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A Benchtop Robotic Automation Approach for Manufacturing Prefilled Syringes

Yehua Zhong
yehuaz@g.clemson.edu

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Yehua Zhong
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Dr. Yue Wang, Committee Chair
Dr. Wagner, John R.
Dr. Schweisinger, Todd

Abstract

Automation and robotics have become a staple in the biological manufacturing sector due to their ability to efficiently work without operator inputs, with a high degree of accuracy and repeatability. Industrial robotic arms, in particular, present themselves as valuable tools for biological manufacturing scenarios that require customized solutions due to their ease of programming and flexibility. The traditional hospital-focused healthcare system was organically developed to address acute conditions, however, in recent years, due to the unprecedented occurrence of emergencies happening more frequently, fast and efficient drug production becomes important [17]. This thesis represents the use of a benchtop robot and automation system capable of manufacturing in-syringe liquid drugs. The compacted production space and design is aimed to provide an efficient production rate. The International Organization for Standardization (ISO) compliant robotic arm (Stäubli TX2-60), customized designed end-effector, syringe venting system, and Cartesian gantry platform were designed, prototyped, and integrated to create an automated solution for manufacturing cyclic olefin copolymer (COC) polymer syringes. A Siemens programmable logic controller (PLC) system is developed to interface with the robot (through the Stäubli Robotic Suite (SRS)) and the Nema-17 motor-driven Cartesian gantry platform. Automated filling of a tray of 50ml syringes was proven to be feasible, and the process of stoppering a COC syringe utilizing a customized designed venting tube was demonstrated as a proof of concept. An automated gantry system was also demonstrated as a proof of concept for a complete manufacturing system.

Dedication

I dedicate my dissertation work to my family, friends, and my academic advisor. A special feeling of gratitude to my loving parents, whose words of encouragement and push for tenacity ring in my ears. My academic advisor, Dr. Yue Wang who has supported me throughout the process. I will always appreciate all they have done.

Acknowledgments

I would like to thank my academic advisor Dr. Yue Wang for providing the opportunity of the automation project and the guidance throughout the whole process of the work includes my publication and thesis dissertation. I wish to thank my committee members Dr. Todd Schweisinger and Dr. John R. Wagner who were more than generous with their expertise and precious time. Another thanks to my project partner Jared Chamberlin for designing the gantry robot of the project.

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Chapter 1

Introduction

Robotics automation has been popular for decades in many fields, one of the biggest advantages of having the automated process in pharmaceutical field is the sterile environment could be guarantee so that the efficiency could be improved drastically by eliminating operator's intervention, in addition, the automated robotic process reduces contamination that could lead to potential risk for healthcare usage. Ever since COVID-19 pandemic, the growing demand for the vaccine illustrates the importance of the production of the vaccine. The production of pharmaceuticals is one of the most strict and regulated industries, placing tight requirements on the product, environment, and workers. In-syringe drugs require strict rules for technicians, such as cell-level protective suits in the manufacturing cleanroom. The cleanroom itself needs meet at least ISO 7 standards ([33]) and contains booths that meet more strict requirements where the actual production takes place. Research estimates that 1,500 bacteria can live on each square centimeter on an individual's hands ([29]), so it is critical to minimize human contact. Conversely, manual manufacturing operations can increase technician exposure to toxic active pharmaceutical ingredients (APIs) ([15]). Furthermore, producing filled syringes is a repetitive task with ergonomic concerns due to the cramped space in the production booth ([12, 22]). Robotics and automation present a solution to all these issues. Cleanroom grade robots can meet the ISO class 5 and 6 standards for drug production and are resistant to chemicals and toxins ([23]). They are also easily cleanable and require fewer person-hours to operate. On the other hand, many commercial-grade biomanufacturing automation systems require a large area, proprietary hardware, and specialized training.

Prefilled syringes have proven to be a popular innovation in recent years because of their ease of use and safety ([21]). Prefilled syringes are convenient if there are emergent medical situations that the patient needs an injection immediately, they have better sterility in the long term, standard syringes would only remain approximately 12 hours for effectiveness, and prefilled syringes could remain effective for two to three years ([21]), also they improve the accuracy of the dosages because the automated production process is usually equipped with pharmaceutical repeater pumps. However, a very limited amount of literature focuses on the manufacturing of prefilled syringes using robotics and automation ([28, 10]). Large-scale syringe manufacturing systems, while efficient, are not flexible to deploy, require extensive operator experience, and are challenging to integrate with existing manufacturing infrastructure. A benchtop solution can overcome these deficiencies using a general robotic component while maintaining adequate production rates. Benchtop solutions have the advantage of being rapidly deployed, constraints for the prefilled syringes production would include the ISO standard for the cleanroom and FDA approval for the devices and material, etc. Filling and stoppering mechanisms are the key factors in the development of the automated process. For the validation of the test plan, the focus could be on the accuracy of the fluid, the production rate, safety, and convenience compared to standard syringes production rate. significantly cheaper than the equivalent all-in-one solution, and can be easily operated.

Benchtop methods will still be limited to commercial brands, such as [9, 6, 4, 3]. They can be divided into two automated non-robotic solutions ([9, 4, 3]) and a robotic solution ([6]). Solution [4, 3] fills syringes using a container filling system and then caps and seals them using a second system. It requires substantial human interaction and averages around five cycles per minute. Solution [9] attempts an automated approach using a single system, capping and sealing syringes using a vacuum gripper. This solution can produce 25 units per minute but lacks scalability and is difficult to implement. There is seemingly a gap in automating the production of larger syringes in the 50mL range, which our system addresses. Further, these systems still do not have the flexibility provided by a robotic manipulator, which our system aims to achieve. Our system is most similar to benchtop robotic systems ([6]), which have a significant advantage in that they are designed to be integrated into existing processes. Even these systems struggle to achieve large fill volumes, with [6] only capable of filling up to 20mL syringes. The critical distinctions of this paper compared to the above solutions and our previous work ([10]) are twofold.

1. The manufacturing using new Schlott cyclic olefin copolymer (COC) syringes instead of the conventional Becton Dickinson (BD) polypropylene syringes, as seen in Fig. 1.1, requires in-

novative automation design and integration with the benchtop robot. The growing demand to produce pre-filled syringes due to the cost, safety, sterility, and production efficiency, pre-filled syringes make the whole production process more accessible and better patient safety, correspondingly, more and more pre-filled syringes stoppering machines are accepted in the market. Specifically, pre-filled syringes are convenient if there are emergent medical situations that the patient needs an injection immediately; pre-filled syringes are better sterility in the long term, standard syringes would only remain approximately 12 hours for effectiveness, and pre-filled syringes could remain effective for two to three years (Sagar Makwana, 2011). On contrary, constraints for the pre-filled syringes production inlcudes the ISO standard for the cleanroom and FDA approval for the devices.

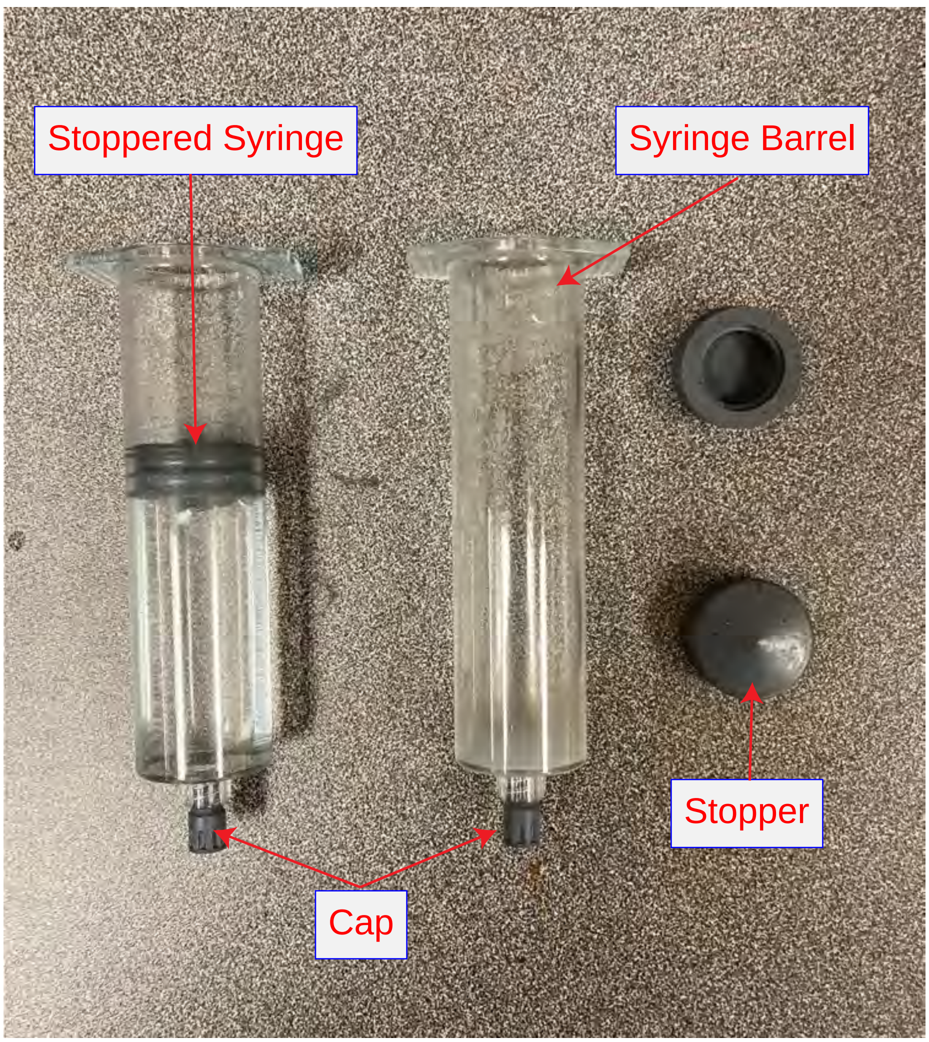


Figure 1.1: A COC syringe and stopper

2. The system programming and control using the Siemens TIA Portal, Stäubli CS9 robot controller and Stäubli Robotic Suite (SRS) software ([31]) meets the electronic records and electronic signatures requirements set forth by the US Food and Drug Administration (FDA) for pharmaceutical manufacturing instead of the open-source Robot Operating System (ROS).

Chapter 2

Prototype Design and Methodologies

2.1 Benchtop Robot and Automation System for COC Syringes

2.1.1 System Overview

Batch filling of the prefilled syringes could greatly improve production efficiency which is widely applied in pharmaceutical field. The process of batching filling for the prefilled syringes proceeds specific amount of syringes within a specified amount of time [32]. Traditionally, it would take 30 seconds for two humans to finish filing and sealing one 50ml BD syringe, since each operator could only handle one single syringe at a time, on contrary, prefilled syringes stoppering machine could make the production rate up to 100 syringes per minute.The primary objective of this system is to create an easily deployable and relatively high yield, low-cost automated pharmaceutical manufacturing platform. Additionally, we want to use readily available materials for the hardware and encourage the use of in-house machined parts for ease of maintenance. Readily available consumer robotics software is also desired to integrate the robot and automation solution into preexisting pharmaceutical manufacturing systems and comply with the FDA 21 CFR Part 11 specifically for drug production. Figure 2.2 shows a schematic of the overall robotic automation system for manufacturing COC prefilled syringes. The system input is comprised of syringes and silicone stoppers, both of which are pre-packaged by the manufacturer and exist in sterile containers. Additionally, a liquid drug substitute is presented utilizing a separate peristaltic repeater pump system, as seen in Figure 2.20. The system is designed to perform its automated manufacturing process once a technician places the stoppers and syringes in a proper position in the booth. The system automates the drug filling and stoppering process using the robotic arm with a customized end-effector and a vent tube assembly attached to a Cartesian gantry system. On completion of the process, the output product is a tray of twenty 50mL COC syringes that have been filled with the liquid drug and stoppered. Like many other pharmaceutical manufacturing systems, both physical and cyber components critical to the overall system. Verification of the manufacturing process was performed by testing components individually and as a whole, as shown in Section 3.2.

In order to encourage an easily repairable and modular design, components for the gantry and the end-effector are sourced by commercially available methods or by custom 3D printing. The gantry and end-effector can be seen in Figure 2.1, in relation to the Stäubli TX2-60 robot, pump, syringe tray and stoppers. A description of the materials used to construct the end-effector and the Cartesian gantry robot can be found in Sections 2.1.2.2 and 2.1.2.3. The Cartesian gantry robot and end-effector are designed to interact with each other in order to fill and stopper the tray of syringes. The end-effector is mounted on a Stäubli TX2-60 pharmaceutical-grade robot arm, coupled with a Siemens PLC to interact with the Cartesian gantry robot. The gantry is responsible for filling the syringes row by row using a separate peristaltic repeater pump, as described in Section 2.1.2.3. Additionally, the gantry is responsible for manipulating the attached venting block, which secures the four venting tubes in place. It has the capability of positioning these venting tubes above each syringe, and lowering them into the syringe barrel so that stoppering may commence. The end-effector is responsible for manipulating the stoppers utilizing a suction force, and forcing them through the venting tubes, into the syringes. The overall system process is described as follow: the Cartesian gantry robot will position itself so that the filling nozzles are directly above the first row of syringes. Next, the peristaltic pump will activate and fill up the first row of syringes. The Cartesian gantry robot will move further so that the middle arm is directly above the first row of syringes (which are now filled) and will lower its middle arm so that the venting tubes are inserted into the syringe barrels. Next, the Stäubli TX2-60 will move the end-effector in such a way that it will press down upon the first row of stoppers on the stopper plate. The vacuum pump will activate, and the end-effector will move the four gripped stoppers above the inserted venting tubes. Finally, the Stäubli TX2-60 robot will insert all four end-effector rods through the venting tubes, forcing the stoppers into the syringes. The vacuum pump will be disabled, and the robot will remove the end-effector and reset to a home position, where the cycle will then repeat for the next rows of syringes.

