FRAUNHOFER CENTER FOR MANUFACTURING INNOVATION

The Fraunhofer Center for Manufacturing Innovation (CMI), together with its partners, Boston University and the Fraunhofer Institute for Production Technology in Aachen, Germany, conducts advanced research and development leading to engineering solutions for a broad range of industries, including biotech/biomedical, photonics, and renewable energy. Fraunhofer engineers, faculty and students scale up basic research into advanced technologies for client companies in the U.S. and abroad. CMI's primary focus is on next-generation, high-precision automation systems as well as medical devices and instruments that lie at the intersection of engineering and biology.

In the life-sciences area, during 2013, CMI won another highly competitive research grant from NIH on "Rapid Antibiotic Susceptibility Testing." In conjunction with its other NIH grants, including "Bacterial Drug Susceptibility Identification by Surface Enhanced Raman Microscopy," its participation in the "NIH Center for the Future Technologies of Cancer Care," in which it will serve as the engineering arm for this multi-organization, multi-year program, and its grant from NSF on "Charge-Assisted Protein Sensing," CMI is establishing itself as a key player in the biotech/biomedical areas with the U.S. government funding agencies.

On the industrial front, CMI has acquired repeat business from industry leaders, as well as new key accounts from major U.S. Corporations. CMI also acquired a new a project from the US Treasury Department's Mint to develop alternative laser-based technologies for making coins (money). In fact, CMI was selected as a "preferred vendor" by the US Mint.

Also, in 2013, Prof. Andre Sharon, CMI's Executive Director, was awarded the prestigious Joseph von Fraunhofer Prize for Science and Innovation, for the development of a fully automated factory for the production of plant-based pharmaceuticals. Prof. Sharon shared this prize with his colleague Dr. Vidadi Yusibov, Executive Director of the Fraunhofer Center for Molecular Biotechnology (CMB). The Joseph von Fraunhofer prize is awarded annually in recognition of outstanding scientific work by Fraunhofer scientists that provide solutions to real-life problems. Jointly, Prof. Sharon and Dr. Yusivov were able to harness the natural protein production machinery of plants in a commercially-viable automated process. With the assistance of talented engineers and scientists at CMI and CMB, they were able to build a fully automated, first-of-a-kind, GMP-compliant manufacturing facility capable of producing proteins for use in a variety of applications, including vaccines, therapeutics and diagnostics.

Dr. Andre Sharon (foreground) with Dr. Vidadi Yusibov inspecting plants in the automated factory for plant-based pharmaceuticals.

