

SIMULATION ADVANCES THE DESIGN OF A MICROFLUIDIC THERAPEUTIC CELL SORTER

Researchers at The Technology Partnership (TTP) in Cambridge, UK, used multiphysics simulation to help create a novel cell sorting device for the treatment of cancer.

By **GEMMA CHURCH**

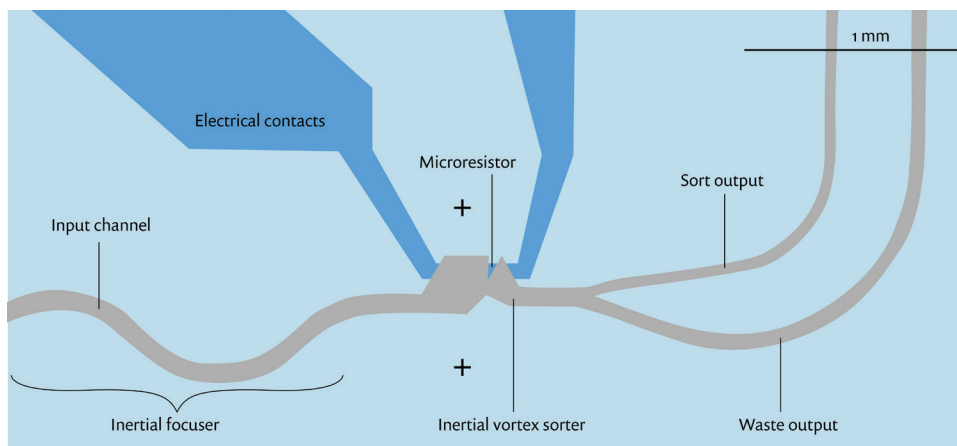


Figure 1. Geometry and components of the vortex-actuated cell sorter.

RESEARCHERS AT The Technology Partnership (TTP plc) in Cambridge, UK, have created a novel cell sorting device that could provide a manufacturing process for cell therapies to treat a range of diseases, including cancer, with many other applications in basic research, diagnostics, and bioproduction.

Current cell sorting systems can isolate rare cell phenotypes or subpopulations of cells that behave differently for biological research. However, cell sorting does not translate well to the clinic. Robyn Pritchard, a life sciences consultant at TTP, explained: “While a lot of exciting new developments in the field of cell therapy need better cell separation technology, current cell sorters are not capable of producing cell therapies.”

The primary traditional method of cell separation is known as jet-in-air sorting, or by its trademark fluorescence-activated cell sorting (FACS). Cells are first measured individually by a laser and subsequently stream through the air in droplets to be individually deflected by high-voltage electrodes. Commercially available jet-in-air systems are not suitable for therapeutic use due to relatively

low cell processing rates, the need for highly skilled operators, and the risks to both patient and operator from nonsterile fluid handling and the production of droplets in the air, which may carry pathogens.

» BEYOND JET-IN-AIR: THE VORTEX-ACTUATED CELL SORTER

TTP HAS INVENTED a new microfluidic cell sorting technology, the Vortex-Actuated Cell Sorter (VACS). Similar to jet-in-air sorting, fluorescently labeled

cells are measured optically, and cell sorting decisions are made in real time.

VACS consists of an input channel and uses a novel geometry to sort cells into two output channels, one for the waste cells and one for the cells of interest (Figure 1).

The new sorter could address many of the issues associated with existing cell sorters, as Pritchard explained: “For cell therapy, the key challenge is to sort fast enough. Any single-stream sorter, including jet-in-air, reaches a speed limit caused by killing the cells. To go faster requires multiplexing: operating many cell sorters in parallel. To create a multiplex cell sorter without making the measurement and control system too complicated, the best approach is by minimizing the size of the individual sorters. This is so that enough of them fit under just one microscope objective lens. The team was looking to process about half a billion blood cells with high purity and yield in an hour; in other words, about 10 to 20 times than what conventional cell sorters can manage.”

Pritchard added “The biggest challenge to making a faster cell sorter is to make a much smaller cell sorter that can operate at similar speeds to conventional instruments.”

VACS will be a safer option because it is enclosed and does not produce hazardous aerosols, unlike the jet-in-air systems. The new sorter is also disposable, which mitigates the risk of contamination and cross-contamination across