The cyber system utilizes the commercially available PLC and SRS, which have user log-in authentication and signature records to comply with 21 CFR Part 11. PLC is the central unit in this integrated system. All the communications via I/Os will go through the PLC, which will send out corresponding signals to drive sub-systems like robot motion, sensor detection, actuators control. SRS can be used to program the robot and its digital twin, while also communicating with a separate PLC system. SRS can be used to program the robot and its digital twin while also communicating with a separate PLC system. An off-board computer is used to access the SRS Graphical user interface (GUI) and upload programs to the robot controller. A touchscreen teach pendant can be used to run uploaded programs or manually jog the robot. These systems are user-friendly and ideal for “plug and play” scenarios where the system must be quickly set up.

A complete cycle of the manufacturing process integrating the hardware and software is

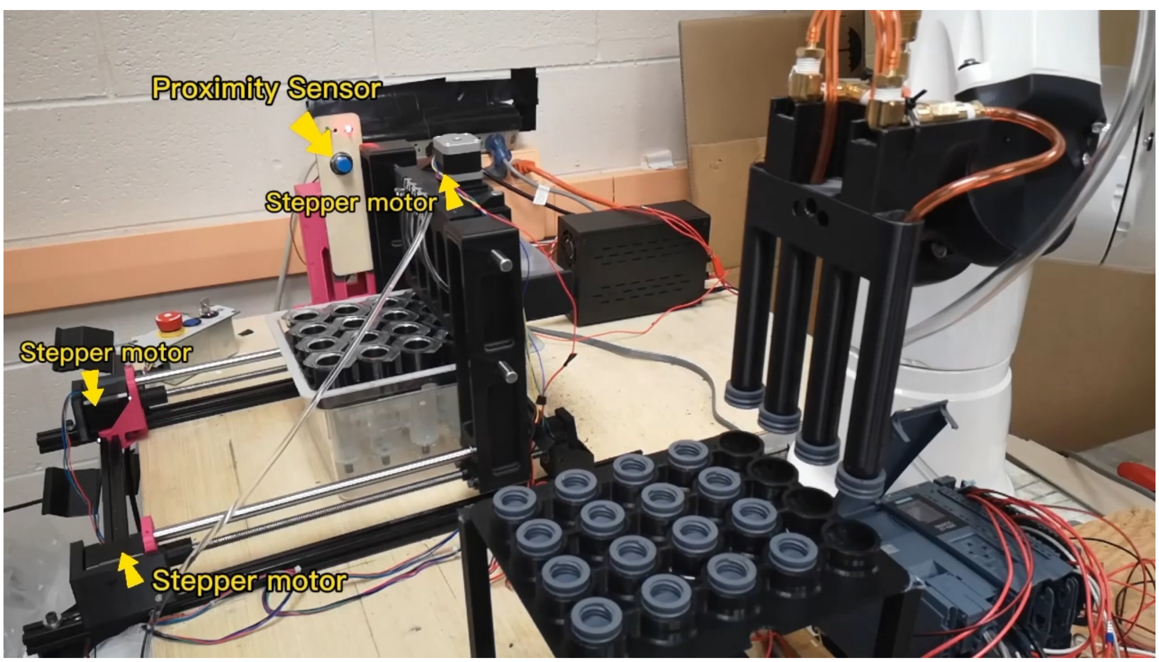


Figure 2.1: Gantry and Robot End-effector

illustrated in Section 3.2.2, and the pseudocode for the process is detailed in Section 2.1.3. In the following sections, the system's physical hardware and cyber components will be detailed, respectively.

2.1.2 Hardware Architecture

For the main part of the physical construction of the experimental components, which is the cartesian gantry robot that is shown in Figure 2.2, is primarily constructed out of custom 3D printed parts, and off-the-shelf components. The gantry carriages are 3D printed and fitted with two linear bearings that were press-fit into a hole in the carriage. In this way, the carriages are free to move along the linear shafts. A 3D printed thread is attached to the carriage and interacts with the lead screw that is attached to the motor, effectively driving the system. The gantry is symmetrical in design, with identical components on each side. For the upper part of the Figure 2.2, it is observed that the robot end-effector vacuum system is comprised of commonly available brass air fittings and couplings connected with plastic fuel hosing and rubber suction cups. The robotic arm is a pharmaceutical-grade Stäubli TX2-60, coupled with a Siemens PLC, a pharmaceutical-grade peristaltic pump, and an air compressor . Due to the complexities of biomedical manufacturing, specifically designed robot end-effector tools are more feasible than using a commercial gripper. As such, we designed a rigid end-effector with a vacuum grip system for manipulating syringe stoppers. In order to keep the end-effector lightweight, a simple Cartesian gantry robot was built to manipulate the syringe venting system as well as the syringe filling system. The syringe venting system was specifically designed to insert into 50mL COC syringes and engage with the automated gantry system. A separate peristaltic repeater pump is connected to the gantry and splits into four separate nozzles, which provide the filling action. Another separate vacuum pump also generates the required gripping force that the end-effector utilizes.

2.1.2.1 Syringe Venting Tube

A primary consideration in this work is the ability to insert a stopper into a 50mL COC syringe that has been filled with the liquid drug product. This is a difficult task, as the rubber stoppers are designed to be larger than the syringe barrel in order to provide a proper seal. As such, it is difficult to insert a syringe stopper without compressing it in some manner. Additionally, if the air in the syringe is not removed prior to the stoppering process, it is possible that the syringe

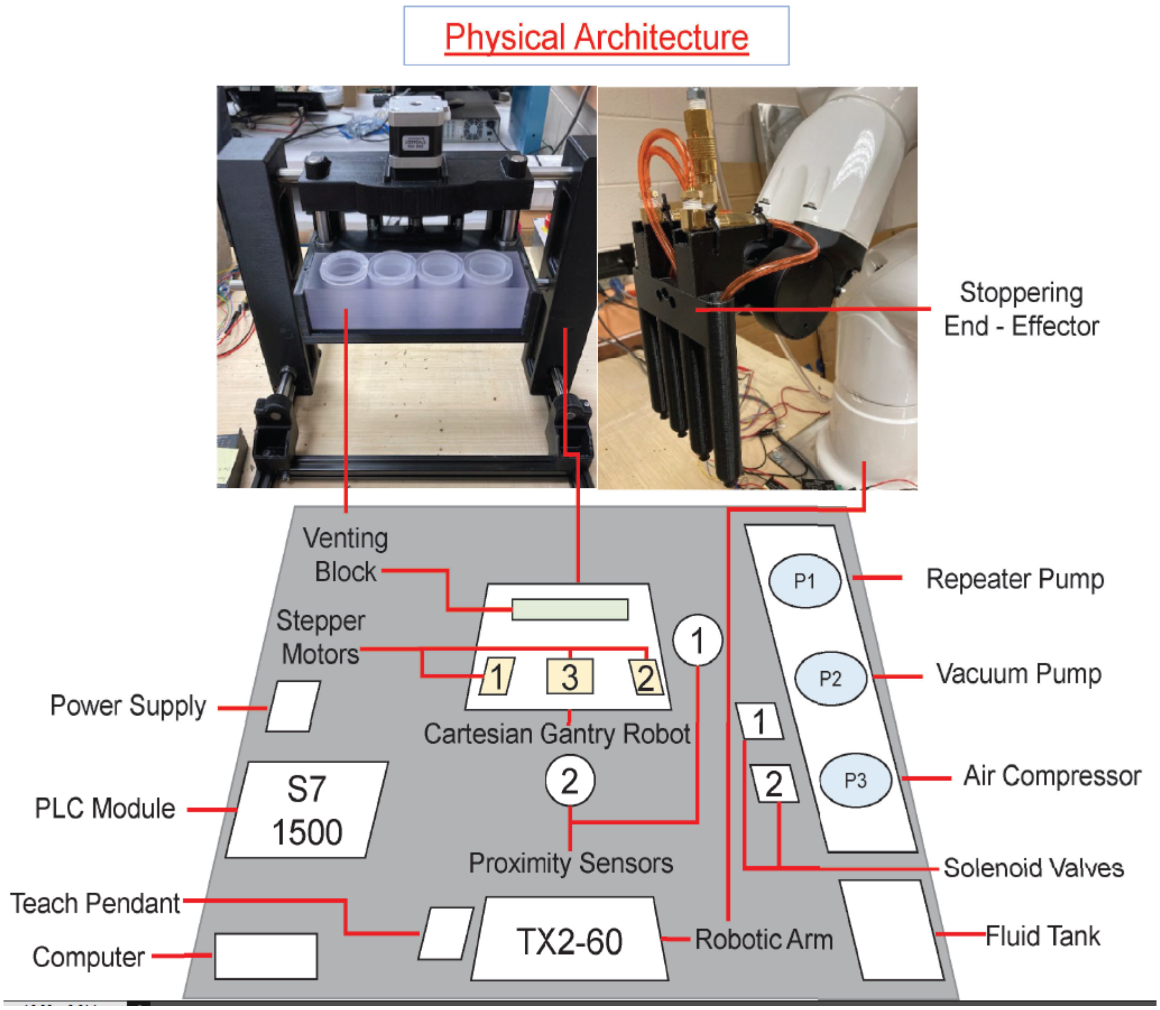


Figure 2.2: Physical architecture of the system

cap will be damaged or even forcibly removed as the stopper compresses the internal air. Research into the subject determined that a venting process is required in order to insert the stopper into the syringe while simultaneously venting excess gasses from the syringe barrel. This process is required in order to avoid damaging the syringe and over-pressurizing the liquid drug product, as well as enabling the oversized stopper to be inserted into the syringe barrel. The venting process is achieved by forcing the stopper through a tube with a tapering cross-section, as shown in Figure 2.3, which compresses the silicone stopper so that its compressed diameter is smaller than that of the syringe barrel. The stopper attached to a linear shaft or push rod is pushed through the stopper entrance, which is slightly larger than the stopper itself. The stopper's diameter is reduced by the compression funnel as it is pushed through toward the stopper exit, which sits inside the barrel of the syringe. Since the processing of multiple syringes is ultimately desired, a manifold holding block, as seen in Figure 2.4, was also manufactured out of the thermoplastic resin. This block has four specifically designed receptacles for holding four vent tubes, allowing them to be manipulated and operated on as a group. The venting tube shoulder rests on the surface of the venting block, providing enough clearance for air to vent out of the top of the syringe barrel. The venting tube is inserted into the syringe barrel so that when the stopper is pushed out of the venting tube, it will expand to seal against the interior walls of the syringe barrel.

Both the venting tubes and the venting block were manufactured using the stereolithography (SLA) 3D printing method, using a thermoplastic resin that results in a smooth finish compared to traditional fused deposition modeling (FDM) 3D printing methods. The result is a translucent venting tube that is both light and resistant to pressure. In a pharmaceutical environment, this tube

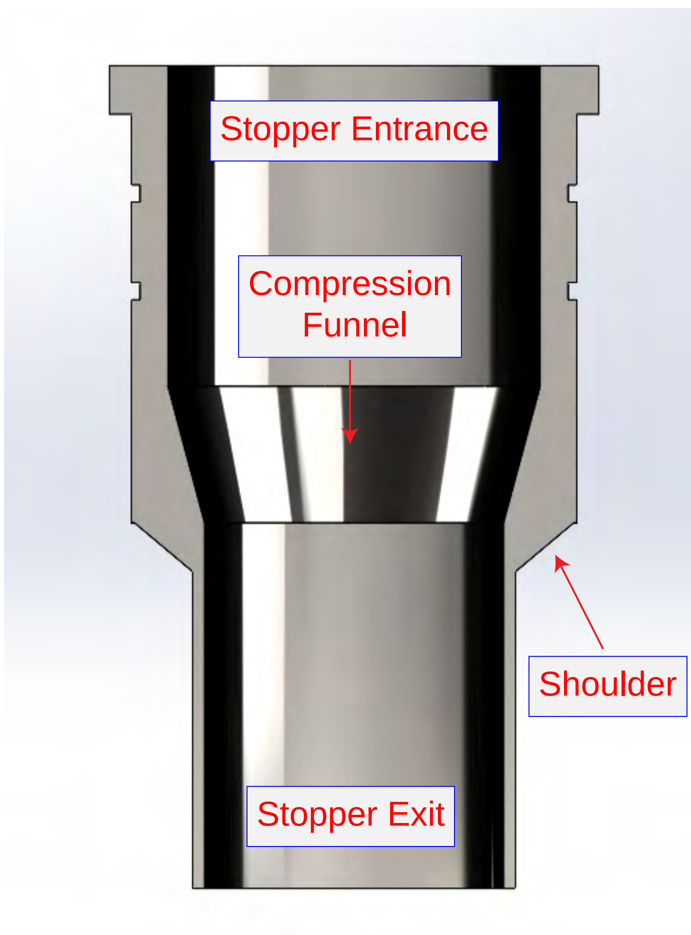


Figure 2.3: Cutaway diagram of a venting tube.

