Development of an Automated Liquid Handling System for Science Lab Automation

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Abstract

In recent years, various automation technologies developed in engineering fields have been gaining attention from scientists and researchers to improve productivity, accuracy and quality of work in their science labs. This paper presents a unique case study of a private company sponsored project to develop a prototype of an automated liquid handling system for science labs. The device is especially intended for applications such as proteomics, oligonucleotides and high throughput screening. The system is composed of assembled syringes, pneumatic devices, linear drive, stepper motor, PLC and other miscellaneous devices. Two graduate students were involved in this project to satisfy the master's project requirement of our Mechanical Engineering curriculum. The development of the prototype was divided into two major stages. The first major stage conducted by the first graduate student consisted of requirement definition, conceptual design, modeling and simulation. The second stage conducted by the second graduate student consisted of design reviews, prototype fabrication, and testing. The project provided the students with an excellent opportunity for exposure to mechatronics technologies as well as the experience of being a part of a real-world engineering product development.

Introduction

In engineering education, it is essential for both students and faculty members to experience solving real world technical problems through industry sponsored projects. The key for developing successful industry-sponsored projects is to identify clear mutual benefits for both the educational institution and sponsoring companies[1,9,11]. This paper describes the activities at the Computer Integrated Manufacturing (CIM) Laboratory at California State University, Sacramento for generating industry-sponsored student projects especially for master's degree students. The most of those projects have been mechatronics and manufacturing automation in nature. For sponsoring companies, working with a lab such as ours is a very cost effective way to solve technical problems. For students, those projects provide excellent opportunities to experience a wide variety of real world challenges in technical issues, communications, and time management. As an example of our projects, a project of developing an automated liquid handling system for science labs is described in details.

Computer Integrated Manufacturing (CIM) Laboratory at CSUS

Missions of the CIM Lab

Computer Integrated Manufacturing (CIM) Laboratory at CSUS has two major missions. One mission is to provide quality lab activities in the areas of manufacturing automation and mechatronics in our Mechanical Engineering and Mechanical Engineering Technology curriculum. The other mission is to support and conduct undergraduate and graduate student projects. In the lab, there are two state-of-the-art Mori Seiki CNC machines: ACUMILL4000 machining center and CL-203B CNC lathe. These CNC machines are made available for our use by the generous support from Mori Seiki Co. and the IMS Mechatronics Laboratory at University of California, Davis. The lab also has Sankyo SR8438 SCARA robot, Allen Bradley 5/05 PLC and miscellaneous mechatronics devices.

Process for Generating Industry-Sponsored Student Projects

In our Mechanical Engineering curriculum, each master's student must take either a master's thesis or a master's project as a partial requirement for completing his/her master's degree. In a master's thesis, strong theoretical analysis is emphasized and a student can obtain 5 units of course credit. In a master's project, practical application is emphasized and a student can obtain 2 units of course credit.

Topics for industry-sponsored projects for master's theses and projects related programs are usually generated by faculty members using their network with industry. Most of the projects generated so far have been mechatronics in nature including technical elements such as design, prototype fabrication and testing. After having a series of meetings with a possible sponsoring company to identify technical needs, the team of faculty members and students submits a proposal to the company. Typically a proposal specifies technical objectives, technical approach, deliverables, schedule, and a request for funds. We are careful to avoid projects which may critically affect the company's future business status. We prefer to focus on the type of project which offers the potential to give a reasonable positive impact but no significant business risk to the company. With regard to the funding, a proposal is usually based upon the costs for hardware and software, stipends for students, and a contribution for the trust fund of the school. The trust fund of the school is managed by a carryover account. Compared to other school accounts, there are not many restrictions on how the account should be used and therefore it is a very convenient vehicle to support lab development and maintenance.

