In collaboration with Boston University, the Fraunhofer Center for Manufacturing Innovation (CMI) conducts advanced research & development leading to engineering solutions for a broad range of industries, including biotech/biomedical, photonics, and renewable energy. Engineers, faculty, and students at the center scale up basic research into advanced technologies that meet the needs of client companies both in the U.S. and abroad. The primary focus is on the development of next-generation high precision automation systems, instruments and medical devices.

During 2008, CMI worked on a number of systems, including a fully automated system for the production of plant-based pharmaceuticals (jointly with Fraunhofer CMB), molecular-based micro-diagnostics platform, high-precision cymbal shaping system, an endoscope with integrated optics for in-vivo analysis of colon polyps, a production-assist system for fuel cells, and a sample preparation system for the concentration and isolation of bacteria in blood.
Molecular-Based Micro-Diagnostics Platform

CMI has been working on an instrument and integrated consumable for molecular-based bacterial and viral diagnostics. During 2008, tremendous progress was achieved both in the instrument development as well as the actual process. CMI has demonstrated complete end-to-end diagnostics on a chip. This includes sample introduction, cell lysing, DNA extraction, PCR, and detection. CMI now joins a select, small group of organizations that have reported complete end-to-end diagnostics on a chip.

Currently, the majority of the bacterial infection diagnoses are conducted via culture which takes many hours to days to identify the bacteria. Thus, physicians will typically prescribe an initial broad-spectrum antibiotic drug therapy at the initial examination and then change the therapy as needed upon receipt of the culture results. This practice contributes to the rise in antibiotic resistance and is often ineffective at treating the patient. To address these concerns, rapid diagnostics have been developed; both immuno-assays and nucleic acid based tests. The immunoassays often suffer from inadequate sensitivity and/or specificity, while the nucleic acid based tests (NAT) are expensive. The NATs require specialized laboratory space, expensive reagents, and extensively trained technicians to appropriately conduct the assays. In practice, these factors lead to batch processing once a day in most clinical labs making the effective turn-around-time 24 hours. To address these challenges and provide a truly rapid test that meets the demands of high sensitivity and specificity, many have proposed to develop a point-of-care molecular diagnostic that automates the sample preparation, nucleic acid amplification, and detection in a low cost miniaturized lab-on-a-chip format. The benefits of this format include reduced costs (less technician time, no need for specialized facilities, less reagent use), improved reproducibility, and fast results. However, much of the work in this field has not yet resulted in a completely integrated lab-on-a-chip or a design that is truly low cost to manufacture.

Jointly with Prof. Catherine Klapperich of Boston University, CMI has developed a completely integrated lab-on-a-chip and associated instrument for the detection of bacteria from liquid samples. The system conducts bacterial lysis, nucleic acid isolation and concentration, polymerase chain reaction (PCR), and end-point fluorescent detection of the target amplicon. To enable truly low-cost manufacture of the single-use disposable chip, we designed the plastic chip in a planar format without any complicated active components. A novel method that enables fluid control without valves or pumps on the chip was employed. The integrated functionality of the chip was demonstrated using Bacillus subtilis as a model bacterial target. A Taqman assay was employed on-chip to detect the liberated bacterial DNA.
Automated Concentration and Isolation of Bacteria from Blood Samples

One of the major challenges in detecting bacterial pathogens in physiological and environmental samples is that the bacterial concentration is very low. Standard methodologies overcome this hurdle by amplifying the target, either through culture to multiply the number of pathogens, or through molecular or chemical means of amplification (e.g. PCR or ELISA). Over the past decade, a number of novel detection technologies, such as bioMEMS-based methods, have been reported in the literature. These methods are very promising in terms of their application to the point-of-care setting and their sensitivity, but require purified and concentrated pathogens to be delivered to a surface which often is not addressed. To enable implementation of these new detection technologies, new methods are needed for automatable and rapid sample preparation of pathogens. In the field of medicine, there is an urgent need for the rapid identification of bacteria in bloodstream infections at the point-of-care. To implement bioMEMS detection technologies in this setting, new methods for isolating and concentrating bacteria from blood are needed.

CMI has developed a prototype system for sample preparation of bacteria from blood. The prototype system was designed to isolate bacteria from all blood components and concentrate the bacteria by a factor of $10^3$ in less than 15 minutes. The input to the system is 10 mL of blood with 10-100 cfu/mL bacteria and the output is 5 µL of purified and concentrated bacteria.
The prototype consists of (1) a three-chamber disposable component with two metering valves between each of the chambers and (2) a mechanical device that actuates the valves. The entire prototype fits inside a bucket of a 250 mL swinging bucket centrifuge rotor. The macrofluidic process consists of mixing the infected blood with a lysis buffer, which preferentially lysed the blood cells over the bacteria. Then the sample is centrifuged and the bacteria pellet collects at the bottom of the first chamber. A metering valve transfers 5 µL from the bottom of the first chamber to the second chamber of 100 µL of water. The bacteria are washed in the second chamber and then the sample is centrifuged again to concentrate the bacteria at the bottom of the chamber. A second metering valve then transfers 5 µL of concentrated bacteria into a third chamber. The macrofluidic concentration process requires three centrifugations and two valve actuations.

For these reasons, CMI developed a device that automatically actuates the valves as the centrifuge decelerates. When used with a centrifuge controlled by a programmable controller, the purification process becomes a one-step, automated operation. The device stores energy while the centrifuge is accelerating and uses the energy to move the valves during deceleration. Such a device will have broad application in centrifuge processes.