The scientists tested their method on a tiny worm called *Caenorhabditis elegans* and could identify known as well as new types of cells.

A speedy way to catalogue human cells

New method helps scientists look at large numbers of cells at the same time, but they have miles to go before they can catalogue all 37 trillion cells

CARL ZIMMER

THERE ARE some questions in biology that you'd think were settled long ago. For instance: How many types of cells are there in the human body?

"If you just Google this, the number everyone uses is 200," said Jay Shendure, a geneticist at the University of Washington. "But to me that seems absurdly low." A number of scientists like him want to build a more complete catalogue.

Yet there are an estimated 37 trillion cells in the human body. The traditional ways to identify cell types — such as carefully tracing the shape of individual cells under a microscope — are too slow and crude for the job.

Last week, Dr Shendure and his colleagues published a report describing a speedy new method for taking such a cell census. Instead of inspecting one cell at a time, they measured the activity of genes inside 42,035 cells at once.

Although still at an experimental stage, the method may become an essential tool for cataloguing every cell type in the human body, experts said. "It's a really important piece of work," said David M Miller, a cell biologist at Vanderbilt University, who was not involved in the study. "With this approach, you can do more for a whole lot less work, and a whole lot less money."

Genetically speaking, all cells in the body are identical. They carry the same 20,000 or so protein-coding genes. What distinguishes each type is the particular combination of genes the cell uses to make proteins. The first step in this process is making a copy of the gene in the form of RNA. The cell uses the RNA molecule as a template to build a protein.

Dr Shendure and his colleagues reasoned that the distinctive collection of RNA molecules inside a cell could provide clues about the cell's type. To measure that RNA, they developed a kind of molecular "bar coding."

In the first step, the researchers pour thousands of cells into hundreds of miniature "wells". Each well contains molecular tags that attach themselves to every RNA molecule inside the cells. The process is repeated two or more times until each cell ends up with a unique combination of tags attached to its RNA molecules. Dr Shendure and his colleagues then break open the cells and read the sequences of tags at once.

The "bar codes" allow the scientists to see which genes are active in each cell. Cells of the same type should share many of those genes in common. "We came up with this scheme that allows us to look at very large numbers of cells at the same time, without ever isolating a single cell," said Dr Shendure.

He and his colleagues call their method sci-RNA-seq (short for single-cell combinatorial indexing RNA sequencing). To test it, they set out to classify every cell in a tiny worm, *Caenorhabditis elegans*. They raised 150,000 *C. elegans* larvae and then doused them with chemicals that broke them apart into individual cells. They then tagged all the RNA in the cells. With the new method, the researchers were able to identify 27 cell types that had been identified in previous studies. The team also was able to break them down into smaller groups, each with a slightly different pattern of gene activity. They identified 40 different kinds of neurons, for example, including rare types. In few cases, only a single such neuron develops in each worm.

"I was excited because it worked extremely well — they uncovered results that will be valuable for me and for the whole field," said Cori Bargmann, an expert on *C. elegans* at the Rockefeller University.

Yet for now, sci-RNA-seq falls far short of capturing the full complexity of cell types. Dr Shendure and his colleagues could not match some of their clusters of neurons to a known type of cell, and they did not find most of the 118 different types of neurons that earlier studies have documented. "We don't consider this a finished project," said Dr Shendure.

Aviv Regev, a computational biologist at the Broad Institute and MIT, said that differences between the human body and that of C. elegans would require some different strategies. For one thing, humans are huge compared to C. elegans. The researchers certainly will not try to dissolve human bodies into 37 trillion loose cells and analyse them all at once.

And *C. elegans* follows a tightly controlled genetic programme to build its body. Its cells always end up in the same place, in the same numbers. Humans are a lot more flexible in how they develop: the locations of cells vary from one person's body to the next.

"The trick is to relate cells to the place they came from," Dr Regev said.

Nevertheless, sci-RNA-seq may well become a useful tool for work in humans. "The major benefit is that it could scale to capture many more cells in one experiment," Dr Teichmann said. "It's an elegant and potentially very powerful approach."

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