Each industry-sponsored project is usually pursued based on the following product development stages:

1. Requirement definition (at the Proposal stage)
2. Conceptual design: Alternative designs and trade-off analysis (at the Proposal stage)
3. Detailed design and analysis
4. Prototype building
5. Testing
6. Reporting

The above product development stages are similar to those given by Priest, J.W. and J.M. Sanchez[8]. More detailed activities of each product development stage will be explained in the later section for the case study of the development of an automated liquid handling system.

For some industrial-sponsored projects, two identical prototypes are constructed. In such cases, one prototype device is given to the sponsoring company and the other prototype is kept in our lab. This approach allows sponsoring companies to request our team to do any necessary debugging or trouble shooting work using the prototype at our lab. In addition, the prototype device at our lab can be effectively used for educational purposes in our future courses.

Recent industry-sponsored projects at CIM lab includes, the development of universal spring mechanism for the McPherson type front automobile suspension system sponsored by NHK International Co, Wixom, MI[5,6], the development of a miniaturized golf club swing pattern analyzing system (SPAS) sponsored by Nippon Shaft Co., Tokyo, Japan, and the development of Water Pasteurization Indicator Maker sponsored by CSUS Department of Biology and Solar Cooker International.

Our department also generates a significant number of industry-sponsored projects for our undergraduate capstone design courses. For these undergraduate industry-sponsored projects, sponsoring companies often provide materials, hardware, software, and technical mentoring for students. In turn, students provide their reports to the companies. For sponsoring companies, this is often a very economical way of obtaining technical support and analysis. In such cases, project funds are not usually requested from companies and therefore, such projects are not considered to be contract based. In contrast to these undergraduate projects, industry-sponsored projects at CIM Lab for graduate students are usually funded and therefore considered as contract based projects. For this reason, these projects must be pursued in a professional manner to accomplish, and account for, the objectives stated in the proposals.

Case Study: Development of an Automated Liquid Handling System

This case study describes the project of developing a prototype of an automated liquid handling system for science labs. The device is especially intended for applications such as proteomics, oligonucleotides, and high throughput screening. In recent years, there has been a strong trend of applying automation technologies to improve efficiency and accuracy in liquid handlings in science labs[2]. The quotation below from an article of the January 24th issue of Science[3] clearly describes an important role of lab automation in today's science lab environment:

> Within the past few years, life scientists have successfully sequenced the genomes of mice and men – and several other organisms. That research has stimulated the emergence of genomics, a discipline that sets out to understand the meaning of the sequence data, helped by such essential subdisciplines as bioinformatics. Taking the work a stage further, life scientists have transformed old-style protein chemistry into proteomics, a vibrant field of study that aims to provide essential clues to the complex ways in which living cells function.
>
> These changes have had a significant impact on drug discovery, by revealing a huge quantity of new targets with potential as drugs. The number of targets far exceeds

> scientists' ability to deal with them using traditional manual methods. In response, vendors have developed high throughput screening (HTS), a process that can test large numbers of samples efficiently in very short periods of time. That ability has made HTS a key element in modern drug discovery [. . .].
>
> Laboratory automation tools range from simple semi-automated liquid handling devices to fully integrated automated systems that consist of multiple robot arms, pipetting stations, incubators, plate washers, and detectors. Many laboratory managers start their move away from manual methods by purchasing semi-automated work stations that can pipette and deliver small volumes of reagent or wash the samples in micro-well plates or other vessels for virtually 24 hours a day, seven days a week. By freeing lab technicians and scientists from such non value added tasks, these work stations allow them to focus on activities, such as designing experiments, that are more critical to the success of their programs.

