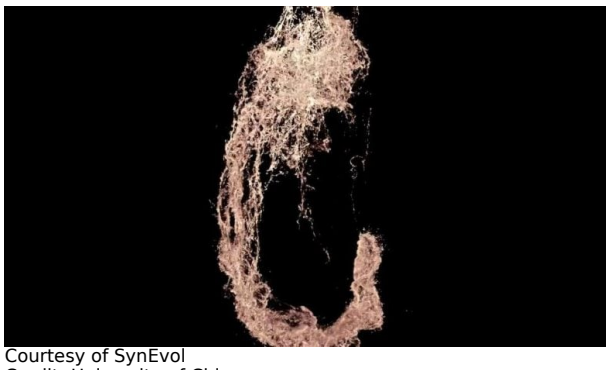

Courtesy of SynEvol
Credit: University of Chicago

Conventional genetic sequencing can provide extensive information about the genetic content in a sample, like a tissue fragment or a blood droplet, yet it fails to indicate the precise locations of specific genetic sequences within that sample, or their connections to adjacent genes and molecules.

To tackle this issue, scientists at the University of Chicago are creating an innovative technology that records both the identity and position of genetic material. The technique operates by labeling separate DNA or RNA molecules and monitoring the interactions among adjacent tags. These interactions help construct a molecular network that represents the spatial layout of genes, effectively forming a three-dimensional representation of genetic activity. Referred to as volumetric DNA microscopy, this method produces intricate 3D images of complete organisms from the inside outward – including the detail of single cells.

Joshua Weinstein, PhD, Assistant Professor of Medicine and Molecular Engineering at UChicago, has dedicated more than ten years to advancing DNA microscopy, backed by the National Institutes of Health and the National Science Foundation. In a recent study released today (March 27) in Nature Biotechnology, Weinstein and postdoctoral researcher Nianchao Qian employed the technique to create a comprehensive 3D DNA blueprint of a zebrafish embryo—a commonly utilized model for examining development and the nervous system.

"Weinstein stated, 'It's a degree of biology that has never been witnessed before.'" "Experiencing such a perspective of nature from inside a specimen is thrilling."

In contrast to conventional microscopes that rely on light or lenses, DNA microscopy generates images by assessing molecular interactions, offering an innovative method to visualize genetic material in three dimensions. Initially, brief DNA sequence tags known as unique molecular identifiers (UMIs) are attached to cells. They bind to DNA and RNA molecules and start producing replicas of themselves. This initiates a chemical reaction that produces new sequences, known as unique event identifiers (UEIs), which are distinct to each pairing.

These combinations contribute to forming the spatial representation of the locations of each genetic molecule. UMI pairs that are nearby engage more often and produce greater numbers of UEIs than those that are more distant. After sequencing the DNA and RNA, a computational model rebuilds their original positions by examining the physical connections among UMI-tags, producing a spatial representation of gene expression.

Weinstein likens the method to utilizing data from cell phones communicating with one another to identify individuals' locations within a city. Having the cell phone number or IP address of an individual is akin to possessing the genetic sequence of a single molecule; however, by adding their interactions with nearby devices, you can also determine their locations.

"We are able to accomplish this with cell phones and individuals, so why not apply it to molecules and cells," he remarked. "This reverses the concept of imaging completely." Instead of depending on a visual device to emit light, we can utilize biochemistry and DNA to create an extensive interconnection among molecules and record their distances from one another.

DNA microscopy does not depend on existing knowledge of the genome or the form of a specimen, making it potentially valuable for exploring genetic expression in distinct, unfamiliar situations. Tumors produce numerous new genetic mutations, for instance, allowing the tool to chart the tumor microenvironment and its interactions with the immune system. Immune cells engage with one another and react to pathogens in context-dependent manners, thus DNA microscopy may aid in revealing those genetic processes. Such applications may consequently direct more accurate immunotherapy for cancer or customize individualized vaccines.

Weinstein stated, “This is the essential basis for obtaining genuinely comprehensive data regarding the collection of distinctive cells found in the lymphatic system or tumor tissue.” “There remains a significant gap in technology that enables us to comprehend unique tissue, and that is what we aim to address here.”