No magic wand required: Scientists propose way to turn any cell into any other cell type

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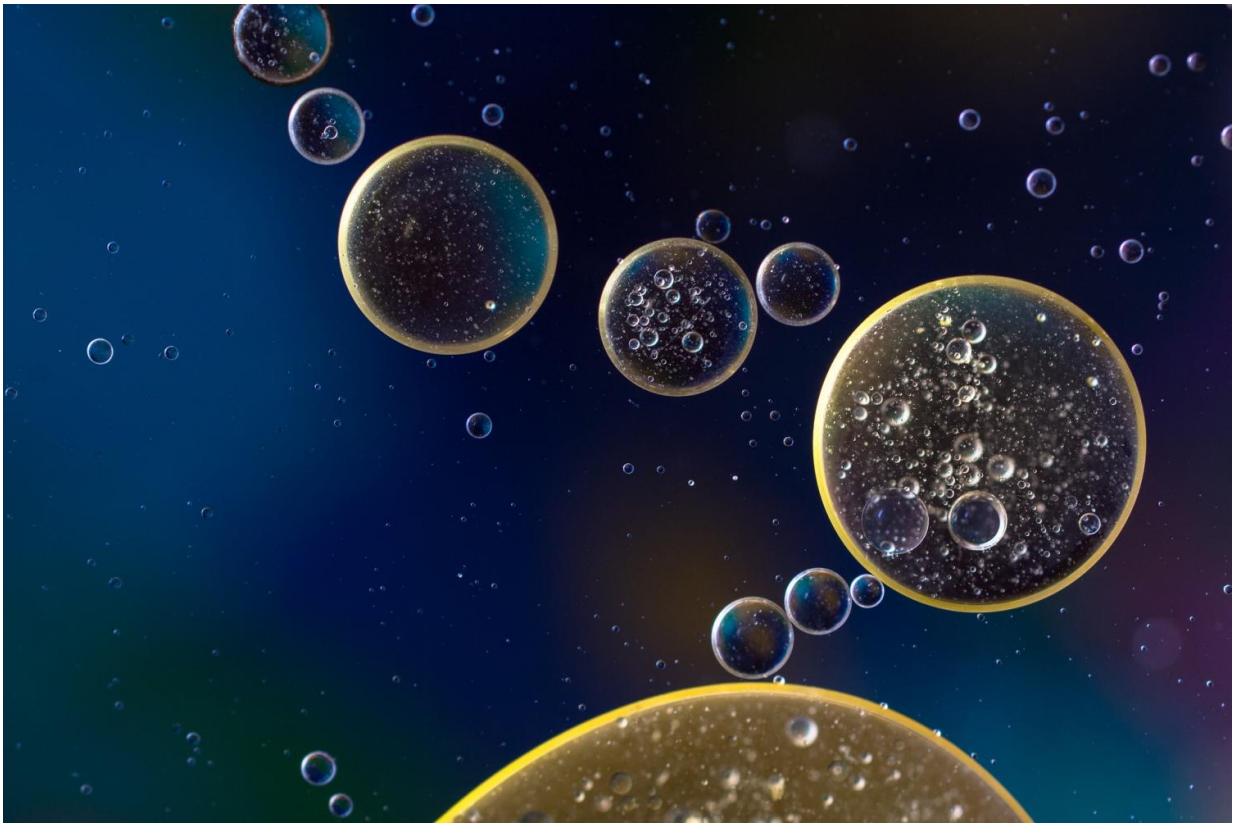

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In fairy tales, all it takes to transform a frog into a prince, a servant into a princess or a mouse into a horse is the wave of a magic wand.

But in the real world, transforming one living thing into another isn't so easy. Only in recent years have scientists discovered how to do it, with tiny individual living cells.

In fact, the team that figured it out won the Nobel Prize, for discovering how to take an ordinary human skin cell and transform it into a stem cell—the same kind of cell found in embryos. With painstaking effort, such cells can grow up to become any other kind of cell in the body.

And in the last decade, that time-consuming transformation technique has opened the door for discoveries about many diseases, from birth defects to cancer.