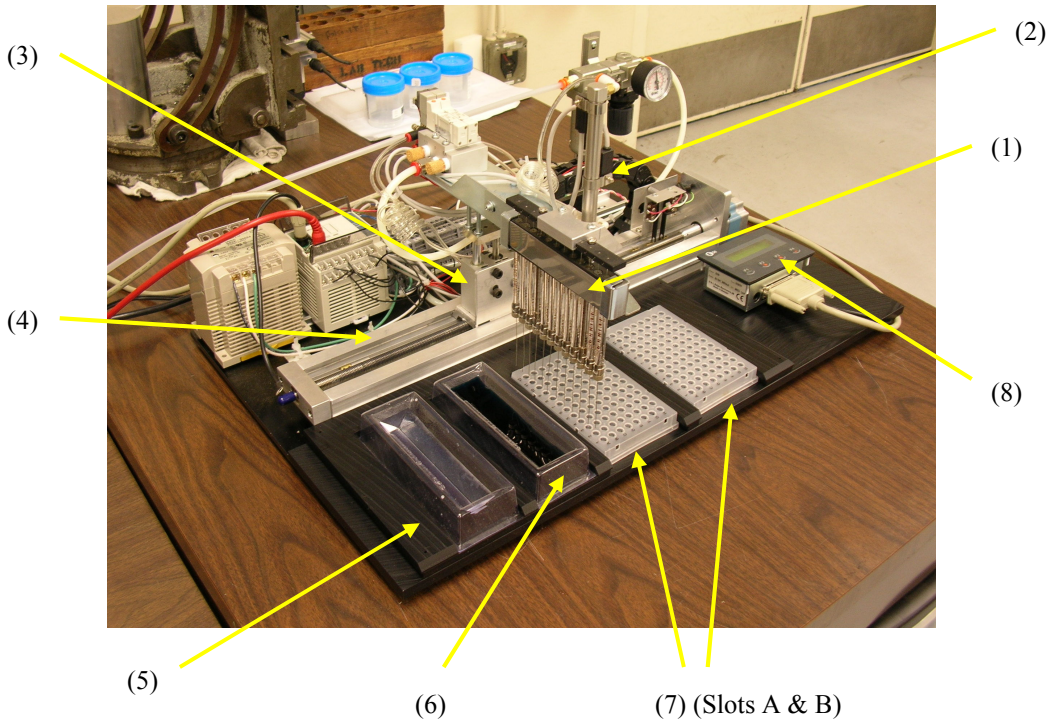
The project was recently conducted by the CIM lab and Reflect Scientific Co, Mountain View, CA. Two graduate students, Stefan Setiadharma and Yasuhisa Komura were involved in this project to satisfy their master's project requirement of our Mechanical Engineering curriculum.

Description of the system

Two identical prototypes of this device were made for the reason described above. Figure 1 shows a photo of the prototype available at our lab. The system consists of the following major components.

- 12-row assembled syringes.
- Pneumatic cylinder for syringe pistons.
- Pneumatic cylinder to move up or down the entire assembled syringe unit: This movement is necessary to position the 12-row syringe needle tips to be either above or below the liquid surface level.
- Stepper-motor-controlled linear drive.
- Wash station: A reservoir for clean water is set in this slot. The clean water is used for the syringe wash cycle in which the remaining reagent in the syringe unit is washed out.
- Reagent station: A reservoir for reagent is set in this slot.
- 96-well plate stations: There are two slots A (on the left) and B (on the right). When only one 96-well plate is needed, Slot A is used. When two 96-plates are needed, both slots are used.
- Human-Machine Interface (HMI): Program selection and manual operations of the device are made through this HMI device.

The system also contains a PLC, stepper motor driver, solenoid valves, sensors, switches and other miscellaneous devices to provide all necessary hardware functions. The system is capable of transferring reagent from the reagent station to any selected rows of two 96-well plates. It is also capable of transferring reagent samples from any selected row of the 96-well plate at Slot A to any selected row of the 96-well plate at Slot B. After a given liquid handling task, the assembled syringe unit is cleaned at the wash station.



1) 12-row assembled syringes
2) Pneumatic cylinder for syringe pistons
3) Pneumatic cylinder to move up or down the assembled syringe unit
4) Stepper-motor-controlled linear drive
5) Wash station
6) Reagent station
7) 96-well plate stations
8) Human-Machine Interface (HMI)

Figure 1: Prototype of the automated liquid handling system

Product development

This project was conducted through the following product development stages.