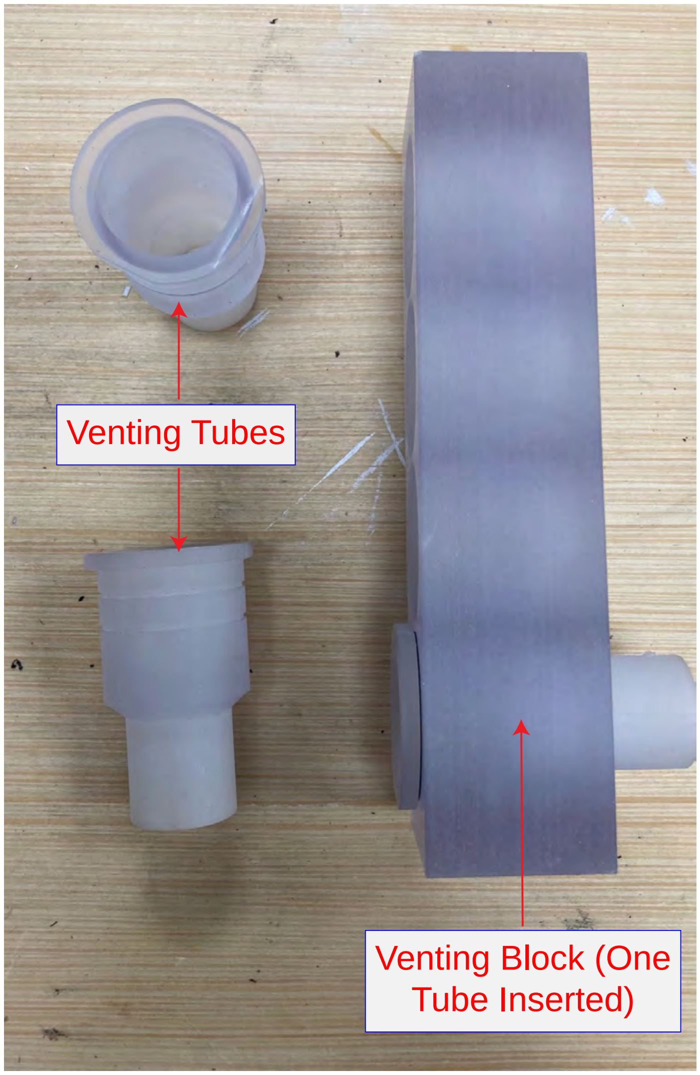


Figure 2.4: 3D printed venting tube samples with venting manifold block.

would be machined out of spun stainless steel [3]. In order to further mimic the smooth properties of a stainless steel venting tube, a small amount of silicone grease was applied to the interior body of the 3D printed venting tube to reduce friction from the stopper against the plastic. The vent tube can be used on individual syringes by inserting it into the syringe barrel and holding it in place using a 3D printed fixture, which is detailed later in Section 3.2.2.

2.1.2.2 Vacuum Gripping End-Effector

In order to automate the filling and stoppering processing of the syringes, the manipulation of the syringe stoppers will be addressed next. The technique utilized to stopper COC syringes involves inserting them into the barrel of the syringe after the liquid drug is deposited. This is diametrically opposed to the process of using the BD syringes in our previous work, which used a Luer-Lock cap on the bottom of the syringes and arrived already stoppered from the manufacturer [10]. A significant concern presented with the syringe stoppers was manipulating them in such a way that allowed for them to be deposited directly into the syringe without damaging them. It was determined that utilizing a vacuum-based gripper is the best option for manipulating the stoppers, as it does not present a risk of deforming the stopper and is the current industry standard. A small suction cup is used to grip the smooth inner surface of the stopper, and the suction force can be cut off with a valve in order to leave it deposited in the syringe. This process can be repeated simultaneously with multiple gripping heads, meaning a row of syringes can be stoppered concurrently. Due to sterility requirements, a maximum of one row, or four syringes, will be operated on at a time.

In order to encourage an easily repairable and modular design, components for the end-effector, as shown in Figure 2.5, are sourced by commercially available methods or by custom 3D printing. In this case, the end-effector is primarily comprised of printed polylactic acid (PLA), brass hydraulic fittings, and polyurethane fuel hosing. While the materials for these components would not be able to survive the harsh cleaning that would be required of a production version, they can be replaced with printed Polyether ether ketone (PEEK), certain acrylonitrile butadiene styrene (ABS) mixtures, or milled from 316 stainless steel, which would be compatible with pharmaceutical cleaning processes. This is critical to the mission statement of an easily used system that can be quickly adapted even in periods of supply chain instability (such as pandemics). The suction gripping system was tested by attaching a single suction cup and air fitting to the compressor, which was used to pick up and manipulate a single stopper. After verifying its functionality, a hollow, 3D printed end-effector was created to house multiple air fittings and vacuum hose routes, with the suction cup grip extended outside of the tip of the end-effector. A manifold was also created in order to secure the air hoses and connections. Both the end-effector and manifold are 3D printed using a standard PLA filament and secured together using M5 machine screws. The gripping force is created utilizing a separate vacuum pump configuration that is connected to the end-effector with air tubing and hydraulic quick-disconnecting fittings. The manifold splits the gripping force into four smaller air hoses that connect directly to each suction cup, allowing for an equal gripping strength on each stopper. The robot is thus able to pick up stoppers by simply pressing the end-effector down onto them, utilizing a one-way solenoid valve to activate the air flow for the gripping force

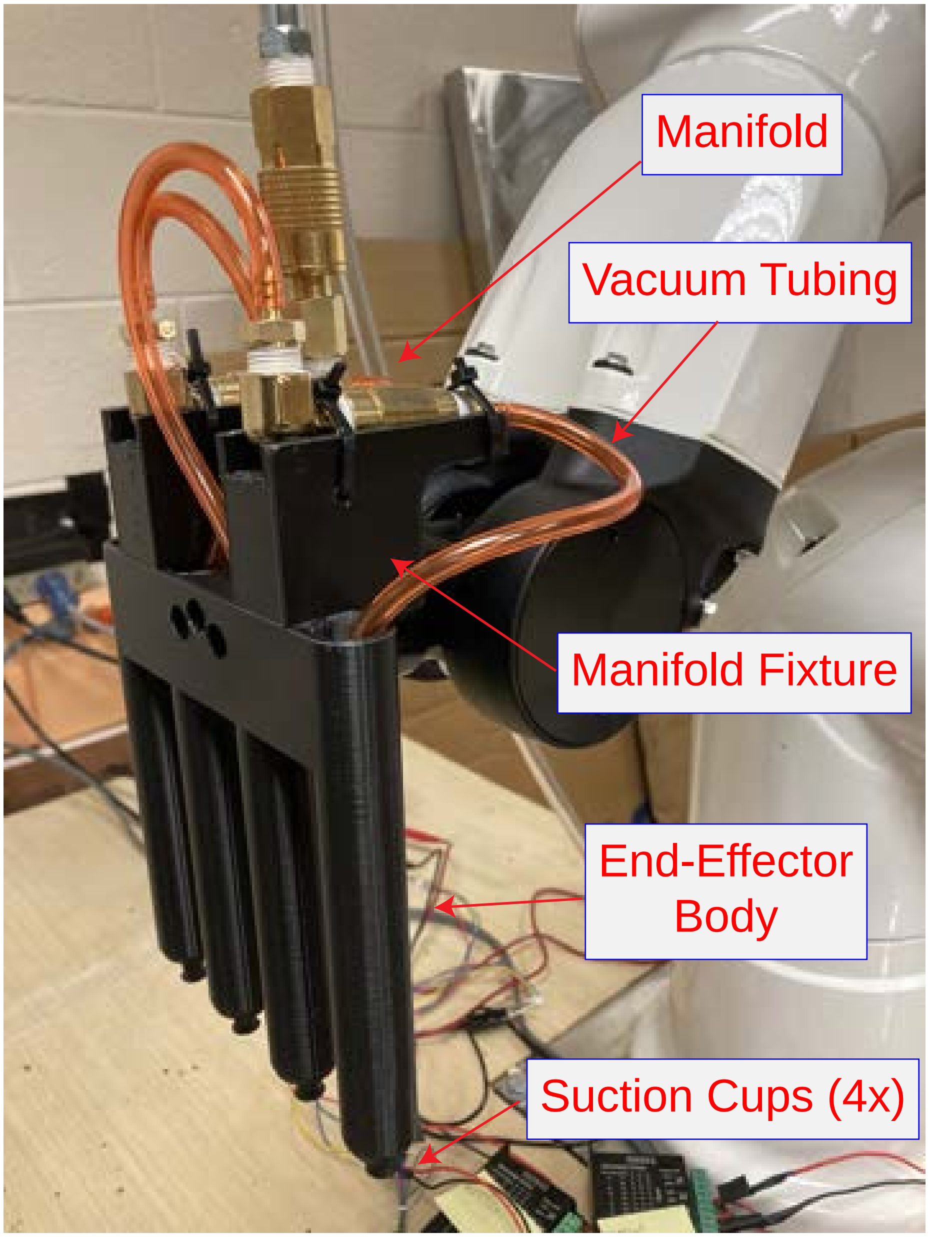


Figure 2.5: Multi-syringe gripper and stoppering end-effector.

when necessary (Figure 2.21). The end-effector is designed only to be able to grip stoppers sitting directly below its four gripping heads, so a simple 3D printed plate was designed in order to align the stoppers properly, which can be arranged by a technician or operator, as shown in Figure 2.21. Early experiments found that the stoppering process would require an end-effector that is rigid and non-compliant. This is due to the need to overcome the friction of pushing the stopper through the venting tube, which requires a strong and constant downward force from the end-effector. As such, the end-effector is completely manufactured out of 3D-printed PLA filament. The opening of the venting tubes is slightly oversized compared to the end-effector and stopper, allowing for some positioning error in the stoppering operation.

2.1.2.3 Cartesian Gantry Robot

Early versions of the end-effector were found to be incredibly cumbersome, and the addition of too much weight would cause strain on the robot and deformation in the 3D printed plastic. Therefore, we decided to use a separate gantry-style Cartesian robot to house the venting tubes and align them in the syringes. This customized robot would be a proof-of-concept design in order to determine the feasibility of using a small Cartesian robot in an ISO5 hood. Hence, no vision systems or force/torque sensors are permissible in our design due to the complexity invovled and the difficulty of using them in a strict ISO5 enviornment. The gantry design is inspired and based on several open-source computer numerically controlled (CNC) routers that are designed to be easily 3D printed and assembled. This particular iteration of the gantry utilizes the motor mounts from [5], and is otherwise entirely original in its design. Similar to the end-effector, a combination of commercially available materials and 3D printed designs were utilized to create the prototype Cartesian gantry robot, which is shown in Figure 2.7. The two primary custom aspects of the design are the carriages and the middle arm, both of which are 3D printed out of PLA. Strong yet workable materials such as aluminum extrusion are used to build up the frame, while commercial 12mm stainless steel linear shafts are used in both motion transfer and as part of the structure. Commercially available linear bearings are used to create the smooth movement of the carriages along the linear shafts. The bearings are press-fit into holes that were designed in the carriage body. These holes are tightly toleranced and sanded smooth, so that the bearing slides in and remains stationary due to friction. The M10 lead screws are also commercially sourced, and utilize a fine 2mm pitch so that the gantry's movement is precise. The screws interface with a 3D printed threaded attachment that is fixed to the carriages, providing forward and backward movement from the motors. The distance the gantry carriages travel along the screw can be calculated using the below equations

$$i = \frac{n_{out}}{n_{in}} \tag{2.1}$$

$$d = i \times pitch, \tag{2.2}$$

where i is gear ratio, n_{in} and n_{out} are the revolutions per minute (RPM) at the output shaft and the motor shaft, respectively, and d is the travelled distance of the lead-screw. It was decided that a simple lead-screw system would be used to move the gantry as they are cheap, reliable, and the distance traveled is easily calculated from the pitch of the screw. The lead screw structure is shown in figure 2.6. The expectation is that a finalized version of the automated system will use a sealed, ISO5 compliant lead screw assembly or equivalent. The gantry system utilizes two stepper motors, as shown in Figure 2.8, to rotate the lead screws and move the gantry carriages forward and backward. A central arm is attached to both gantry arms, which is centered above the work area. The arm contains another stepper motor attached to a smaller lead screw, which can drive a central carriage vertically. The center carriage contains the venting tubes and the venting tube manifold, and has four holes that allow the venting tubes to extend below the carriage. As such, the gantry has the capability to move forward until aligned with a syringe row, where the center carriage will then extend down until each venting tube is inserted into the syringes. Lastly, four fluid hoses are attached to the rear of the gantry arm and are aligned with the syringes. A separate peristaltic repeater pump is used to fill the syringes utilizing these fluid hoses, when the gantry aligns itself above a row of syringes. In this way, the gantry is capable of filling the syringes whilst simultaneously enabling the venting process.

2.1.2.4 Filling Component

The main hardware component of the filling process is the 4-5 way distributor splitter with check value. Specifically, the inlet and outlet diameter is 3/16" and the fluid is able to output into 4 ports without going reversely due to the existence of the check valve. In addition, the levers of the splitter can adjust the fluid volume from 0% to 100%. In Fig 2.9 and Fig 2.10, it is observed that there are four syringes in a row, and the filling process starts before the stoppering process.