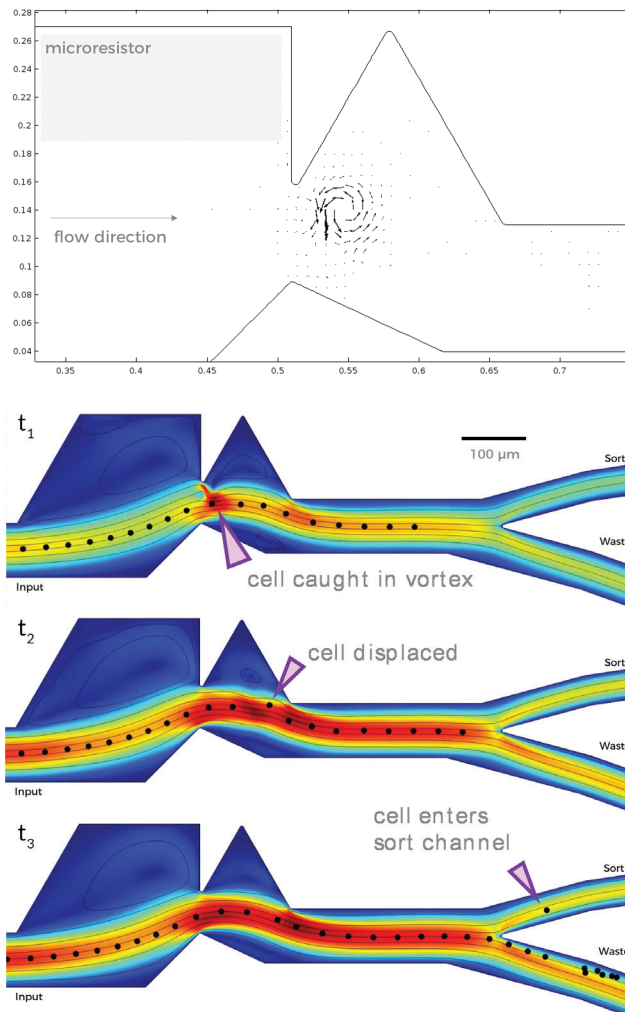


Figure 2. Simulation results showing the working of a VACS device. Plot showing the position of the microresistor actuator, which produces the thermal vapor bubble, and a vector plot of the vortex according to the simulation (top). The time slices (bottom) show the cell caught in the vortex, causing the displacement of the cell across the streamlines, before the cell eventually enters the sort channel.

samples. Finally, the sorter is highly practical and portable, easy to automate, and a cost effective solution for good-manufacturing-practice (GMP) cell therapy production.

»» HIGH SPEED IN SMALL PLACES

THE VACS DEVICE measures 1 mm by 0.25 mm, including the actuators, and can be arrayed on a chip with a pitch of ~1 mm, including all plumbing. “We believe this makes our design the smallest high-speed cell sorter technology in the world,” Pritchard asserted.

“The team started with a short list of actuators that were small enough to fit inside the VACS device. One notable mention was a thin-film microheater, which could create

thermal vapor bubbles and was both small (~0.1 mm wide) and easy to manufacture. However, the experiments and COMSOL Multiphysics® simulations quickly showed that the listed actuators were too fast and weak to move a cell on their own.”

Pritchard said, “Then we had a moment of inspiration. What if we could amplify the displacement caused by the actuator by using the ideas of inertial microfluidics?” This is currently a hot new research field, utilizing inertial effects to manipulate cells on tiny length scales. “We postulated that if we could use the actuator to generate a tiny vortex, that vortex could flow downstream with a cell of interest, gradually moving it from the waste stream to the sort stream. The idea of VACS was born.”

»» CLOSING THE LOOP WITH MULTIPHYSICS SIMULATION

“IT WAS UNTHINKABLE to design VACS devices without multiphysics simulation,” according to Pritchard. Not only were these microfluidic effects very far from everyday experience, until recently, nobody believed that inertial effects were important in microfluidic devices. Moreover, each iteration of the device

was expensive and time consuming to make and test experimentally.

Multiphysics simulation was instrumental in the conception of this design. Using a fluid dynamics model, the TTP team simulated the effect of the expansion and collapse of the thermal vapor bubble using a “moving wall technique”: moving the boundary locally by a realistic amount to simulate the bubble.

Pritchard said: “This mimicked the edge of the bubble and the effect of the 10- μ s pulse of the thermal vapor bubble but without the need to simulate the complicated physics of the large deformation a bubble would create. As a result of this novel modeling approach, we could iterate between 20 to 30 designs to rapidly get the inertial vortex concept working with enough confidence before we built the real device.” After many iterations of the simulation (Figure 2), the prototype worked as designed for the first time in real life.

Within VACS, when a cell of interest is identified, the actuator creates a thermal vapor bubble, which expands and collapses within 10 μ s. This creates an inertial vortex, which persists for 200 μ m and permanently deflects the cell by around 20 μ m.

“This pace of development would not have been possible without the modeling and simulation tools we have used.”

—ROBYN PRITCHARD, LIFE SCIENCES CONSULTANT, TTP

The cell then travels to a separate sort channel where it is collected. All other cells automatically flow into a waste channel. A composite image of the sort and waste trajectories is shown in Figure 3.

» VALIDATING THE FINAL PRODUCT

THE TEAM HAS ALSO USED multiphysics to validate their designs. Pritchard explained: “We faced various teething issues with chip fabrication, and simulation was often our best tool to work out what was causing the issue and fix it. In particular, the quality of several important features came out differently from our microfabrication processes than specified in our design. We used simulation to tweak the design to improve performance based on features that we could build.”

The team is now building the multiplex version of the chip (Figure 4). Multiphysics simulation is being used to test several aspects of this chip. Pritchard explained: “With 16 input channels and 16 individual sorters, we are working with a highly complex microfluidic system where we have to ensure that equal amounts of fluid and cells flow down each channel.”

