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Integrated Single-Cell RNA-Seq, Array Spatial Transcriptomics Analysis Puts Cells Into Context

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NEW YORK – Researchers from New York University have developed a framework for integrating data from spatial and single-cell transcriptomics, revealing information on how close cells are to each other in tissues.

Their method, which uses a new process they named multimodal intersection analysis (MIA) provides higher resolution and sensitivity than the spatial transcriptomics method developed by researchers at Sweden's Science for Life Laboratory (SciLifeLab) and Karolinska Institute, the researchers said in a paper published Monday in *Nature Biotechnology*.

Spatial transcriptomics and single-cell RNA-sequencing have "complementary blindsides," said senior author Itai Yanai, director of the Institute for Computational Medicine at NYU Langone Health. By analyzing a sample with both methods and coupling the results from each part, "you can have the best of both worlds." The new study did not use a "high-definition" spatial transcriptomics method published by the SciLifeLab team in September 2019, which claims to have sub-cellular resolution, albeit with low sensitivity.

In the proof-of-principle paper, Yanai's team found that their method could help them map cell types, cell subpopulations, and even cells states in a spatial context. In pancreatic cancer tissue, tumor cells in a "stress" state were often found near inflammatory fibroblasts, for example. "Cancer cell states are something that many publications are reporting and people are puzzled about it," he said. "Here we show that if you have the spatial component, you can begin to make sense of them."

Yanai said his lab has been working with the ideas behind spatial transcriptomics for years. "It's insanely powerful," he said. "It addresses so many things and will revolutionize pathology, developmental biology, and tumor biology," among other fields. But existing methods have not yet achieved single-cell resolution with high transcript sensitivity to help classify cells, he said.

The NYU team came up with a way to integrate sets of genes identified as being important from each modality. MIA defines sets of genes associated with entities such as cell types or cell states. For example, in the paper, the team found 555 genes whose expression was enriched in fibroblast cells. After doing a similar analysis for the array "spots" from the spatial transcriptomics method, "all we need to do is ask if the overlap is [statistically] significant," Yanai said.

The NYU team used the older ST method and InDrop single-cell RNA-seq; however, Yanai said MIA could use RNA-seq profiles generated by any platform. He suggested that MIA, the code of which his lab is making available on GitHub, could be used with Visium, the spatial transcriptomics platform developed by 10x Genomics after acquiring the technology in 2018. His lab has begun using Visium, which was released in late 2019, but did not use it for the *Nature Biotech* study, he added.

The authors noted several limitations to their approach. The size of the spatial transcriptomics array — about 6 mm by 6.5 mm — is not always large enough to cover the entire tissue section, they wrote, and diffusion of transcripts across the slide can confound results.

"We may lose something by splitting [the sample] because the spatial transcriptomics is not done on precisely the same cells as the single-cell [sequencing]," Yanai added. "We do feel it is important to do both [analyses] on the same sample because specific samples could have unique subpopulations and cell types."

He added that MIA also does not provide estimates for the number of different cell types present at each array spot. Rather, it offers "a statistical framework to let the researcher set the level of confidence" in determining cell types.

Looking at cancer cells and tumor tissues, as the researchers did in the paper, is an obvious direction for the technology, but Yanai said his lab is also looking at placenta samples. The authors suggested that the method "could in the future be of prognostic value," but Yanai said they have not applied for any patents and don't plan to commercialize MIA.

"You can now use this approach for so many things and be able to generate so many hypotheses," he said.

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