2.1.3 Cyber Component

One of the major challenges in automating the pharmaceutical manufacturing process is compliance with the increasing regulation[11] related to electronic records and electronic signatures. To comply with 21 CFR Part 11, manufacturers have to use electronic authentication to control the

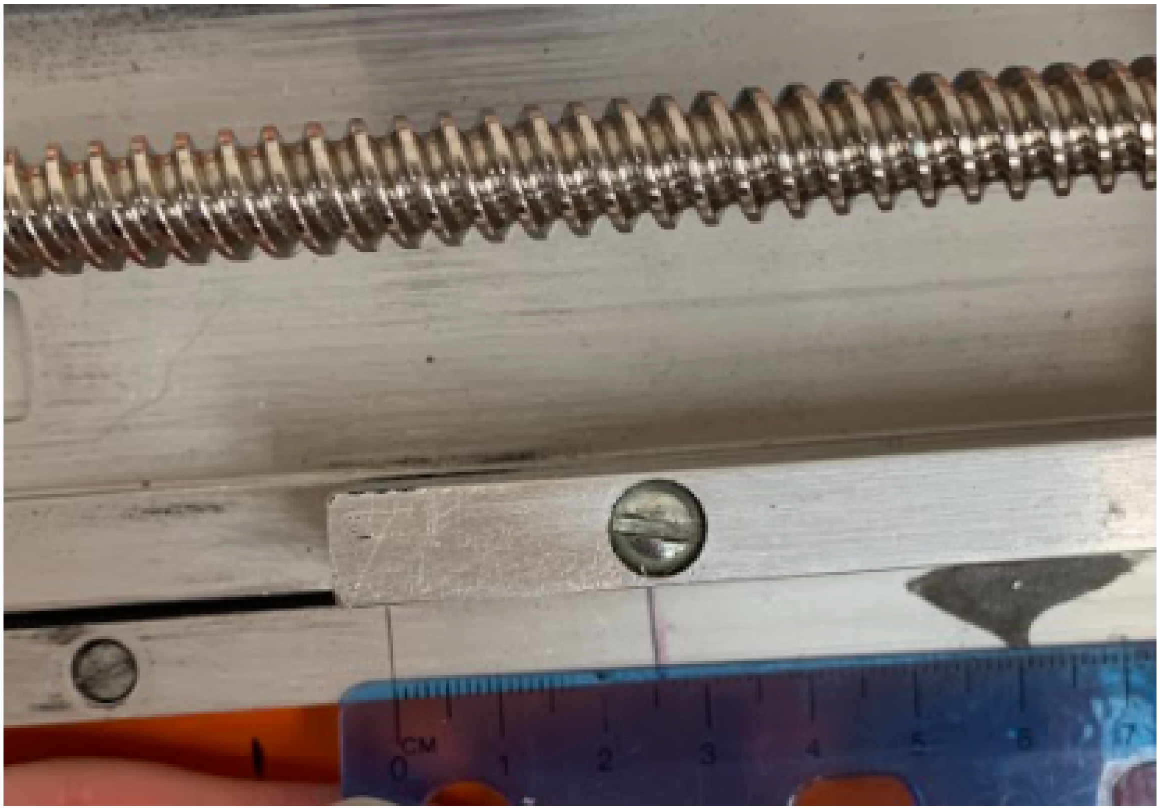


Figure 2.6: Lead screw Structure

user's accessibility to perform certain actions, electronic signatures can provide the security for the authorized individuals have the rights to get access to the management data and system configuration. The requirement of all the electronics signatures and authentication prevents unauthorized change that secure recorded historical documentation. PLC Siemens SIMATIC S7-1500 PLC has the information management software to provide authentication and electronic records of all users to have the access to the human-machine interface (HMI) and programmable logic controllers[24]. Stäubli TX2/CS9 systems are designed for collaborative applications with the highest safety level, and the medical range ensures consistent performance and reliability covered by worldwide Stäubli support and service. Stäubli helps comply with FDA regulations for the requiring electronic records and signatures to demonstrate the tracebility within the system [7]. Hence, the Siemens PLC-based robot control and the integrated system can fully comply with the FDA 21 CFR Part 11 for the life-safety of the products against a wide range of use-case variables and to ensure the trasition to electronic records within system modification. For modern PLC-based robotics automation, efficient communication between the PLC and the robot leads to complete integration of the actuation of

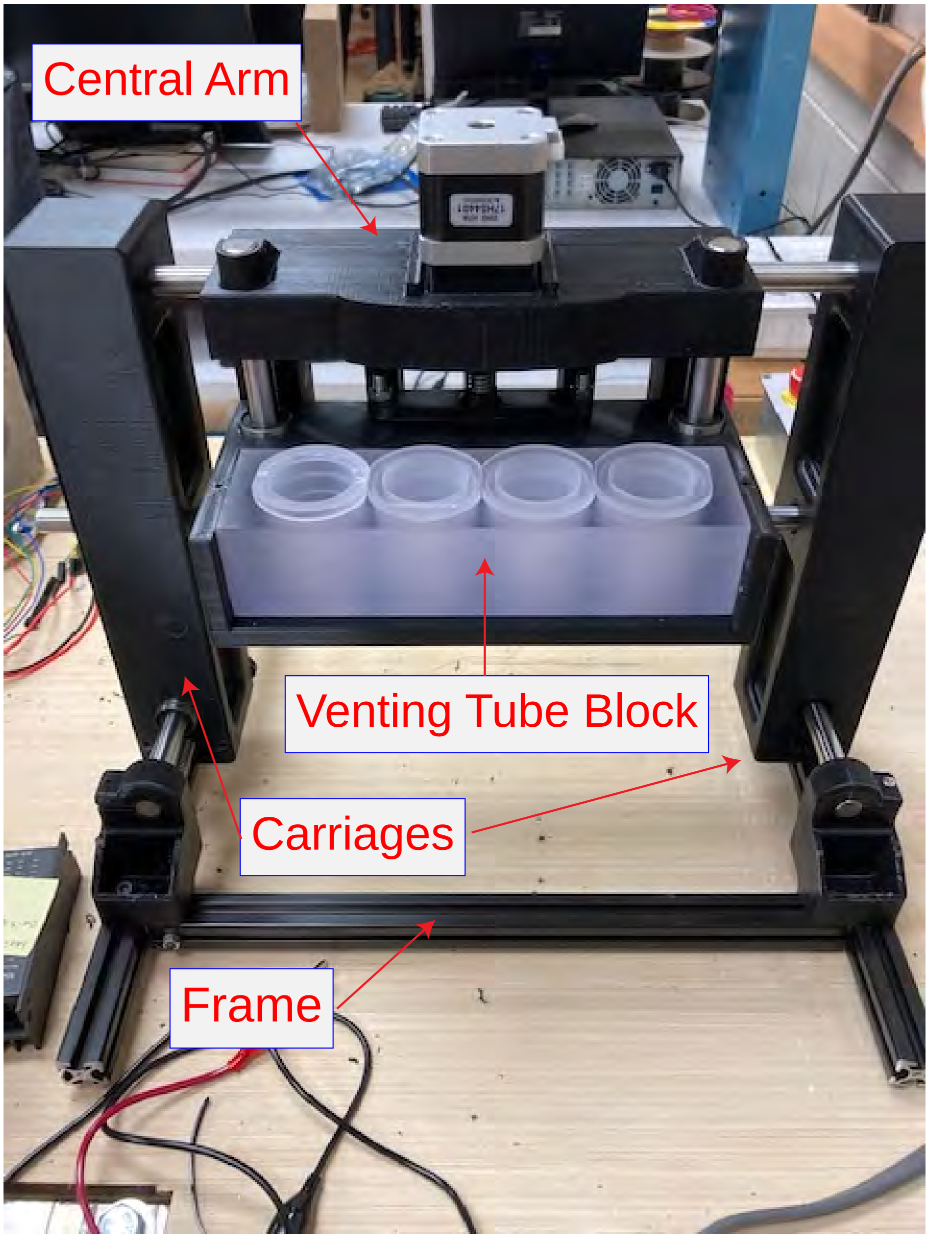


Figure 2.7: The motor-driven gantry, as seen facing the venting tube block. The venting tube block is left uncovered for display.

machines and the robot motion control.In an overall picture in Figure 2.11, the PLC unit is considered as the central unit that receives all the information from the devices and sends the feedback to each device accordingly. Basically, the main system is the PLC system to control the devices which can be decomposed into several subsystems, for example, stepper motors control is a subsystem that has it own control system, the stepper motors are controlled by the motor driver, from a bigger

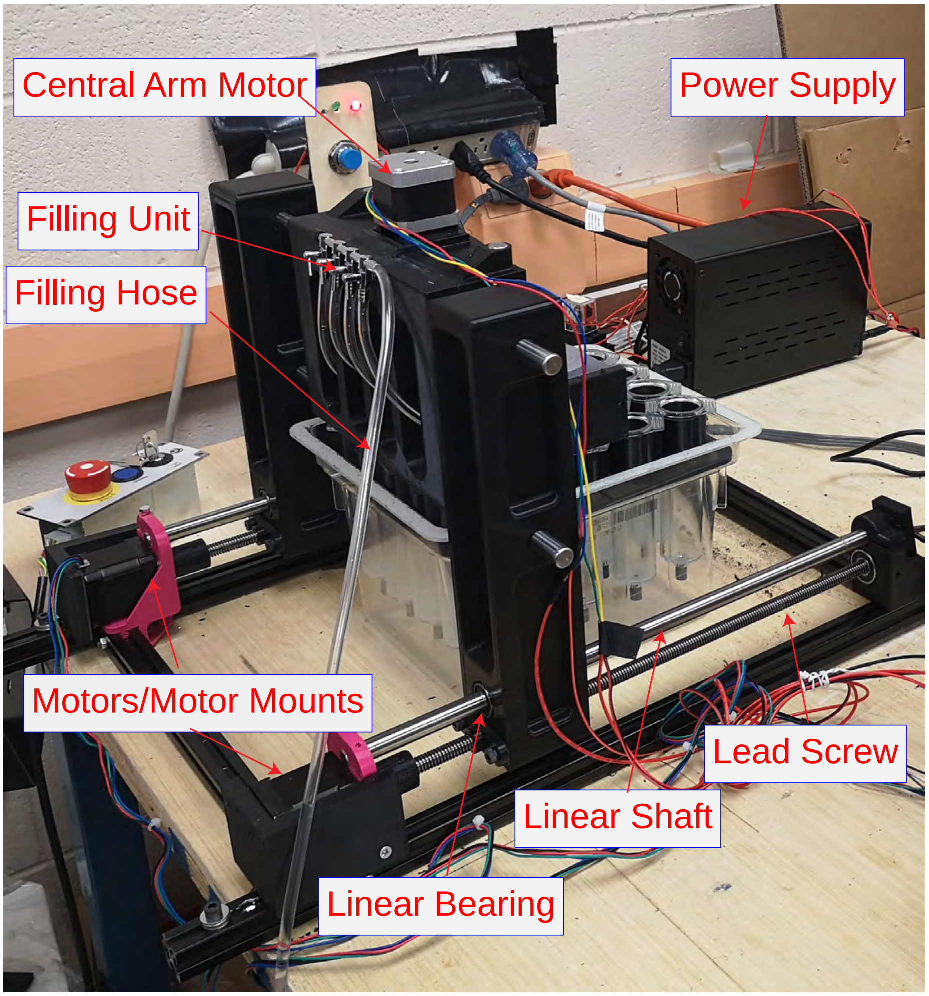


Figure 2.8: The motor-driven gantry, as seen from the side.

system, the PLC sends the pulse signal to the motor driver that controls the stepper motors [30].

The cyber components are consisted of four sub-systems, as shown in Figure 2.11, PLc is treated as the central unit of the whole system that is responsible for all the feedback communication from the devices and sending out the corresponding signals. Each of the subsystem is independent from each other.

