Capillary and Pressure Driven Microchip for Blood Separation and Assay

Erik P. Anderson, Paul W. Leu, Ken M. Martin, Ratul Narain, and Beth L. Pruitt
Stanford University

This paper presents a novel micro-device for blood separation and assay. The blood plasma is separated by small capillary channels and mixed with reagents through chaotic advection. Our device is small (3 cm by 3 cm), allows for fast separation and mixing (< 2 minutes total time), works with small quantities of fluid (about 1 drop or 30 µL) reliably separates 3 micron beads (roughly the size of red blood cells, RBC), and allows for four simultaneous optical tests to be performed on the blood plasma. The device meets needs for a hand-held point-of-care blood separation and diagnostic device to screen for diseases and assess the health of patients.

Many different techniques have been reported for plasma separation from blood cells and cellular components including magnetophoresis [1], electrophoresis [2], microchannel bends [3], and ultrasound standing waves [4, 5]. The most standard technologies for removal of blood components are centrifiguation and membrane filtration [6]. Passive micromixers have also been developed which utilize channel geometry to increase the length over which diffusion occurs and configurations such as distributive mixers [7, 8, 9], a static mixer [10, 11], a T-type mixer [12], and a serpentine microchannel [13] have been demonstrated. Our work presents a unique integrated device where blood is deposited in a center well (Figure 1). Capillary action draws the blood up four separate arms (Figure 2) where small capillaries with inlets smaller than the RBC diameter suck up plasma into plasma wells. The RBCs move past the capillary channels with some aggregating near the capillary inlets and collect in the RBC wells. The pressure from the liquid in the center blood deposition well helps push the plasma out of the capillaries into the plasma wells (Figure 3). The plasma is passively mixed with reagents through chaotic advection.

The devices are made from polydimethylsiloxane (PDMS), which is optically transparent, and then placed on a glass cover. We form the PDMS cartridge from SU-8 molds, which can be fabricated using conventional photolithgraphy with high aspect ratio features. The 55 µm deep SU-8 molds are fabricated using a series of spin, exposure, and develop steps. We test a variety of different sized capillary channels with different flaring to optimize the separation and different mixing geometries to optimize the mixing. The PDMS is spun onto the SU-8 molds, baked, peeled off, and then treated with oxygen plasma at 74 W for 15 seconds to enhance its hydrophilic nature and bonding affinity with glass.

Our device structures have been tested on both 10 µm and 2.8 µm polystyrene beads in water (RBCs are biconcave discs with dimensions 7-8 µm diameter, 2.5 µm thick at the edge and 1 µm at the center) to determine adequate separation. We observe complete separation when the capillary inlets are smaller than the bead diameter. The plasma channels completely fill up with fluid and contain little or no beads in about 15 seconds.

A variety of passive mixing geometries were tested which use chaotic advection to enhance the diffusion dominant at small length scales (Figure 4). Water and methylene blue dye were placed in one well together and the mixed liquid wicked into the opposite chamber with fairly constant color (Figure 5).
Word Count: 531

Submitting author: Paul W. Leu, Stanford University, Department of Mechanical Engineering, 476 Lomita Mall, Room 203, Stanford, CA 94305-4045. Tel: (650) 724-6985. mail: pleu@stanford.edu

References

[1] Ki-Ho Han and A. B. Frazier. Journal of Applied Physics, 96(10):5797 – 802, 2004.
[2] T. Tsuda, N. Yamauchi, and S. Kitagawa. Analytical Sciences, 16(8):847 – 850, Aug 2000.
[3] C. Blattert, R. Jurischka, A. Schoth, P. Kerth, and W. Menz. Proceedings of SPIE - The International Society for Optical Engineering, 5345:17 – 25, 2004 2004.
[4] Muhammet Kursad Araz, Chung-Hoon Lee, and Amit Lal. Proceedings of the IEEE Ultrasonics Symposium, 1:1066 – 1069, 2003 2003.
[5] H. Li and T. Kenny. Annual International Conference of the IEEE Engineering in Medicine and Biology - Proceedings, 26 IV:2631 – 2634, 2004.
[6] K. Sawada, P. S. Malchesky, and Y. Nose. Available Removal Systems State of the Art. 1990
[7] F. G. Bessoth, A. J. de Mello, and A. Manz. Analytical Communications, 36(6):213 – 215, June, 1999.