<u>Requirement definition (at the Proposal stage)</u>

Through a series of meetings between our team and Reflect Scientific Co. the following requirements were identified:

a. Two 96-well plates, one reagent station, and one wash station.
b. Program selection through HMI: For the initial set of prototypes the company requested that any of the following three programs can be selected from the HMI.
    - Program 1: Transferring the reagent from the reagent station to all 8 rows of the 96-well plate in Slot A.

- Program 2: Transferring the reagent from the reagent station to all 16 rows of the 96-well plates in Slots A and B.
- Program 3: Transferring the reagent from Row 1 of 96-well plate in Slot A to Row 1 of 96-well plate in Slot B. In this manner, continuing this operation to transfer the reagent from all rows of 96-well plate in Slot A to corresponding rows of 96-well plate in Slot B.

c. Maximum stroke of 10 μl per syringe.
d. Liquid volume dispensing accuracy of $\pm$ 2%.
e. Process time of one minute to dispense reagent to all eight rows of a 96-well plate.
f. Total hardware component cost of $2,500 or less (excluding labor). This requirement is based on the company's business intention to develop an automated liquid handling system which is simple but reliable for above specifications under a retail price of $10,000 or less. Most automated liquid handling systems available in the market today are relatively complicated and priced over $20,000.
g. Simple in operation.
h. Reliable in operation.

Conceptual design: Alternative designs and trade-off analysis (at the Proposal stage)

Three different designs are developed and the best design based on the comparison matrix was selected[10]. The selected design is represented by the system shown in Figure 1.

Detailed design and analysis

Detailed design and analysis consists of:

- Finalizing appropriate purchased components to be used for the system. The purchased components include the assembled syringe unit, stepper motor, stepper motor driver, linear slide, PLC, HMI, pneumatic devices, sensors, and switches.
- Designing fabricated components.
- Creating a drawing package including all purchased parts, fabricated parts, assembly drawings, and bill of materials. Solidworks was used for all drawings.
- Kinematic simulation to check any potential physical interference.
- Dynamic analysis and simulation to determine a required motor speed-torque characteristic.
- Developing control scheme for three programs.

Prototype fabrication

Two prototypes were built and assembled at CIM lab.

Testing

Testing was conducted to validate all items specified in the requirements definition referred to above. Item (a) was visually confirmed. Items (b), (c), (e) and (g) were tested and validated through a set of running tests. Item (c) was tested by a running test. Item (d) was tested by the standard Cp machine capability test[7]. For a test of filling 7 rows of 20 96-well plates, Cp value of

4.55 was obtained for the spec of 792 μl ± 2% in volume per plate. This Cp value indicates that the device is capable of dispensing liquid with the accuracy which the company expected. The total cost of the hardware components excluding labor was under $2,500 and this result satisfies the condition of item (f). For item (h), there was no system failure during the series of running tests. In addition to this set of running tests, the system has been continuously tested for last 6 months and no significant system failure has been reported.

Reporting

Project reports were submitted to the company in terms of the master's project reports[4,10]. The company is currently advertising the product developed by this project. One of the advertising flyers is shown in Figure 2.

Figure 2: An advertisement for the liquid handling system

Conclusion

The activities of Computer Integrated Manufacturing (CIM) Lab at CSUS with the special emphasis on industry-sponsored master's projects were described. A case study of developing an automated liquid handling system for science lab automation was described to explain such industry-sponsored project activities. Industry-sponsored projects provide both students and faculty members opportunities to experience real world technical challenges which are not usually experienced through regular courses. For industry-sponsored projects, it is always important to identify clear mutual benefits for both the educational institution and sponsoring companies. Expectations of sponsoring companies differ depending on projects. We hope to continue to develop appropriate industry-sponsored projects for students through effective communications with prospective sponsoring companies.

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