1. Robot control sub-system: The Stäubli TX2-60 robot is controlled using the Variable Assembly Language (VAL3) which is based on control system to command the pick and place tasks in SRS. The VAL3 in SRS can be used to control the robot directly. The Fig 2.12 shows a pick and place task loop control in SRS, it is observed that there are two motion control commands: one is ”movel” which records a command for a linear movement towards the

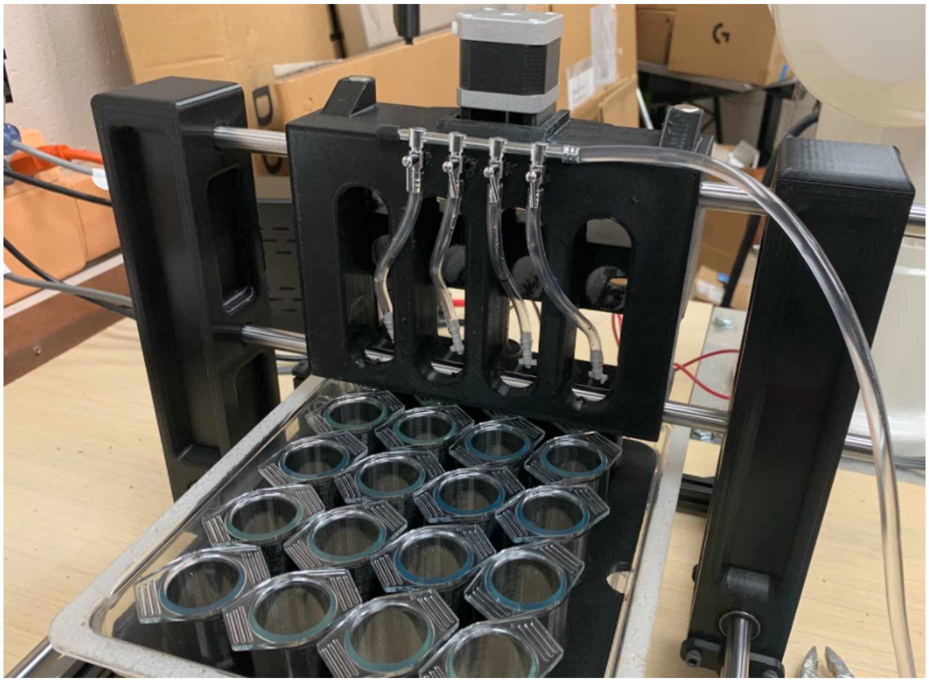


Figure 2.9: Filling Component

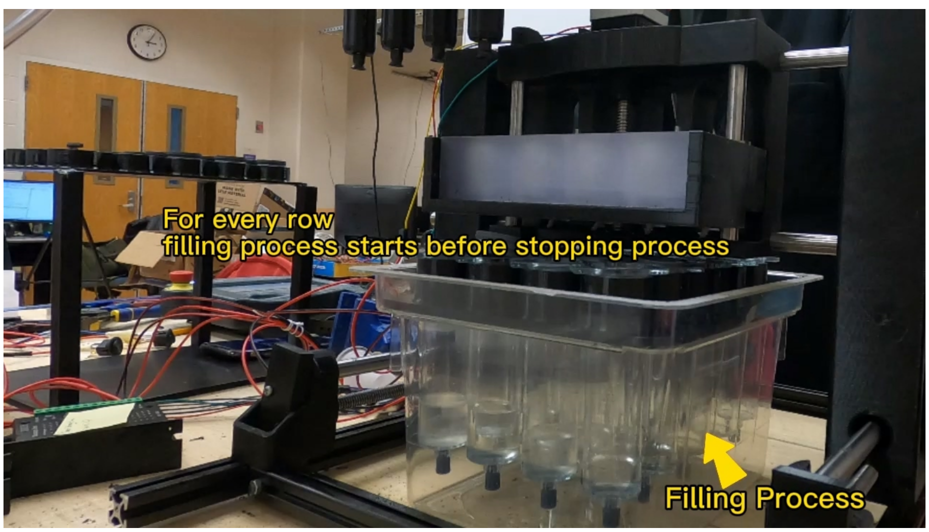


Figure 2.10: Filling Process

desire position (according to the input arguments), the other one is "movej" which records a command for joint movement towards the desired position. "waitEndmove" is important for the stop control mechanism in SRS, because this instruction cancels the blending of the last movement command recorded and waits for the command to be executed, this instruction

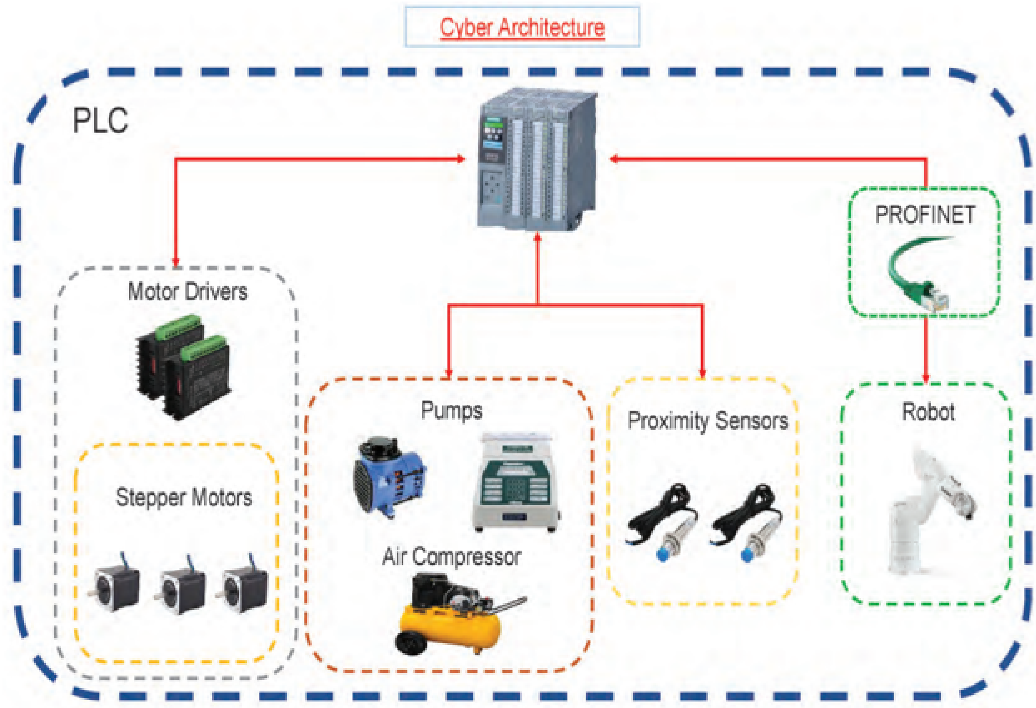


Figure 2.11: Cyber architecture of the system

does not wait for the robot to be stablized in its final position, it only waits until the position command sent to the drives corresponds to the desired final position. For the data, the "diobutton" is the output from the PLC which is the input to the CS9 controller. The signal is used as a conditional statement for the while loop in the program which processes through I/O communication between the PLC and the robot. Memory bits in PLC are created for information storage and reading.

2. Sensor control sub-system: capacitive proximity sensors are controlled inside the PLC. Proximity sensor 1 Figure 2.14 is for verifying the initial position of the gantry, and sensor 2 is responsible for the stoppers detection. The sensors' ground wires are wired to the negative zone of the terminal block and the positive wires are wired to the positive of the terminal directly without connecting to the relay. Both sensors will input digital signals to the PLC when they are energized. The control logic in PLC and SRS shows in Fig 2.13 that the sensors' signal could be used to in multiple programs in SRS, specifically, the signal could be used triggered the robot's programs. Capacitive proximity sensors in Fig 2.14 work by detecting changes in capacitance between the sensor and the cartesian gantry robot. Due to factors like

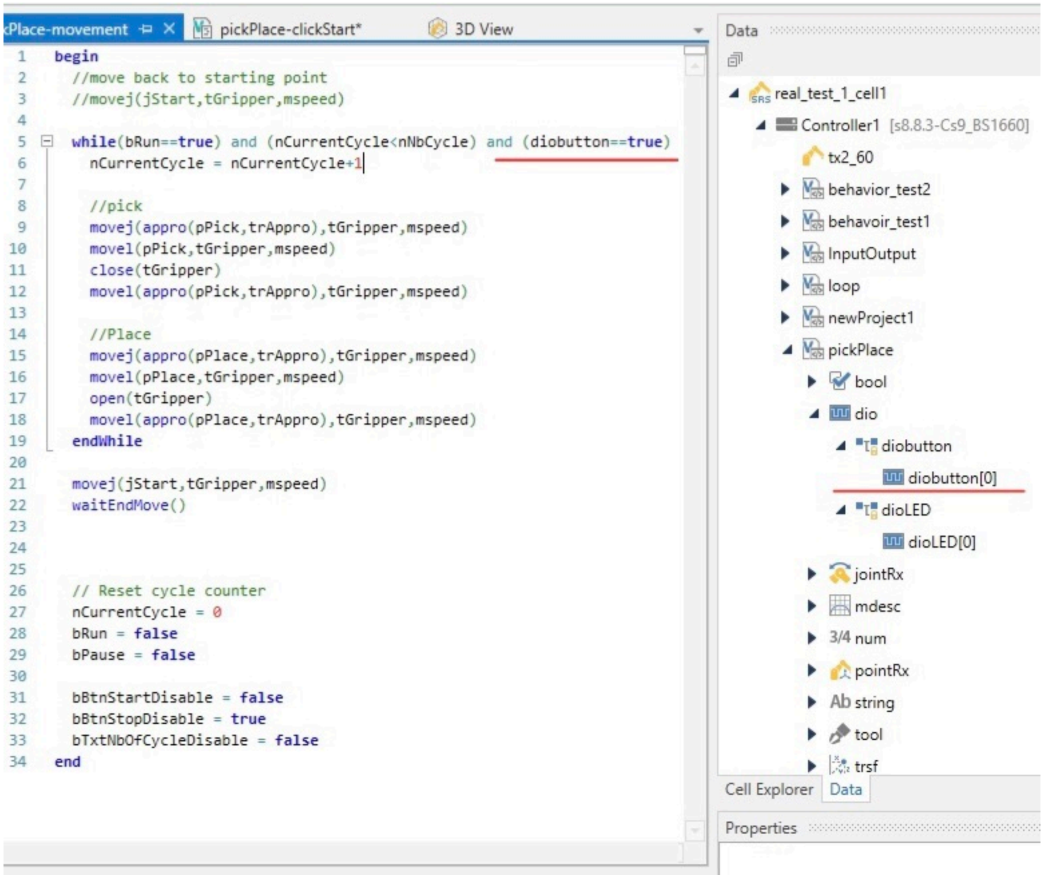


Figure 2.12: Pick and Place command in SRS

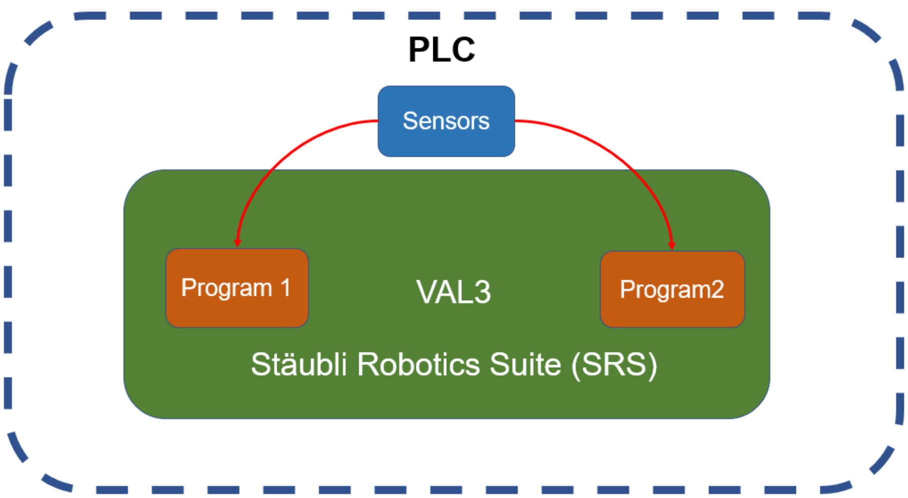


Figure 2.13: Sensor control in PLC and SRS

distance and the size of the cartesian gantry robot might have an impact of the sensitivity of the sensor, the proximity sensor is set up to outside the gantry motion range.

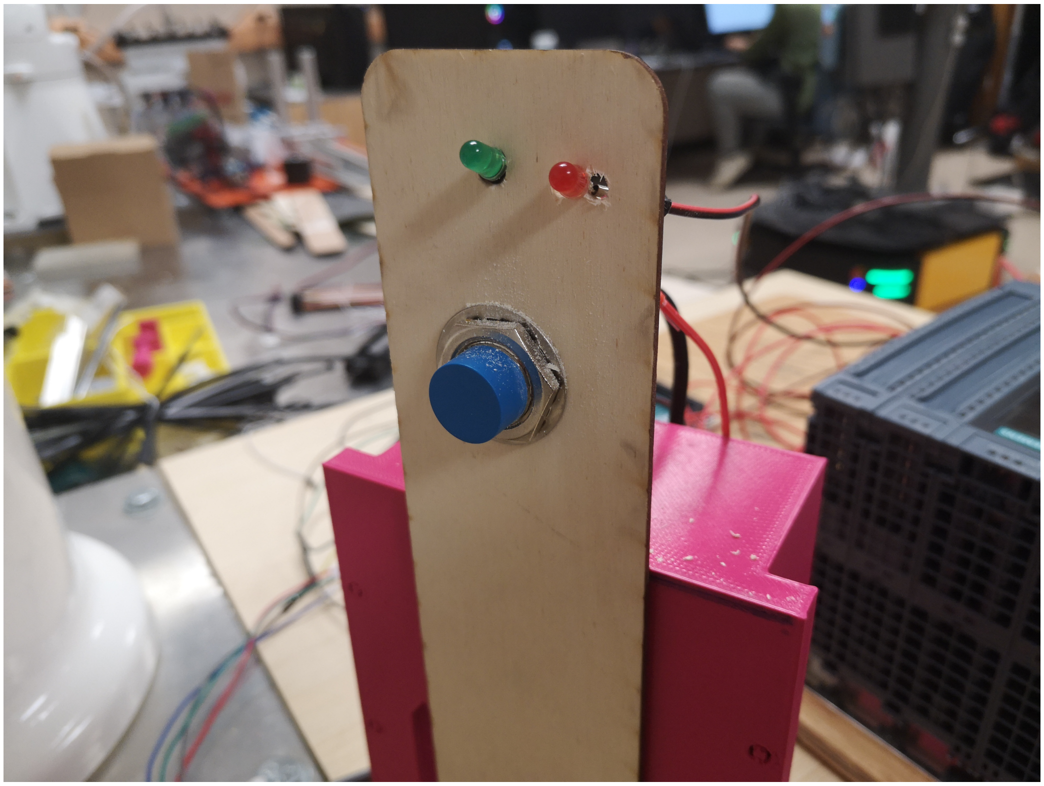


Figure 2.14: Proximity Sensor

3. Stepper motor control sub-system: Three stepper motors are utilized in the system that are responsible for the gantry motion control which are controlled by the motor driver 2.15. Stepper motor 1 and 2 are responsible for the horizontal movement of the gantry, both of the stepper motors are receiving the same pulses from the PLC Speed Axis module which stabilize the gantry's horizontal motion. They are aligned at the end of the gantry. Stepper motor 3 is responsible for the vertical movement of the venting block that its Speed Axis" module in PLC is programmed differently from the other two stepper motors. In the Siemens PLC TIA portal, by adding Technology Object for the stepper motors, we are able to create Speed Axis to send a sequence of pulses to control the stepper motors [30]. In Figure 2.16, "timer" is added before the Technology Object which are components of the system memory of the CPU, is used to limit the run time of the stepper motor. The model number of the stepper motor is TB6600 that is a professional stepper motor driver, which could able to drive two-phase

