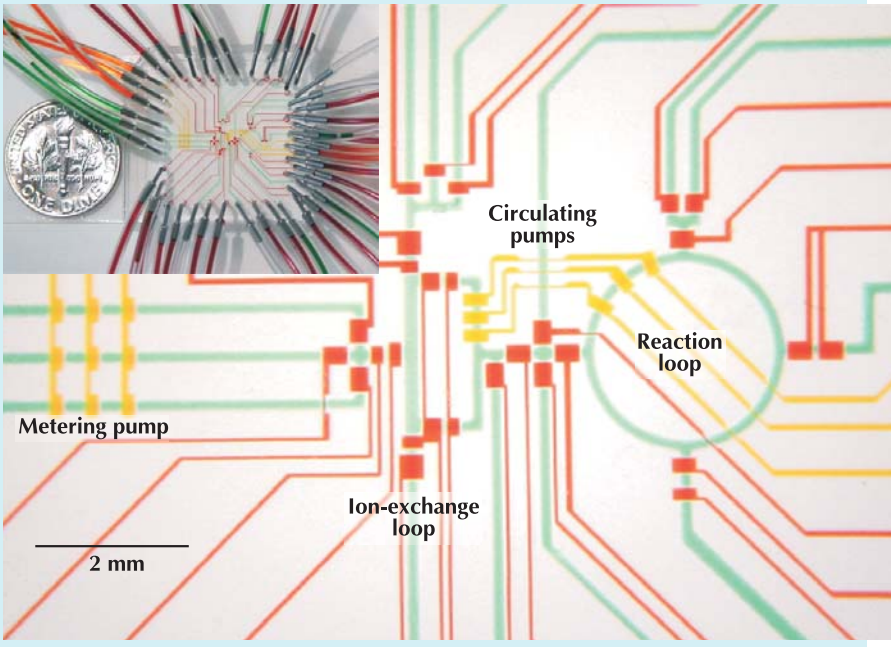
Microfluidic Chip Synthesizes Radiolabel for Positron Emission Tomography

For the past two decades, researchers have envisioned creating microfluidic circuits to control the mixing and reactions of chemicals that flow within 100-micron-wide channels on a single chip. The high surface-to-volume ratio in such hair-thin channels lowers the diffusion times of reagents, and each circuit can be computer designed to exploit the flexibility that an integrated platform provides. To realize that vision, researchers have developed miniaturized versions of the required plumbing: valves, pumps, mixers, filters, and separators. And thanks to photolithography advances inherited from the microelectronics industry and more recent soft lithographic methods, fabricating microfluidic circuits is straightforward (see the article by George Whitesides and Abraham Stroock in PHYSICS TODAY, June 2001, page 42).

Much less straightforward is the handling of complex chemistry in the confines of a microfluidic circuit. An electronic chip needs to manipulate only electrons; a microfluidic one may have to manipulate a host of possibly volatile liquids, gases, and their reaction products over a range of temperatures and pressures. Avoiding such complications, researchers in recent years have applied the integration platform primarily to biochemical problems—protein crystallization, DNA separation, and cell sorting, among others—in which aqueous solutions, balmy temperatures, and moderate pH levels are the norm.

Stanford University's Stephen Quake and UCLA's Hsian-Rong Tseng, with 15 coauthors from 9 universities, industrial labs, and medical schools, now offer a proof-of-principle demonstration that multistep organic synthesis can also work well on a chip.[1] Their device, pictured at right, produces 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG), the most commonly used radiopharmaceutical tracer in positron emission tomography imaging. The design incorporates concentrating, isolating, mixing, heating, and evaporating various reagents—"certainly the most complex [microfluidic] system of synthesis anyone has yet implemented," according to Harvard University's Whitesides.



Transported into cells in the body like ordinary glucose, FDG becomes redistributed in the various organs, blood vessels, and tissues, which can then be imaged in a PET scanner. Radioactive fluorine is toxic, expensive, short-lived (its half-life is 110 minutes), but usable in tiny amounts. Those properties make FDG an ideal candidate for synthesis in a very inexpensive portable device that handles small volumes and could be discarded after each use. From a microliter of chemicals, Quake and his team produced enough FDG, in less than a third the usual reaction time, to image tumors within a mouse. Commercial synthesizers require 50 minutes to synthesize FDG; the microchip, about 14 minutes.

Micropipettes introduce the raw ingredients through tubes attached to the chip. A network of channels (green) and valves (red) fashioned out of soft polydimethylsiloxane (PDMS), the rubbery polymer used to caulk leaks around bathtubs, control how circuit components work together. Pneumatic hoses within a PDMS layer under the circuit expand under pressure to restrict or close fluid channels and then relax to open them. To optimize yields, the valves confine individual reactions and avoid cross-contamination among reagents.

In microfluidic channels, the Reynolds number—that is, the ratio of inertial forces to viscous forces—of fluids is low. Absent any turbulence in the flow that would naturally mix reagents, the circuit design integrates rotary pumps (yellow) made of three valves placed in sequence. Pressure waves drive the circulation by peristalsis. Fortunately, as reagents enter the reaction loop in sequence, viscous drag of the fluid layers closest to the channel walls slows that part of the flow. The layers become stretched and dispersed as they nest into each other like stacked paper cups.

The ion-exchange column, a new component Quake developed for the design, concentrates the radioisotopes by nearly three orders of magnitude to increase reaction kinetics. A miniature sieve strains the solution through beads located in the column as that solution is pumped around a rectangular loop. The PDMS matrix also helps optimize kinetics. It is semipermeable so solvents can evaporate directly through walls of the circuit. During heating stages, when temperatures reach as high as 135 °C in FDG synthesis, the porosity plays a role akin to a safety valve on a pressure cooker, automatically keeping pressures within a critical range.

To test the effectiveness of their device, the team subjected their reaction products to liquid and gas chromatography, a challenge itself considering the nanogram amounts synthesized. FDG tested better than 90% pure, and the authors argue that subsequent circuit designs should yield large enough amounts for multiple human PET scans.

The integration of simple and similar parts that can be fabricated together is, however, largely what distinguishes microfluidic reactors from their conventional counterparts. An entire system can quickly be designed de novo: Each new circuit typically takes two days from computer-aided design to working chip.

The flexibility of the approach is one of its principal attractions, says Tseng. He and colleagues from UCLA and Siemens Medical Solutions have just built a microfluidic circuit that runs as many as 32 reactions in parallel. Such circuits are ideal for combinatorially screening the huge libraries of molecular compounds that the pharmaceutical industry now synthesizes in the search for new drugs, vaccines, and antibodies.

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Reference

1. C.-C. Lee et al., *Science* **310**, 1793 (2005).