Device draws cells close -- but not too close -- together

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In a popular children's game participants stand as close as possible without touching. But on a microscopic level, coaxing cells to be very, very close without actually touching one another has been among the most frustrating challenges for cell biologists.

Now MIT researchers led by Sangeeta Bhatia, associate professor of electrical engineering and computer science at the Harvard-MIT Division of Health Sciences and Technology (HST) and Brigham and Women's Hospital, have solved the problem with a novel device. The work promises to allow researchers to perform cellular experiments that were previously impossible.

Bhatia and HST postdoctoral associate Elliot Hui describe the device in the March 27 online issue of the *Proceedings of the National Academy of Sciences*. Hui is first author of the paper.

The new device, a microelectromechanical system (MEMS), allows biologists to physically arrange cells to be either touching, close but not touching, or completely separated from one another. Further, they can change that configuration at will. And the device works without the use of tools such as the microscopes or robotic control arms typically required by MEMS devices.

Because cells communicate via signals transmitted both through the touching of cell membranes and through soluble molecules that flow between separated cells, biologists need to vary the spacing of cells to

study their interactions. Also, since some signals induce a cell to change its internal programming, it is important for biologists to be able to rearrange cells over time to learn which signals spur change and which don't.

In the past, researchers erected chemical "moats" around cells in an attempt to keep them close but separate. Over time, however, cells invariably breech the divide. "They are very good at crossing the moat," said Bhatia, who performed several such experiments in graduate school.

Bhatia and Hui's first thoughts about how to solve this cellular space and time problem involved another children's game: plastic puzzles with squares that slide around on a grid. They wondered if they could put different cells on each square and then move them around.

This idea quickly evolved into an elegant tool designed expressly for biologists.

The device involves two separate comb-shaped pieces coated with living cells. These two pieces can click into place at two settings: One allows cells on the edges of the combs to touch, the other maintains a gap of 80 micrometers, or about four cell widths. The assembly is geared so that switching between these two settings involves a movement of two millimeters, an amount controllable by the human hand. Hui selected 80 micrometers as the gap setting because at shorter distances, cells sometimes migrate across the gap and end up touching. And at wider distances, some soluble signals drop off.

Bhatia and Hui have used the new device to study liver cells. The two found that to get liver cells to express specific liver functions, they needed to touch supporting stromal cells for 18 hours. For the liver cells to survive and continue to act as liver cells, they don't have to keep touching these stromal cells, but they do need to stay close.

The finding will allow Bhatia and Hui to examine more deeply which surface molecules trigger liver cell differentiation and which soluble molecules maintain it.

Such information will help the team devise different approaches to engineering liver therapeutics by helping them understand exactly which signals are needed to support specific liver cell functions. Instead of building an entire liver from scratch, Bhatia wants to isolate the key cell type, "the business end of the organ," and get it to work without replicating the entire cellular environment that supports it. "If you can get away with it, you want to get rid of the supporting cells," she says.

This simple device will also be useful for exploring a host of other cellular interactions. Most prominently, the device could be very useful in exploring embryonic development, during which the local cellular environment dictates development of major organs over time, and cancer, in which supporting cells are thought to play a role in tumor formation.

Source: Massachusetts Institute of Technology