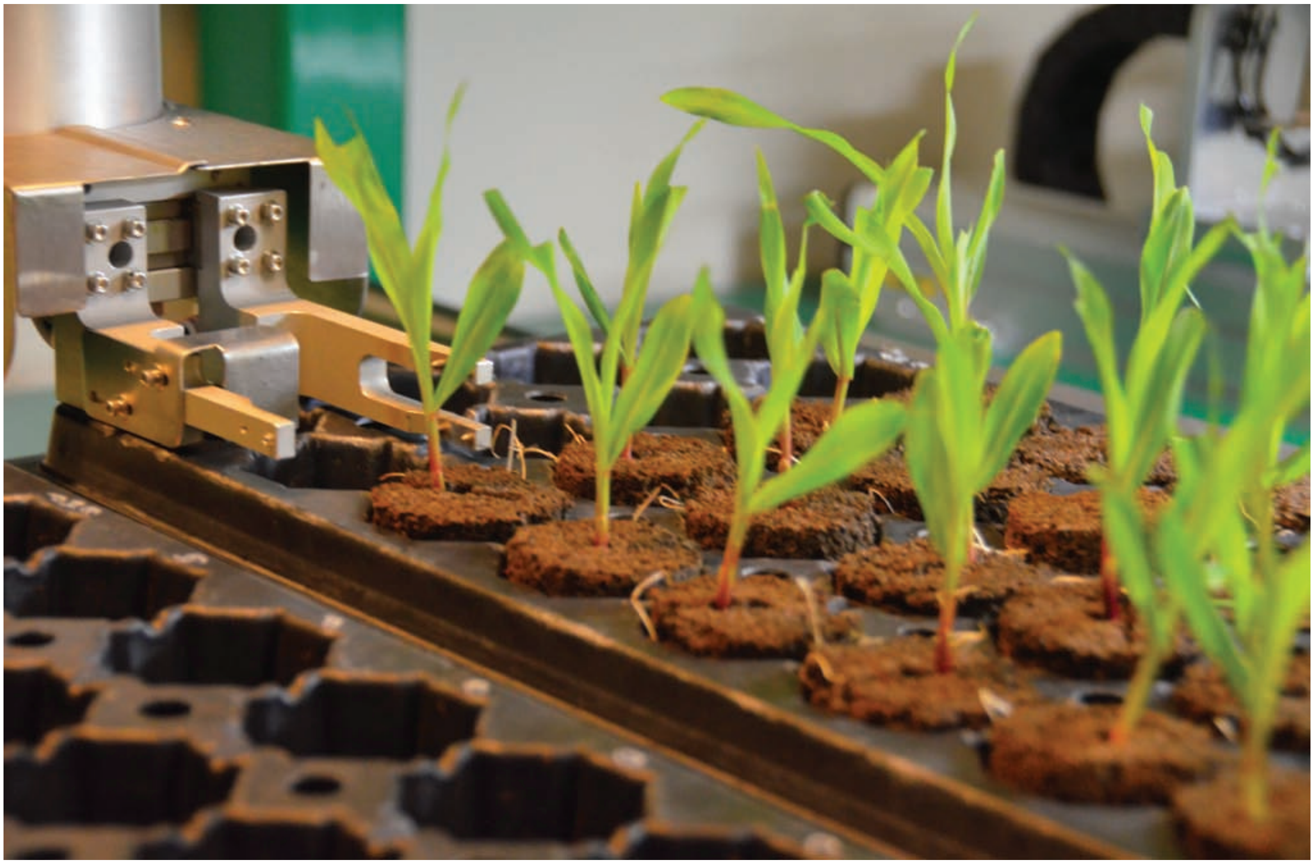
Finally, CMI has further enhanced its reputation in the scientific community with several new journal publications in 2013.

Representative systems under development at CMI during 2013 include:

Sampling of Plant Tissue

Fraunhofer CMI has designed and fabricated a system to automatically take tissue samples from live corn plants for genetic testing. The young plants, which are grown in hydroponic plugs, are automatically removed from plant trays and transported to the sampling location. An optimized algorithm ensures the leaf material to be spread out on a vacuum chuck. This presents the leaves to a sophisticated vision system which determines if there is sufficient leaf material to take a defined sized sample. The sample shape is optimized based on the width of the largest available leaf.

A CO_2 laser, combined with an X-Y scan head, is used to then cut the sample at the optimal location. The separated samples are robotically picked up and placed in micro titer plates for bulk DNA testing. Integration into a central sample



Live corn plants ready for genetic testing

database ensures the traceability of each sample back to the corresponding plant.

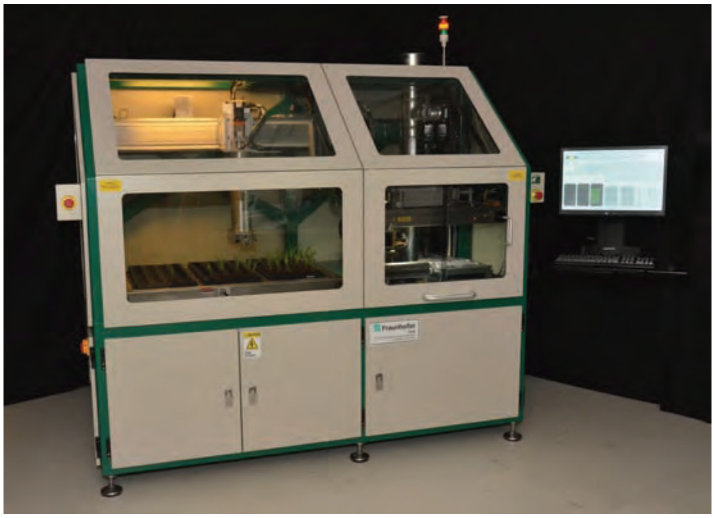
The plants that were successfully sampled are placed in outgoing trays while those which are too small to be sampled are placed on a separate tray that is then returned to the green house to be re-sampled at a later date.