The team predicts that the single-channel inertial vortex sorter will be commercially available in the near future, with the multiplex design expected to follow shortly thereafter. Pritchard added: “We hope to prove

the multiplex design in the coming months and have a full proof of concept machine working shortly after this to demonstrate the technology. This pace of development would not have been possible without the modeling and simulation tools we have used.” ©

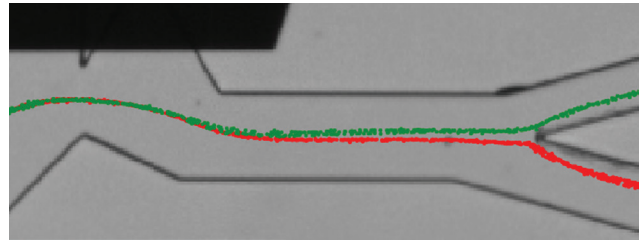


Figure 3. Trajectories of cells going to sort (green) and waste (red) in the VACS device.

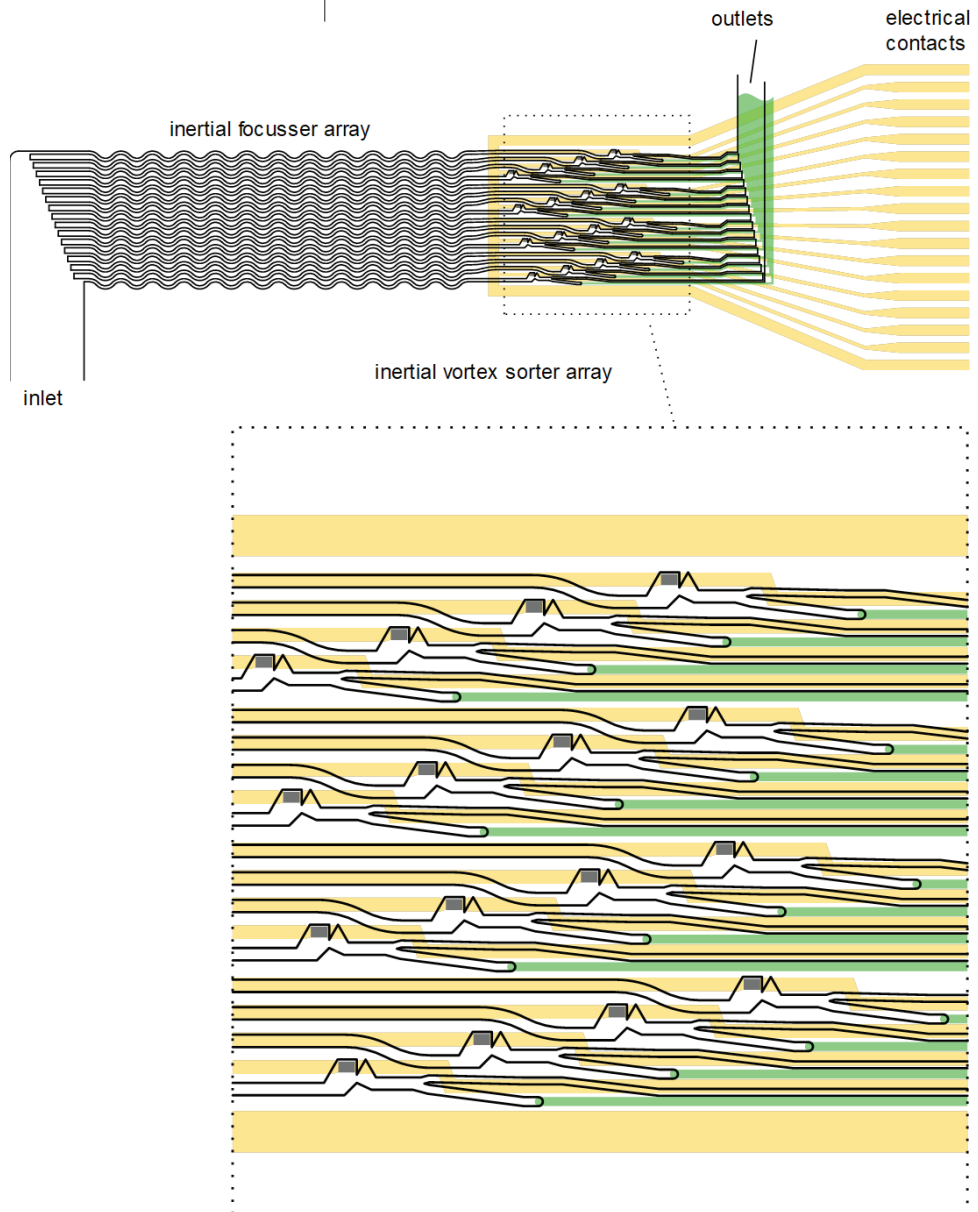


Figure 4. Inertial vortex sorter with 16 input channels and 16 individual sorters.