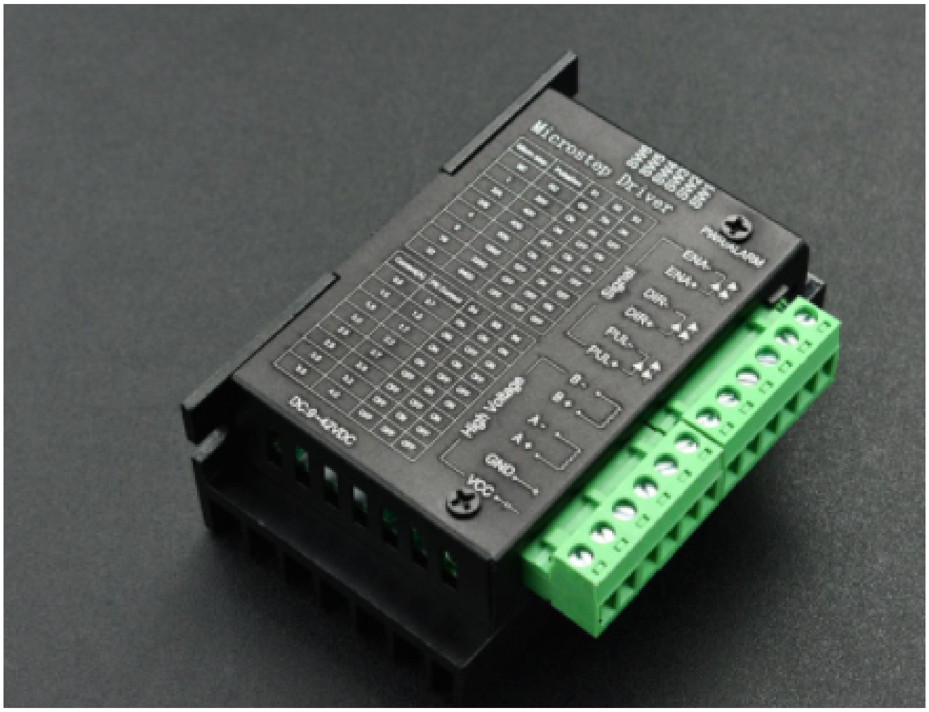


Figure 2.15: Motor Driver: TB6600

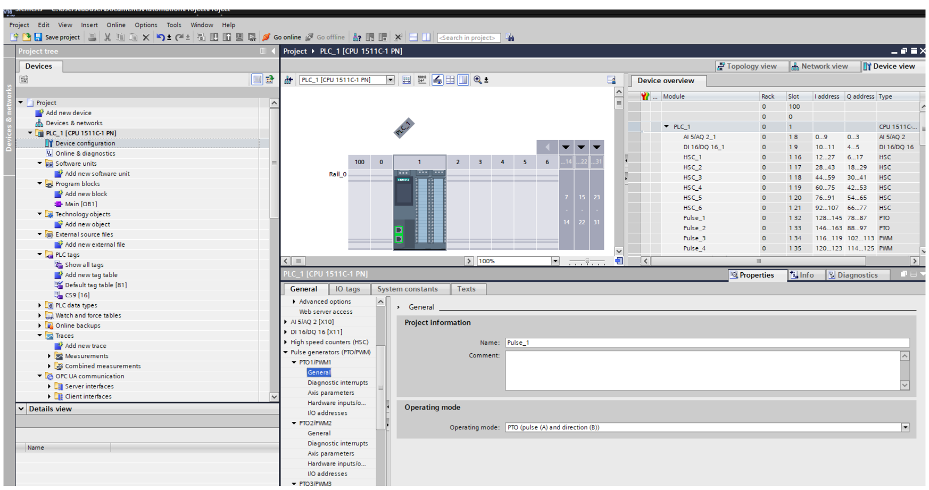


Figure 2.16: Speed Axis Configuration

stepper motor for this specific automated process. It is compatible with ”speed-axis” module in Siemens PLC that can output a 5V digital pulse signal. The motor driver has a wide range power input, 9 40 VDC power supply which is able to drive the bi-polar stepper motor. The stepper driver supports speed and direction control that is great for control the motion of the cartesian gantry robot by using the pulse signal from the PLC.

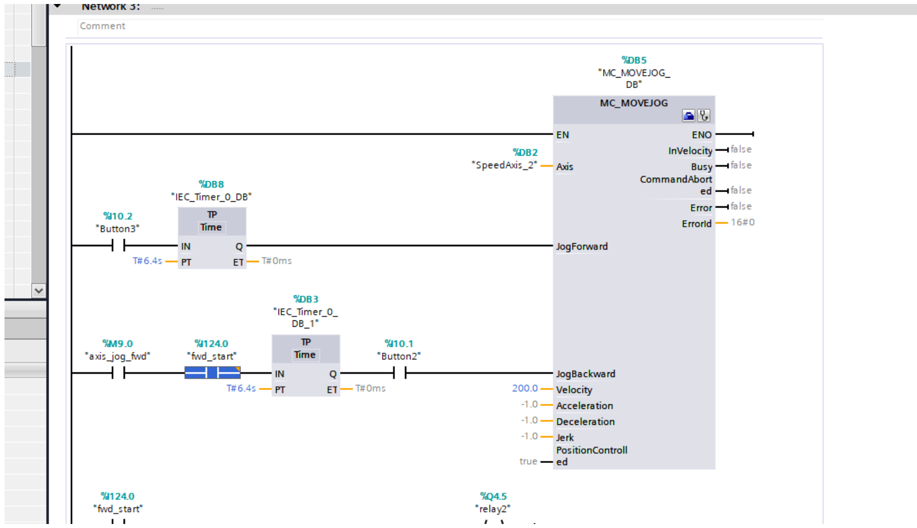


Figure 2.17: Functional Block to Control Stepper Motor

4. Pump/compressor control sub-system: There are two pumps and one air compressor in this sub-system. Pump 1 is a peristaltic repeater pump Figure 2.20and responsible for the filling process controlled by the solenoid valve 1 (see Figure 2.19). The mechanism to trigger the repeater pump is to push air into its air port, instead of using the original foot step pump, solenoid valve 1 was installed to the system to control the repeater pump, every time the solenoid valve is open for 0.5 seconds that the air compressor 2.18 will release pressure and push a small amount of air into the air port to run the repeater pump. It is observed that the pharmaceutical repeater pump have the setting to adjust the filling volume, 50 ml is the preset volume for the experiment.

   Pump 2 refers to the vacuum pump that is responsible for picking up the stopper and is controlled by the solenoid valve 2. The circuit control of the solenoid shows in Fig 2.21, the Siemens PLC S7-1500 is powered through a 24VDC voltage source, the ground and hot wires are parallel connected to the terminal block,

2.1.3.1 PROFINET Connection between PLC and CS9 controller

PROFINET connection is an Ethernet standard based industrial protocol that enables the data exchange between devices faster [26]. In addition, PROFINET provides higher level security than PROFIBUS, plus, it greatly reduces the cost of the connection installation. The cyber components surround one central unit, the PLC, as the brain of the integrated system. The cy-

Figure 2.18: Air Compressor

ber part is responsible for two principle communications: the communication between the robot and the PLC via PROFINET, and the communication between the robot and the control circuits that use the proximity sensors to control the motion of stepper motors and solenoids to control the vacuum pump and the air compressor via PLC. We first introduce the communication between the robot and the PLC via PROFINET. PROFINET is an Ethernet-based communication protocol designed for real-time data exchange between controllers and devices. Due to Ethernet-based local network, the data exchange speed is much higher than PROFIBUS connection. Both PROFINET and FROFIBUS are IEC standards [25], but they are entirely different protocols that use different cables. The PROFINET connection between the PLC and robot makes the industrial operation less costly with improved product quality as well as increased output. The SRS is the software to operate the robot. It has a visualization of automation in a 3D environment and can perform validation of the operation simulation. A dedicated robotics language, VAL3, in SRS commands flexible and powerful function sets to plan the motion of the robot and build up a wide range of accessibility in connection, including digital I/O and analog I/O within PROFINET communication. The snap

Figure 2.19: Solenoid control wiring

function of VAL3 makes the robot positioning easier and makes the positioning reachability easier to check. The following steps are used to build the connection between the Siemens S7-1500 PLC and the Stäubli robot TX2-60:

1. In SRS, we need to manage the physical I/Os Fig 2.25 and export them as a General Station Description Markup Language (GSDML) file. As Fig 2.26 shows that the J207 and J208 are two real time Ethernet ports that be used for EtherCAT, Profinet or EtherNet/IP on the CS9 controller. The ports are digitally shown as IO cards in SRS. The GSDML files are General Station Description (GSD) written in the Extensible Markup Language (XML)

Figure 2.20: Pharmaceutical repeater pump

format, containing information about the device capabilities [26].

2. In the PLC TIA portal, we need to locate the GSD file management by selecting the exported SRS GSDML file, and upload the GSDML files to the portal to build up the connection between the PLC and the Robot, specifically, under the hardware catalog in TIA portal, it is observed that “Other field devices” and follow the sequence of folders until it reaches the CS9 file. Now the connection could be built by dragging the CS9 controller file to the ”Network view” window Fig 2.28.

3. We need to assign an I/O address for each corresponding byte memory on the PROFINET work. Note that the I/Os board in SRS is structured for 8 bits (one byte) per module, but it is for 1 byte per module in the Siemens PLC. From the ”Device overview” windown Fig 2.29 where the inputs and outputs addresses are assigned for each byte of memory on the Profinet network. In SRS, the IO board was structured for 8 bits per module, which is one

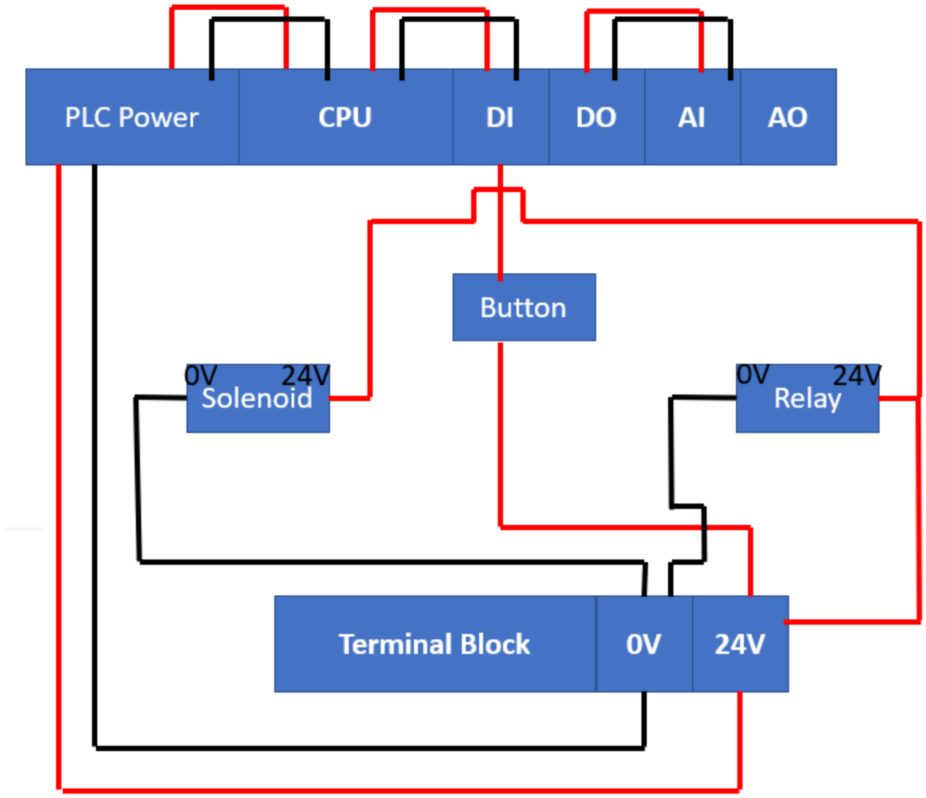


Figure 2.21: Electrical System Layout

byte of data. Therefore, on the PLC side it is displayed as 1 Byte for each Input or Output module that what setup in SRS. For example, in Fig 2.22 the first module below is an input byte and is allocated to the "I address" 36. (This address can be changed if you so choose.) Within this Byte exists the bit addresses of 36.0, 36.1, 36.2, 36.3, 36.4, 36.5, 36.6, 36.7. The "I address" seen in the Fig 2.23 below are SRS outputs. The "Q addresses" in TIA Portal are SRS inputs. I suggest an Excel spreadsheet be created to organize which SRS dio is assigned to which input/output in TIA portal.