[8] M. Koch, D. Chatelain, A. G. R. Evans, and A. Brunnschweiler. Journal of Micromechanics and Microengineering, 8(2):123 – 6, June 1998.
[9] P. Hinsmann, J. Frank, P. Svasek, M. Harasek, and B. Lendl. Lab on a Chip, 1(1):16 – 21, 2001.
[10] N. Schwesinger, T. Frank, and H. Wurmus. Journal of Micromechanics and Microengineering, 6(1):99 – 102, Mar 1996.
[11] A. Bertsch, S. Heimgartner, P. Cousseau, and P. Renaud. Lab on a Chip, 1(1):56 – 60, 2001.
[12] D. Bokenkamp, A. Desai, X. Yang, Y. C. Tai, E. M. Marzluff, and S. L. Mayo. Analytical Chemistry, 70(2):232 – 236, Jan 1998.
[13] R. H. Liu, M. A. Stremler, K. V. Sharp, M. G. Olsen, J. G. Santiago, R. J. Adrian, H. Aref, and D. J. Beebe. Journal of Microelectromechanical Systems, 9(2):190 – 7, 2000.

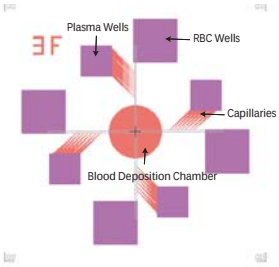
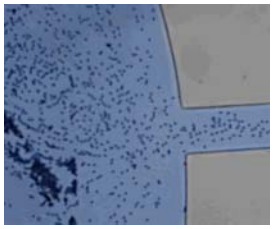
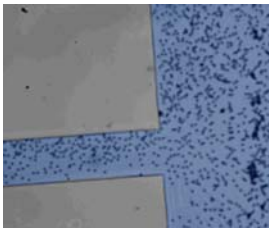


Figure 1: Basic device design. Blood is deposited in the center well and wicks up the arms from capillary action. Plasma is sucked up the plasma wells, while the RBCs move past the capillary inlets and collect in the RBC wells at the ends of the arms.



(a) Beads entering the arms from the center chamber

(b) Beads moving past the capillary inlets. The beads will not enter capillaries when their diameter is smaller than inlet width.



(c) Beads collecting in the RBC wells at the ends of the arms.

Figure 2: Beads moving down the arms of the device.

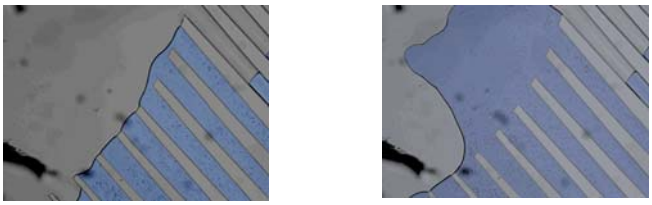


Figure 3: Liquid pressure pushing the fluid out the capillary channels into the plasma wells. 2.8 µm beads were used here with 4 µm capillary inlets resulting in beads located in the capillaries.

Figure 4: Some passivate mixing concepts tested. The geometry utilizes chaotic advection to enhance diffusion dominant at small length scales.

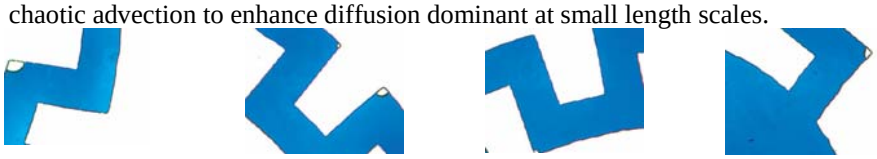


Figure 5: Mixing concepts results. Methyl-blue crystals were inserted into one-end of the well. When a droplet of DI water is introduced into the same well, capillary action draws both the water and methyl-blue crystals down the channel. Figure 5 was taken 30 seconds after the water droplet was introduced into the well.