Using this system, Fraunhofer CMI was able to significantly improve the sampling throughput of the client's sampling process over the previously-used manual operations. More importantly, the automatic process produces a significantly more repeatable sample size than the manual sampling process. This allows for better quantification during DNA testing. The use of bar code readers which automatically identify both plant trays and sample titer plates, along with the database integration, ensure global traceability of each sample and plant throughout the whole process.

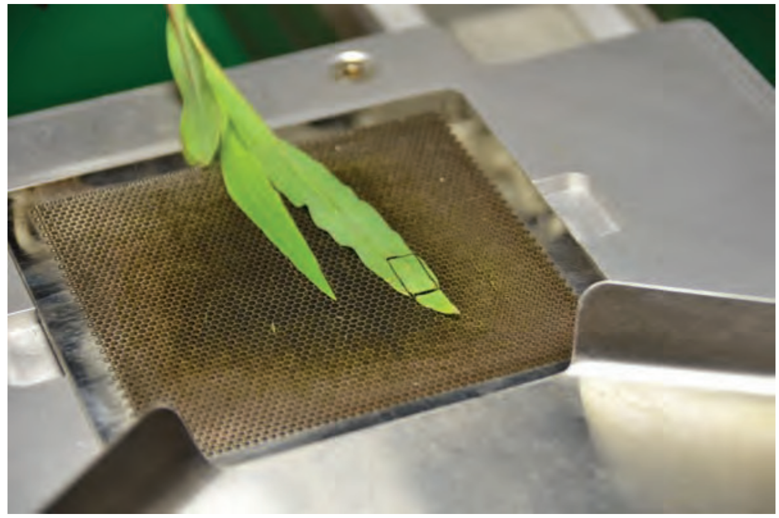
Eccentric Positioning System for I.D. Grinding

Precision internal grinding is a process used in the manufacture of round or cylindrical internal surfaces on hardened materials. It is often used in the production of gears and bearings, and can account for 30% of their cost of manufacture. A new internal diameter (I.D.) grinding system which reduces grinding costs while maintaining or improving part quality would have broad market appeal. Fraunhofer CMI is developing, jointly with its sponsor, a new three axis positioning system capable of linear and angular motions for I.D. grinding. This system has a novel and unique implementation, using eccentric rotary bearing spindles, that allows arbitrary trajectory motion within the X, Y, and θ coordinate space.

This new approach provides several advantages to I.D. grinding machines. The use of rolling element bearings in the spindles will reduce the cost and complexity by eliminating



Automated Plant Sampling Machine



Plant Leaf Being Imaged and Laser-cut for Sampling

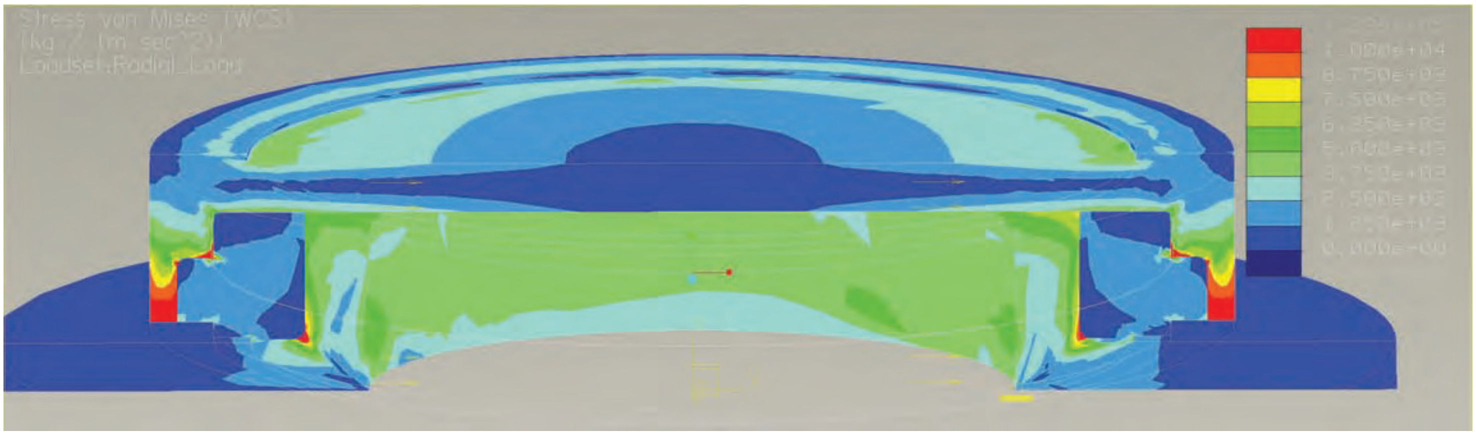
hydraulic systems for hydrostatic bearings, as well reduce energy consumption. The performance of the equipment will also improve, as the integrated linear and angular positioning would allow real time measurement of forces and grinding spindle deflection. This allows grinding wheels to be compensated in order to run true to the workpiece, improving part accuracy. It also allows instant transition between "rate-feed" and "controlled force" grinding to reduce production time.