But what if scientists could cut out a step, and go straight from skin cell to any other kind of cell?

A new paper in the *Proceedings of the National Academy of Sciences* lays out a way to do it - and avoid all the intermediate steps involved in the other technique, which produces induced pluripotent stem cells.

In the paper, they lay out a way to harnessing the wealth of data now available about DNA activity, and reprogram cells directly. The formula also provides a blueprint for determining the optimal combination of factors and when they should be added to accomplish this reprogramming. Using this formula, the authors were able deduce the factors that the Nobel-winning team discovered, a process that required many years of trial and error.

The concept, developed by a team of University of Michigan scientists together with colleagues from the University of Maryland and Harvard University, combines biological information on genome structure and gene expression with a fair bit of math, using an approach called data-guided control. The paper's authors include Roger Brockett, Ph.D. of

Harvard and U-M mathematics department chair Anthony Bloch, Ph.D.

Though the paper spells out an algorithm for transforming cells—and successfully predicts factors that are already known to reprogram cells—it does not directly test the formula in the laboratory. The authors have plans to further test their method, and hope that it can be tried by scientists at Michigan and around the world.

If it bears fruit, they predict it could have applications including regenerating diseased or lost tissue, and fighting cancer.

"Cells in our body naturally specialize," says Indika Rajapakse, Ph.D., the U-M bioinformatics and mathematics researcher who is senior author of the new paper. "What we propose could provide a shortcut to doing the same, to help any cell become a targeted cell type."

Rajapakse notes that the idea of direct reprogramming is not new. In the late 1980s, a team led by the late scientist Harold Weintraub turned skin cells directly into muscle cells by bathing the cells in a type of molecule that encouraged certain genes in the cells' DNA to be "read". Rajapakse trained with Weintraub's colleague Mark Groudine, Ph.D. at Fred Hutchinson Cancer Research Center.

The new model builds on that idea, by also harnessing the power of these molecules, called transcription factors or TFs.

But instead of bathing the whole cell culture in one TF, the scientists aim to target cells with specific TFs at specific crucial times in their lifespan. They lay out a mathematical control model for harnessing all the information that can now be learned about cells at the molecular level, and combining it to map out the timing and sequence for injecting TFs to get the desired cell type.

"We have so much data now from RNA and transcription factor activity, and from Hi-C data of chromosome configuration that tells us how often two pieces of chromatin are near one another, that we believe we can go from the cell's initial configuration to the desired configuration," says Rajapakse.

The Hi-C technique lets scientists track the location of, and contact between, portions of the DNA/protein complex called the chromatin. So even if two genes sit far apart on a long strand of DNA, they may come in close contact with one another when those looping, folding strands end up next to one another. If one of those genes gets "read", it may produce a transcription factor that then sets in motion the "reading" of the other gene, and the production of a certain protein that plays a key role in transforming the cell in some way.

The amount of data that would come out of analyzing these "topologically associating domains" in just one type of cell is huge. But modern bioinformatics techniques make it easier to make sense of it all.

The first author of the paper is Scott Ronquist, a Ph.D. student who began working with Rajapakse in the Computational Medicine and Bioinformatics department as an undergraduate at U-M. He and former postdoctoral fellow Geoff Patterson, Ph.D., led the effort to use gene expression and TAD data generated in the Rajapakse lab and publicly available gene expression and TF data to test their model. They were able to see patterns in the data that reflected the pace of normal cell differentiation.

Now, they're working on testing the model proactively, in the laboratory of Max Wicha, M.D., the Forbes Professor of Oncology at Michigan Medicine, U-M's academic medical center, and former director of the U-M Comprehensive Cancer Center.

"This algorithm provides a blueprint that has important implications for cancer, in that we think cancer stem cells may arise from normal stem cells via similar reprogramming pathways," says Wicha, who is a co-author on the PNAS paper. "This work also has important implications for regenerative medicine and tissue engineering, since it provides a blueprint for generating any desired cell type It also demonstrates the beauty of combining mathematics and biology to unravel the mysteries of nature."

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