Micromachined Flow Probe

CNF Project # 807-99

Principal Investigator: Cornelis J. Drost

Users: Bruce McKee, Gary Thomas

Affiliation: Transonic Systems, Inc.
Primary Funding: National Heart, Lung, and Blood Institute of the National Institutes of Health, Grant #5 R44 HL 55082-03, "Tools & Techniques for Measuring Flow & Pressure in Mice"
Contact: cor.drost@transonic.com, bruce.mckee@transonic.com, gary.thomas@transonic.com
Web Site: www.transonic.com

Abstract

Transgenic mouse models are important tools for physiological research, but existing physiological monitoring tools—specifically devices for measuring blood flow—are often too bulky for acute/chronic mouse studies. To meet this need, we successfully fabricated 1200 micron-high ultrasonic blood flow measurement probe bodies from SU-8 photoepoxy. Transonic Systems is now selling probes manufactured with the CNF-developed SU-8 process. Scientists use these probes for basic research on transgenic mice, and pharmaceutical companies use them in developing new treatments for human diseases. In testimony to Congress, the National Institutes of Health cited this project as an NIH SBIR/STTR Commercialization Success Story.

Summary of Research

Medical researchers are increasingly using genetically altered mice as models for studying drug effects and disease treatments. Such studies often require measurements of arterial blood flow to various organs, such as the kidney. However, in mice these arteries are quite small (300-500 μm in diameter), and the required probe dimensions fall into a gray area between the capabilities of deep reactive ion silicon etching (< 200 μm) and traditional metal machining techniques.

A technology that bridges these extremes is the Microchem Corporation's SU-8 photoepoxy [1, 2]. SU-8 is a biocompatible negative photoepoxy designed to create films hundreds of microns thick with a single spin. SUNY Albany's Dr. Bai Xu and the CNF staff helped us extend the standard spin, bake, and exposure recipes [3] so that we could create structures up to 1000 μm thick in a single spin, as well as create dual-layer structures exceeding 1200 μm in height. In contrast, most structures created at CNF are well under 10 μm high.

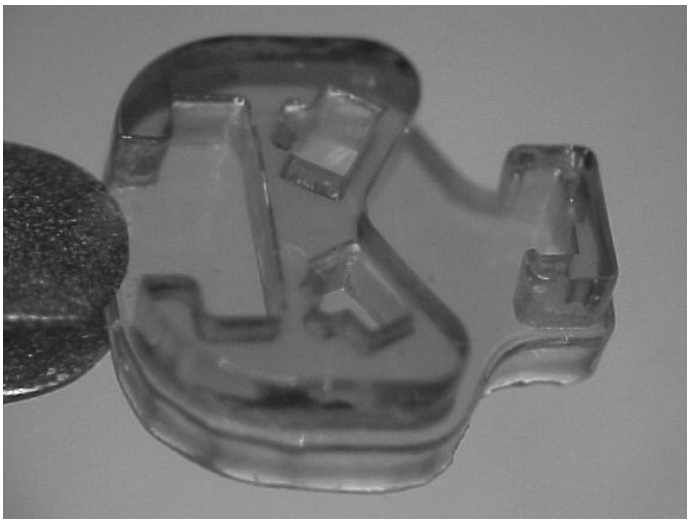


Figure 1: SU-8 probe body (1000 µm high x 3200 µm wide x 3500 µm long).

The fabrication sequence only requires a spinner, a hotplate, an exposure tool, and some wet chemicals. The SU-8 photoresist is spun onto a 3″ silicon wafer at low speed, and then the wafer undergoes a hotplate bake to remove solvent. The wafer is exposed through a chrome-glass mask to polymerize the SU-8 pattern. The spin/bake/expose process is then repeated to produce the second layer, and the wafer is placed in a solvent to remove unpolymerized SU-8. The probe bodies are then released by dissolving the silicon wafer.

Figure 1 shows a typical SU-8 probe body. This particular device is 1000 μm high x 3200 μm wide x 3500 μm long. The body is a precision mechanical fixture for the components of an ultrasonic transit-time flow measurement system [4, 5]. Figure 2 compares the tip of a ballpoint pen to the assembled probe (right) and an older Transonic probe manufactured with traditional machining/molding techniques (left).