4. After mapping the I/O module, we are able to assign I/O tags in both SRS and PLC for specific functionalities. The ladder logic below Fig 2.24is structured to start the robot's cycle based on an HMI Boolean tag reading "1". In my opinion, it is good practice to select a tag name based on that tags function in the programming. The "M" at the beginning of a tag, it is not a related to a physical input or output. It is nothing more than a memory tag that is assigned to the PLCs (and HMI if used) internal memory. This tag is not used to send data

Clemson Output Tags

		Name	Data type	Address	Retain	Acces...	Writa...	Visibl...	Supervis...	Comment
1		Q_CS9_Module_Output3_30.0	Bool	%Q30.0	☐	☑	☑	☑		
2		Q_CS9_Module_Output3_30.1	Bool	%Q30.1	☐	☑	☑	☑		
3		Q_CS9_Module_Output3_30.2	Bool	%Q30.2	☐	☑	☑	☑		
4		Q_CS9_Module_Output3_30.3	Bool	%Q30.3	☐	☑	☑	☑		
5		Q_CS9_Module_Output3_30.4	Bool	%Q30.4	☐	☑	☑	☑		
6		Q_CS9_Module_Output3_30.5	Bool	%Q30.5	☐	☑	☑	☑		
7		Q_CS9_Module_Output3_30.6	Bool	%Q30.6	☐	☑	☑	☑		
8		Q_CS9_Module_Output3_30.7	Bool	%Q30.7	☐	☑	☑	☑		
9		<Add new>			☐	☑	☑	☑		

Figure 2.22: CS9 Controller IO in TIA portal

Clemson Input Tags

		Name	Data type	Address	Retain	Acces...	Writa...	Visibl...	Supervis...	Comment
1		I_CS9_Module_Input3_46.0	Bool	%I46.0	☐	☑	☑	☑		
2		I_CS9_Module_Input3_46.1	Bool	%I46.1	☐	☑	☑	☑		
3		I_CS9_Module_Input3_46.2	Bool	%I46.2	☐	☑	☑	☑		
4		I_CS9_Module_Input3_46.3	Bool	%I46.3	☐	☑	☑	☑		
5		I_CS9_Module_Input3_46.4	Bool	%I46.4	☐	☑	☑	☑		
6		I_CS9_Module_Input3_46.5	Bool	%I46.5	☐	☑	☑	☑		
7		I_CS9_Module_Input3_46.6	Bool	%I46.6	☐	☑	☑	☑		
8		I_CS9_Module_Input3_46.7	Bool	%I46.7	☐	☑	☑	☑		
9		<Add new>			☐	☑	☑	☑		

Figure 2.23: SRS outputs in TIA portal

to external devices. Assigning a memory tag to a "pushbutton" on the HMI. Once pressed, there is a rising edge signal that will go away immediately upon release of the HMI button. However, a constant signal is needed to run the CS9 controller (at least how I have it coded). A latching structure is added on the second rung of Network 1 to hold the signal on, until an output signal is sent to stop the cycle.

The outputs from the PLC are the inputs to the robot and vice versa. It is crucial to understand their mutual reference relationship when setting up the PROFINET I/O in each controller. Specifically for the operation in I/O of the integrated system, every assigned tag will have its own function or reference. If one of the tags is shared in both SRS and PLC, the address in PLC is different from the address in the SRS because the designed module numbers are structured differently in the two systems. We will have a corresponding digital input (output) in the PLC that we can utilize as the output (input) in the SRS to trigger the actuators through ladder logic.

For the control circuits in this system, we have the following components: The proximity

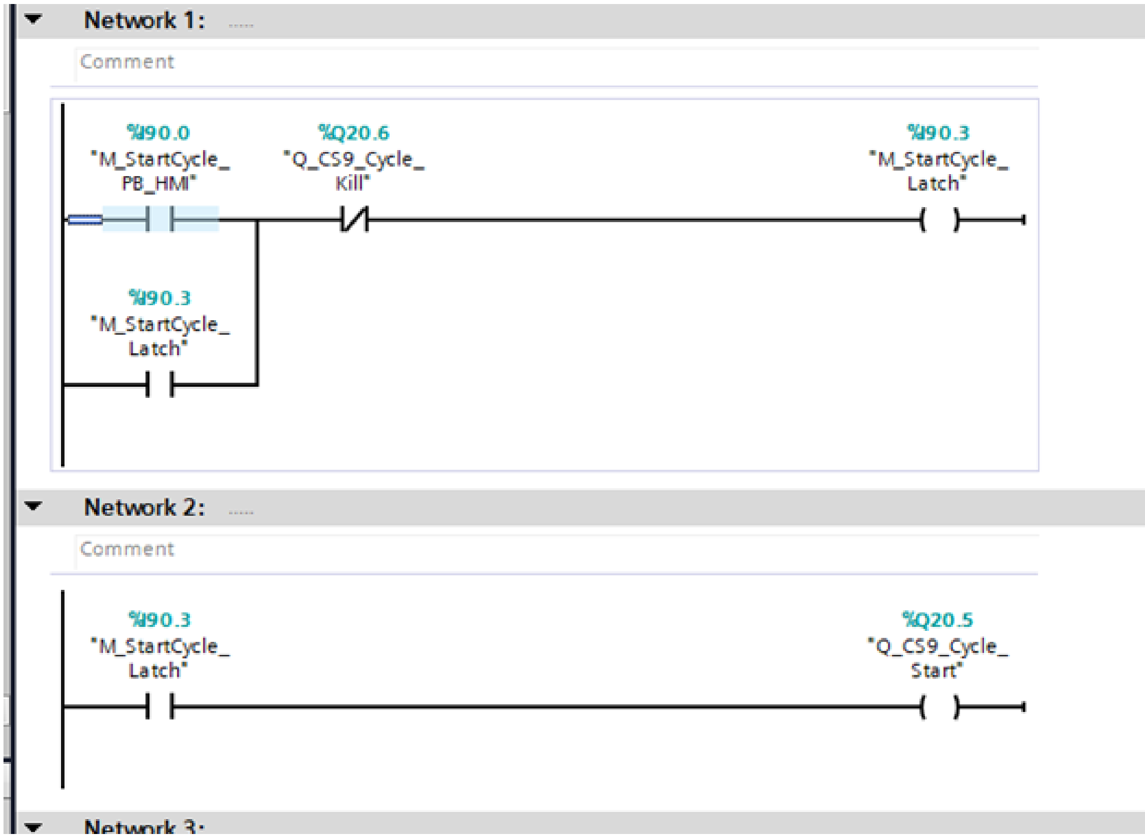


Figure 2.24: Robot cycle ladder logic in TIA portal

sensors 1 and 2 are used to trigger three stepper motors. The stepper motors 1 and 2 are controlled by one motor driver for the horizontal movement of the Cartesian gantry robot, and the stepper motor 3 is controlled by another motor driver responsible for the vertical movement of the venting block. Two solenod valves are used to actuate the vacuum pump and air compressor. Solenoid valve 2 is used to control the vacuum pump, and solenoid valve 1 controls the air compressor's pushing air to the repeater pump. As shown in Figure 2.21, two capacitive type proximity sensors are used in our system. Sensor 1 is used to verify the starting position of the gantry. Once Sensor 1 senses that the gantry is at the correct starting position, it will send a signal to the PLC, and that signal will trigger the stepper motor to move the gantry horizontally. Sensor 2 is placed in between the tray and the stoppers holder. The purpose of this sensor is to make sure all four stoppers are attached to the robot's end-effector before the stopping process. The proximity sensor 2 is used to ensure every stopper is in position. If one of the stoppers is not on the end-effector, the PLC will send another signal to the robot, and the robot will return to the stoppers holder to pick up the stoppers 1.

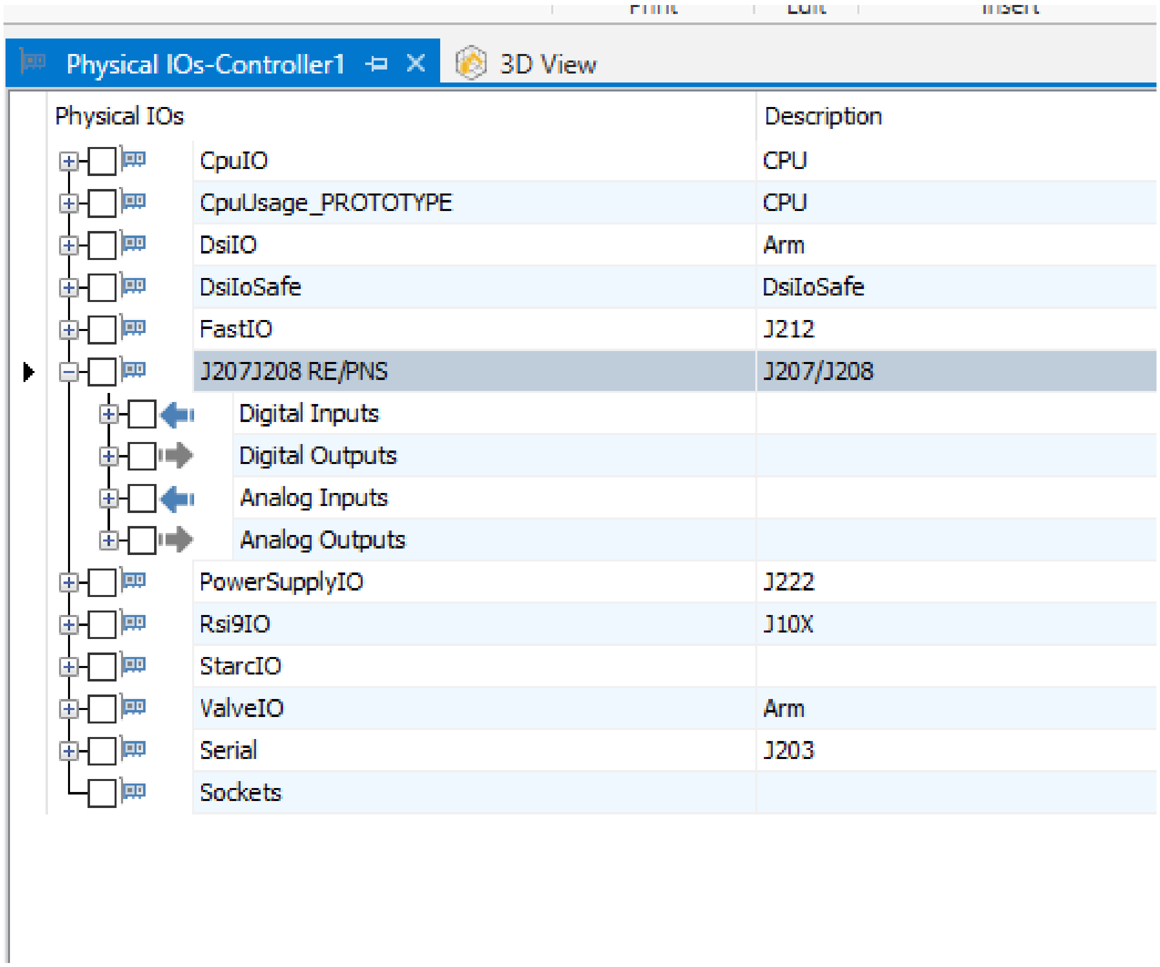
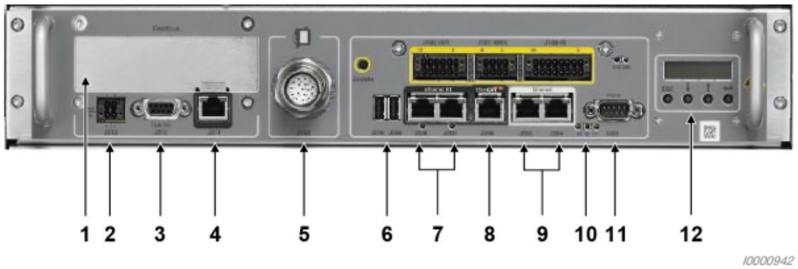


Figure 2.25: IO link in SRS software

2.1.3.2 Mechatronics Control

In the last several decades, an intense shift from traditional mechatronic systems to Cyber-Physical Systems (CPS) is taking place in the pharmaceutical field due to the FDA standard recognition that evaluates consensus standards for appropriateness for the review of medical device safety and performance, subsystems in this project include microelectronics, power electronics, sensors, and actuator technology bringing the automated production higher efficiency and accuracy [27]. Algorithm 1 shows the pseudocode of the robot motion process based on sensor readings. An emergency stop button is set up for safety consideration (Line 1). The stopper pick-and-place task will start if Sensor 1 is on (Lines 2 and 3). If Sensor 2 is on (Line 4), the robot will move to the gantry platform (Line 5). If Sensor 2 does not detect one of the stoppers, the robot will not go for the next move



Item	Description
1	FIELDBUS: Optional PCIe board
2	J213: Optional external 24 V SELV/PELV power supply
3	J212: Fast inputs/outputs
4	J211: EtherCAT port (Reserved)
5	J103: Connector for MCP
6	J209, J210: USB ports
7	J207, J208: Real time Ethernet slave (EtherCAT, Sercos III, EtherNet/IP, PROFINET)
8	J206: EtherCAT master
9	J204, J205: Ethernet ports
10	Status LEDs ▪ D3: Access to flash disk, ▪ D2: Communication status, ▪ D1: MMI interaction status.
11	J203: RS232 serial link
12	Basic Man Machine Interface (MMI)

Figure 2.26: Ethernet ports on CS9 controller (Screenshot from controller manual)

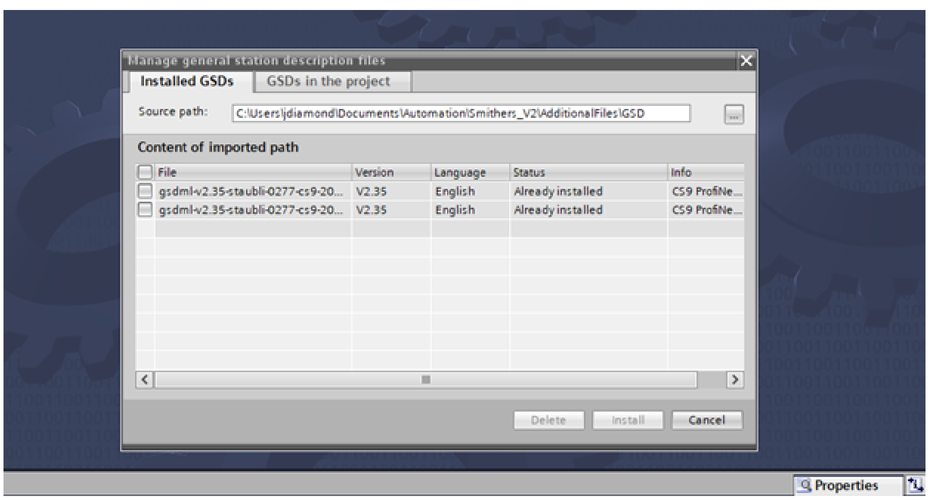


Figure 2.27: GSD file management in TIA portal

command (Line 7). If the gantry is not in the preset position initially, the programs in SRS will not start (Line 10).

