

Actual Size: 20 x 20 mm

## Small-Scale Solutions Miniaturized experiments on a chip could make biomedical research easier and faster.

STEPHEN R. QUAKE WOULD HAVE BEEN THE PERFECT Mr. Fix-it for the Lilliputians, the little people of *Gulliver's Travels*. "I spend a lot of time doing plumbing," he says—on a most diminutive scale. His tinkering is focused on dense networks of tiny pipes, valves, and sinks that are cast within clear rubber microchips no larger than a credit card.

Such devices are the promising new tools of microfluidics, the science of manipulating fluids at nanoliter volumes—one-hundredth to one-thousandth that of a human teardrop. As Quake, an HHMI investigator and biophysicist at Stanford University, has cleverly demonstrated, his plumbing arrangements are capable of running miniaturized molecular biology experiments. In some cases, thousands of reactions can run in parallel—all without the standard muss and fuss of test tubes and fluid-dispensing pipette tips or the hulking robotic machines used in large-scale, automated genetic studies.

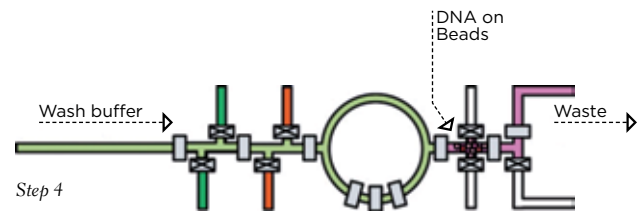
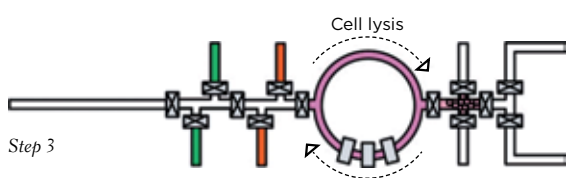
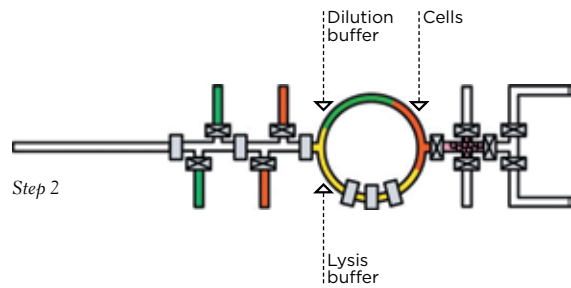
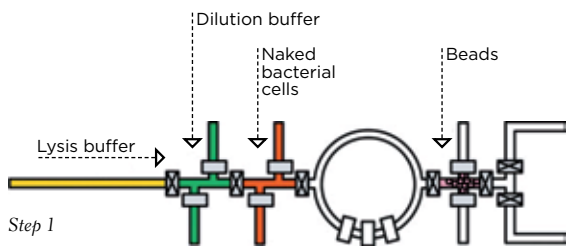
Chemists first invented lab-on-a-chip devices to analyze gases in the 1970s, but the effort to make practical microfluidics tools for biological studies has gained traction only in the past decade. One major advance, led by George Whitesides at Harvard University in

the late 1990s, was to fabricate the chips from cheap, flexible rubber rather than the expensive, stiff silicon used to manufacture computer chips. In a method dubbed "soft" lithography, Whitesides and his colleagues started with the same photographic processes that computer-chip companies use to cast an integrated-circuit blueprint in a single wafer of silicon, but they poured rubber into the chip-making molds instead.

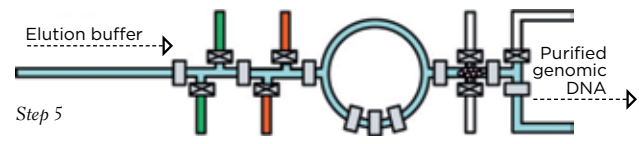
Still, microfluidics researchers needed a way to pipe in reagents and flush them around. "The most powerful way to manipulate fluids on a chip is to have mechanical valves—just like the valves in your sink—so that you can have absolute control over the fluids," says Quake. Creating valves proved difficult, however, and scientists had been able to put only one to three of them on a chip. Quake solved that problem as an associate professor at the California Institute of Technology in 1999, with his students and Caltech physicist Axel Scherer. "We found a way to break through that bottleneck," he says.

The solution was to use two layers of rubber, each containing a channel about 100 micrometers wide—a tad thicker than a human hair—by 10 micrometers high. The thin layers are stacked and sealed

Image by Jong Wook Hong and Stephen Quake. Reprinted with permission from Nature Biotechnology, 2004, 22 (4):435-439. © 2004 Nature Publishing Group.



This particular lab-on-a-chip by Stephen Quake isolates living bacterial cells, lyses them open, and extracts their DNA—all within a footprint the size of a postage stamp. **LEFT** This chip's parallel design allows processing of three samples at once. Food coloring is used here to differentiate the channels. Those filled with green control the opening and closing of the chip's 54 valves. The yellow-, blue-, and red-filled channels bring in reagents. **THIS PAGE** Cells and buffers are moved in and out of a processing unit through fine tubing connected by stainless steel pins. Valves, represented by small rectangles, are marked with an x when closed.



on top of each other, with the channels running perpendicular to each other. Applying pneumatic pressure through the top “control” pipe deflects the walls of the bottom “flow” pipe downward, closing it.

“You squish it,” says Quake. “It’s just like stepping on a garden hose.” In 2002, his team successfully developed multilayered chips with thousands of pneumatic valves—now known in the field as “Quake valves”—connecting hundreds of chambers.

Since then, looking for ways his invention could be used to speed up bench work, Quake and his collaborators have used labs-on-chips to crystallize proteins (a first), to purify DNA from bacterial cells (see diagram), and to calculate the energy it takes for a protein to bind to a piece of DNA.

Most recently, Quake has been working on “interrogating” single cells for genetic data. Several years ago, he read in a journal article by Stanford microbiologist David Relman that many disease-causing pathogens remain unknown because more than 99 percent of microbes cannot be grown in lab cultures. Microbial ecosystems are complex little societies of so many interacting bugs that it is technically challenging to pick out and learn about any one player.

Quake contacted Relman and joined him in studying the microbial jungle of the human mouth. Quake’s group designed a device with nine processing units to analyze bacteria that thrive within tooth plaque. By routing the sample through a series of chambers, each unit could isolate an individual bug, lyse it open, and make hundreds of thousands of copies of its genome. With further work off-chip, the team successfully sequenced most of the genome of one microbe called TM7—the first of its bacterial class for which researchers have any genetic information. They published the results in July in the online early edition of the *Proceedings of the National Academy of Sciences*.

At Stanford, Quake has set up a foundry with a clean room for producing microfluidics chips—2,680 of them last year—for academic researchers. At age 38, he holds more than 30 U.S. patents and is cofounder of two companies that have been developed around his technology, Fluidigm and Helicos BioSciences.

Quake has a big goal for his small devices: he envisions lab-on-a-chip technology accelerating biology research in the same way the silicon computer chip revolutionized mathematical computation.

■ -INGFEI CHEN