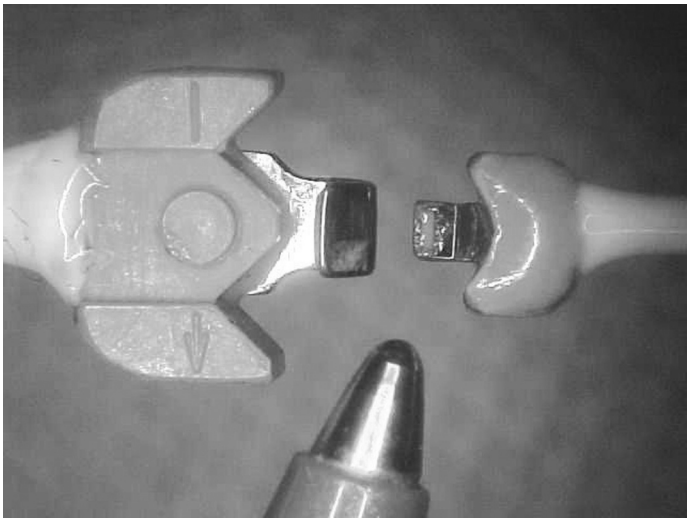
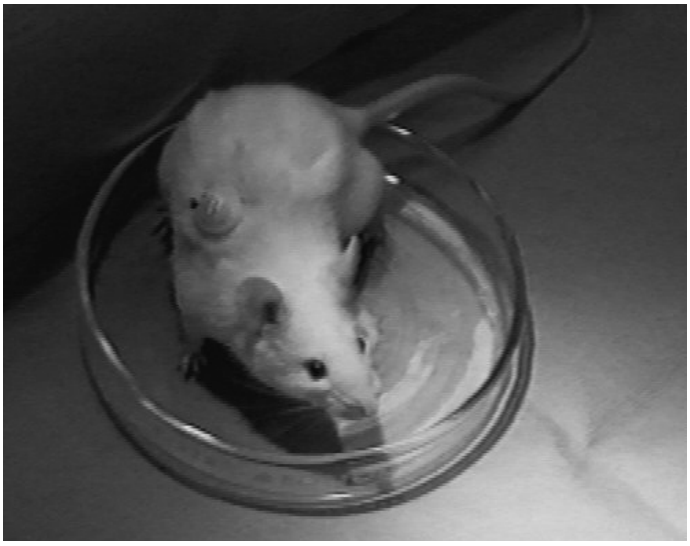


Figure 2: Ballpoint pen tip vs. assembled SU-8 flowprobe (right) and the smallest flowprobe prior to Nanofab research (left).

Probes were then sent to Dr. Michael Callahan (Wake Forest University), who devised a surgical technique for implanting a probe onto a mouse's renal (kidney) artery. Figure 3 shows the mouse two months post-surgery. Dr. Callahan recorded the renal blood flow traces shown in Figure 4 by simply plugging a lightweight cable onto the connector behind the mouse's right shoulder and recording blood flow (ml/minute) as the mouse moved around its cage. This marks the first time that anyone has successfully recorded renal blood flow in conscious mouse.

Transonic Systems is now commercially selling blood flow measurement probes whose bodies are manufactured with the Nanofab-developed SU-8 process. These probes are being used in basic research on transgenic mice, as well as by pharmaceutical companies developing new disease treatments. (See the list of Recent Biomedical Research that cites use of these devices).



Our current Nanofab research has developed a much simpler process for releasing the probe bodies from the wafer.

This work was funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health under SBIR (Small Business Innovative Research) Grant #5 R44 HL 55082-03, "Tools & Techniques for Measuring Flow & Pressure in Mice." In testimony to Congress, the NIH (National Institutes of Health) cited this project as an NIH SBIR/STTR Commercialization Success Story [6].

Recent Biomedical Research that cites use of these devices:

Septic Shock: "Effect of increased cardiac output on hepatic and intestinal microcirculatory blood flow, oxygenation, and metabolism in hyperdynamic murine septic shock", Albuszies G et al, CritCareMed, 2005 Oct;33(10):2332-8.

Kidney Function: "Micropuncture Determination of nephron function in mice without tissue angiotensin-converting enzyme", Seiji Hashimoto et al, AmJ Physiol Renal Physiol 288:445-452, 2005.

Carotid Artery Thrombosis: "Effect of mechanical ventilation on carotid artery thrombosis induced by photochemical injury in mice", Wilson KM et al, J. Thromb Haemost, 2003 Dec;1(12):2669-74.

References

[1] "High Aspect Ratio Resist for Thick Film Applications", N. Labianca, and J. Delorme, Proc. SPIE vol. 2438, SPIE (1995): 846-852.

[2] "SU-8: A Thick Photoresist for MEMS", http://aveclafaux.freeservers.com/SU-8.html#top.

[3] "Nano SU-8 Negative Tone Photoresists, Formulations 50 & 100", Microchem Corp., 1254 Chestnut Street, Newton, MA 02464.

[4] "Volume Flow Measurement System", Cornelis J. Drost, United States Patent #4,227,407 October 14, 1980.

[5] Transonic Systems Inc. Web Site, http://www.transonic.com/transit_time_theory.html.

[6] Testimony by Dr. Jo Anne Goodnight, NIH SBIR/STTR Program Coordinator, to the US Senate Committee on Small Business, June 21, 2001, http://www.hhs.gov/asl/testify/t010621.html.

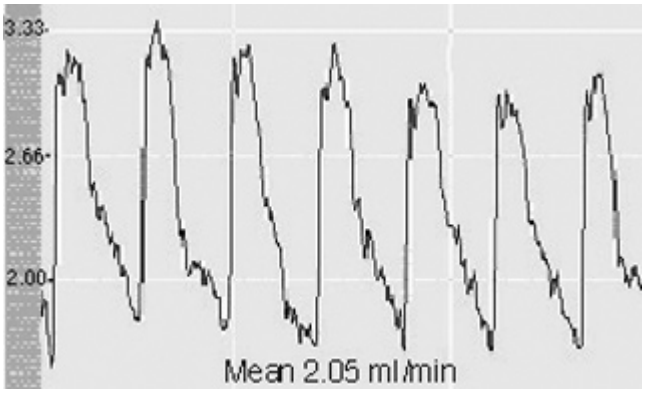


Figure 3, left: Mouse with an SU-8 blood flowprobe implanted on his renal artery (two months post-implant).

Figure 4, above: Conscious mouse renal blood flow.