Detailed mechanical design of the eccentric positioning system is underway. Finite Element Analysis is used to optimize the stiffness of the system and placement of the fluid dampers. The system is being engineered for retrofit onto a commercial I.D. grinder base for workholding and test purposes.

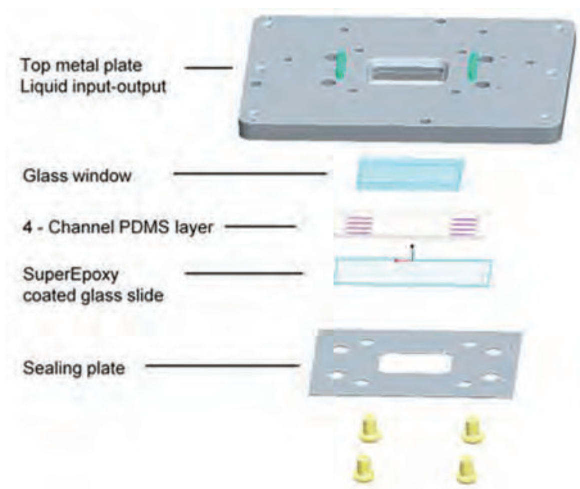
Microfluidic Platform for Rapid Antibiotic Susceptibility Testing

The emergence and spread of bacterial resistance to ever increasing classes of antibiotics intensifies the need for fast phenotype-based clinical tests for determining antibiotic susceptibility. Standard susceptibility testing relies on the passive observation of bacterial growth inhibition in the presence of antibiotics. Fraunhfoer CMI is developing a novel microfluidic platform for antibiotic susceptibility testing based on stress-activation of biosynthetic pathways that are primary targets of antibiotics. We chose Staphylococcus aureus as a model system due to its clinical importance, and selected bacterial cell wall biosynthesis as the primary target of both stress and antibiotic.

Enzymatic and mechanical stresses are used to damage the bacterial cell wall, and a β-lactam antibiotic interfers with the repair process, resulting in rapid cell death of strains that harbor no resistance mechanism. Bacteria, covalently-bound to the bottom of a microfluidic channel, are subjected to mechanical shear stress created by flowing culture media through the microfluidic channel and to enzymatic stress with sub-inhibitory concentrations of the bactericidal agent lysostaphin. Bacterial cell death is monitored via fluorescence using the Sytox Green dead cell stain, and rates of killing are measured for the bacterial samples in the presence and absence of oxacillin. Using model susceptible (Sanger 476) and resistant (MW2) S. aureus strains, a metric is established to separate susceptible and resistant staphylococci based on normalized fluorescence values after 60 minutes of exposure to stress and antibiotic. Because this groundbreaking approach is not based on standard methodology, it circumvents the need for MIC measurements and long wait times. Using this system, CMI was able to correctly designate the phenotypes of 16 clinically relevant S. aureus strains. In addition



Finite Element Analysis of Eccentric Positioning System for I.D. Grinding



Microfluidic Platform for Rapid Antibiotic Susceptibility Testing

to future clinical utility, this method has great potential for studying the effects of various stresses on bacteria and their antibiotic susceptibility.

CMI Internship Program

CMI's internship program continues to thrive, providing a global experience to 12 European interns per year. Since its inception, the program has hosted over 150 interns, mostly from Europe. Interns are provided with housing and a stipend, and are encouraged to experience not only the American workplace, but the American culture as well. The program has been tremendously successful, receiving rave reviews from all involved. These students are subsequently highly recruited in Europe, as they bring a global perspective to the job.

For more information: www.fhcmi.org

Fraunhofer Center for Manufacturing Innovation

Dr. Andre Sharon, Executive Director
Tel: 617 353 8776
asharon@fraunhofer.org