THE AUTHOR FILE

Scott Manalis

Musical microfluidics to watch and weigh growing cells

Around 250 BC, King Hiero worried that the gold in his crown might be fake. Archimedes, with his eureka moment about buoyancy differences between the crown and a solid gold bar, revealed the forgery.

Scott Manalis

Taking Archimedes' ideas to biology, Scott Manalis, a physicist at the Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology (MIT), and his team previously built a microfluidic device—a suspended microchannel resonator (SMR)—that weighs cells as they move through the device. Making big engineering changes to the tiny device, the team has now turned the SMR into cell cycle TV as it weighs multiple generations of single cells over about 100 hours of growth.

These measurements show aspects of single-cell biology "unknown to us before," says MIT biologist and Koch Institute director Tyler Jacks, a regular visitor in Manalis's lab. This device might one day register unique physical properties of circulating tumor cells, he says.

Bringing precision measurement technologies to the life sciences is "the flavor of every project in my lab," Manalis says. He joined MIT in 1999 after finishing his PhD at Stanford University.

Tagging cells with fluorescent cell cycle indicators, Manalis's team watched and weighed them in the device. They clocked the rate at which cells plump up at different phases of the cell cycle. As a cellular weigh station, the SMR registers cell mass with femtogram accuracy when the cell travels past a tiny cantilever strip that juts out into the middle of a microchannel like a diving board. The strip is outfitted with sensors and oscillates at high speeds, changing its tune in the second it takes for the buoyant cell to pass by. The signal is converted to mass measurement.

Previously, frequent transit through the SMR seemed to crimp cell growth, so the team devised a kind of quiet travel lounge where the cells might prefer to grow. Stopping cell movement reliably is as hard as controlling a marble on a plate. Manalis admits he was skeptical when graduate student Sungmin Son began adding control elements such as pressure regulators, gradients and automated pneumatic valves to the device, but "he proved me wrong," Manalis says.

Son's architecture provides unperturbed growth zones between the cell's trips through the weigh station. "So now it is spending only 1/60th of its life in motion," Manalis says. Cells grow more readily in the modified device and, thanks to hydrodynamic focusing, take "a very well-defined path" through it, he adds. By adding an adapted fluorescence microscope, the team also created an imaging window into the cells' travels. The device can now couple measurement of mass to cell cycle phase.

The reconfigured SMR should please biologists and engineers because cells stay happy for multigenerational growth and because it delivers mass measurements ten-fold more accurate than those of the previous version.

SMR measurements hint at the processes governing cell growth and size in healthy and cancerous cells, says study coauthor Marc Kirschner, a systems biologist at Harvard Medical School. Researching such processes requires accurate measurement, he says. In their collaboration, he pushed Manalis "to do more and more amazing tricks." Manalis is "halfway to being a biologist," says Kirschner. "Alas, I have not made any progress in becoming an engineer."

Manalis's fascination with precise measurement dates to an undergraduate internship at Digital Instruments, an atomic force microscope company where his mentor was staff physicist Ken Babcock. They stayed in touch, even after Babcock moved to other positions. In 2006, they cofounded Affinity Biosensors in Santa Barbara, California, where Babcock is now CEO. Grants and support from independent angel investors have financed the firm's efforts to turn the SMR into a 2-foot-by-2-foot benchtop instrument called Archimedes, in honor of the scientist of antiquity.

"We have a dial on the cell's surroundings."

Archimedes has been sold to biotech companies, where the device is used to weigh protein biotherapeutics to ensure the proteins do not aggregate, says Babcock, adding that he plans to keep disseminating approaches developed in Manalis's lab.

Manalis is now working on algorithms to allow the SMR to track multiple cells in a lineage. He is also tailoring the microfluidics so that cell growth can be tested in diverse microenvironments with added nutrients or a drug. "We have a dial on the cell's surroundings," Manalis says, which can let researchers quickly probe cells in ways not possible in bulk cultures.

Vivien Marx

Son, S. *et al.* Direct observation of mammalian cell growth and size regulation. *Nat. Methods* **9**, 910–912 (2012).