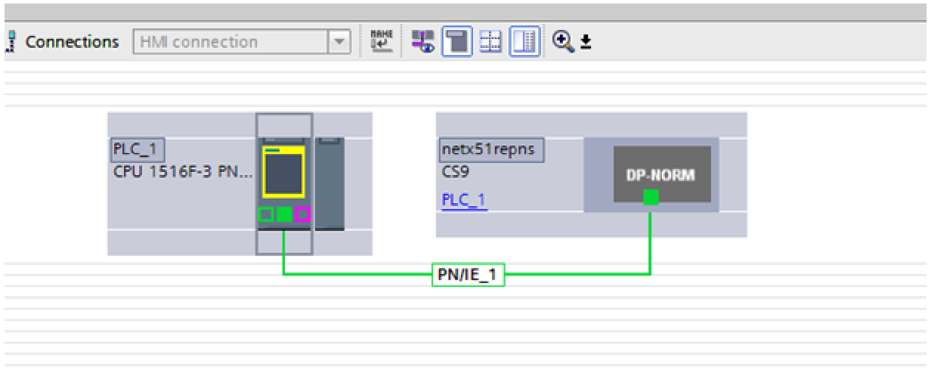


Figure 2.28: Connection between PLC and SRS in TIA portal

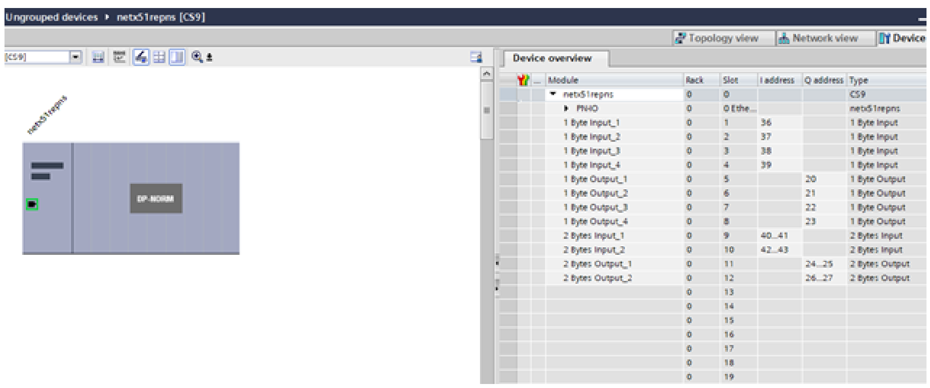


Figure 2.29: IO in TIA portal

Algorithm 1 Robot Motion Control based on Sensor Reading

```
1:  while Emergency stop is off do
2:      if Sensor 1 is on then
3:          Move to pick up first row of stoppers
4:          if Sensor 2 is on then
5:              Move to gantry
6:          else
7:              Action stop
8:          end if
9:      else
10:         No action needed
11:     end if
12: end while
```

The speed of the gantry has a constant value because of the accuracy of the bipolar stepper motors. We use stepper motors instead of servo or any other brushed DC motor since the stepper motors can have relatively high torques at low speeds to drive the lead screw with precise positioning and repeatability of movement. In the PLC, the functional blocks that control the motor driver are assigned to send pulse signals within a certain amount of time, making the travel distance constant as well. The gantry's movement can be taken into two directions: horizontal movement and vertical movement. For the horizontal movement, every iteration has a unique input signal to the PLC, and the PLC will have a corresponding output sent to the robot. The movement iteration is constantly going on according to the assigned ladder logic inside the PLC. To make sure the process is operating in sequence, there will be one unique signal in the PLC and the robot between each movement. For example, if the gantry moves one iteration, it will have a signal sent out to the robot, then the robot will start the next movement. The same is continued for the gantry's subsequent movement, and the robot will send out another distinct signal every time it completes a move command.

Pump 1 and pump 2 are controlled by the same type of solenoid 2.19. Pump 1 is the repeater pump for the filling process, which is controlled by a one-way normally-closed solenoid valve 2.19. Pump 2 is the vacuum pump, which is controlled by another one-way normally-closed solenoid valve 2.19, responsible for picking up the stoppers. Specifically, since the filling process is before the stopping process, Solenoid Valve 1 will open before the robot picks up the stoppers to fill the syringes. Solenoid Valve 2 will open when the robot moves right above the stopper holder. After picking up the stoppers, the robot will move to the tray and apply the stopping mechanism. Valve 2 will close after the end-effector reaches the lowest position inside the syringes. At the same time, Valve 1 will open and start the filling process for the following row of syringes.

Algorithm 2 shows the overall integrated system operation. The task is to complete the automation process for syringe filling and stopping. Once Sensor 1 detects the carriage is on the preset location, it will be activated (Line 2). Because Sensor 1 is a Positive-Negative-Positive (PNP) type, it will input a 24 volts of direct current (VDC) digital signal to the PLC to open the one-way solenoid valve 1 (Line 3) that connects the repeater pump and the air compressor. The one-way solenoid valve will only open for 0.5 seconds to push the air into the air port of Pump 1. This mechanism will trigger Pump 1 (Line 3) for the first-row filling process. At the same time, the digital signal from Sensor 1 will also trigger the robot to move to the stopper holder (Line 4). When the robot finishes moving to the stopper plate, another digital signal from the robot will be sent out to the PLC to open the solenoid valve 2 (Line 5) that connects Pump 2. This creates a vacuum force on the end-effector to pick up the stoppers (Line 6). When the robot picks the stoppers, stepper motors 1 and 2 are turned on due to the digital input from the robot (Line 8). The gantry then moves to the next row and pump 1 will be turned on (Line 3) to start the filling process for the second row of the syringes. When the end-effector is on its way to the venting block, sensor 2 is used for stoppers detection. Sensor 2 will be turned on four times in a four-iteration loop to make sure all the stoppers are on the end-effector (Line 9). If one of the stoppers is not on the end-effector, the loop breaks and the robot stops from going to the next move (Line 16). After the end-effector reaches above the vent tube block, Stepper Motor 3 is on (Line 11) to lower the vent tube block. The robot then pushes the stoppers into the syringes (Line 12). For the rest rows of the syringes, the same operations repeat.

Algorithm 2 Automatic Filling and Stopping Process

Require: 20 empty syringes in the tray at the preset position and fluids in fill line.

```
1:  while Emergency stop is off do
2:    if Sensor 1 is on then
3:      Activate Solenoid Valve 1 and Pump 1
4:      Robot moves to the stoppers holder
5:      Activate Solenoid 2
6:      Pick up stoppers
7:      Wait 6 seconds
8:      Activate Stepper Motors 1 and 2
9:      if Sensor 2 is on then
10:       Move to gantry
11:       Activate Stepper Motor 3
12:       Push the stoppers
13:       Deactivate Solenoid 2
14:       Wait 3 seconds
15:     else
16:       Action stop
17:     end if
18:   else
19:     No action needed
20:   end if
21: end while
```

Chapter 3

Automation Emulation

3.1 Emulation System Between PLC and SRS

3.1.1 Emulation Overview

The virtual commission has been acknowledged as the most important industrial evolution in industrial 4.0. An automated process system is being created to be tested while being built in real life. Emulation provides a real behavior representation that virtual models are similar to reality as possible. For this specific project communication among hardware components in a real system is done through the Internet with the use of the PROFINET protocol. The final goal of the project is to allow the PLC logic created for a real system to be run again the corresponding virtual model without any change. To achieve this, the emulator module in SRS is able to emulate the communication behavior of an The PROFINET module is developed and tested against a real PLC program. The summary report focuses on the current progress of the integration of the Stäubli robot and PLC application. For the robot operation, a dedicated robotic language, VAL 3 language commands powerful and efficient function sets. The flexibility of the wide range of possibilities including digital inputs outputs, analog inputs outputs as well as the field bus that can be connected to the PLC, makes the Stäubli robot great in industrial applications. In addition, TX2-60 Stäubli robotic arm is built for high performance when it comes to Cleanroom requirements. For the PLC application, it is the central computer controls where and when robots perform every single task. The goal of the project is to integrate the robot with the PLC to achieve complete automation of the syringe-filling process. From the software perspective, emulation is the use of the PLC controller device to imitate the behavior of SRS software. There is a lot of benefits when it comes to emulation, especially in automated process. For filling and stoppering process, emulation provides an operating system for the Cartesian robot. SRS has both simulators and emulators functionalities that are similar. The difference remains that simulators and emulators are different applications. Both of them make it possible to run the automated process tests inside software-defined environments which is SRS in this case. From a purely virtual environment without any hardware components concern, simulation in SRS allows you to run tests more quickly and easily.

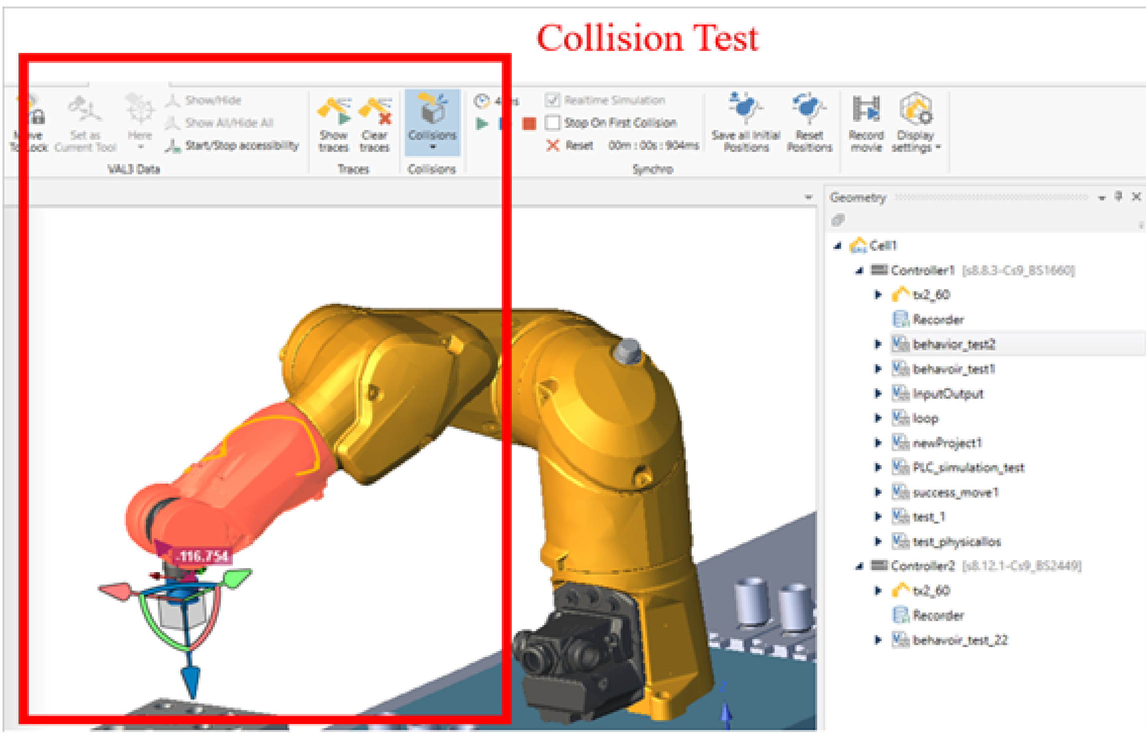


Figure 3.1: Collision test in SRS

In Fig 3.1, the virtual environment was set up properly to match the real test environment, simulation collision test was performed efficiently.

3.1.2 User Interface in Emulation

The customized user interface is another powerful functionality in SRS, the designed user interface can be shown in the physical teach pendant. For the automation emulation purpose, customized requirements and functionalities are shown in Fig 3.2. For our prefilled syringes production, each cycle would have 20 syringes to be filled with, the customized user-interface would allow the operator know the amount of production.

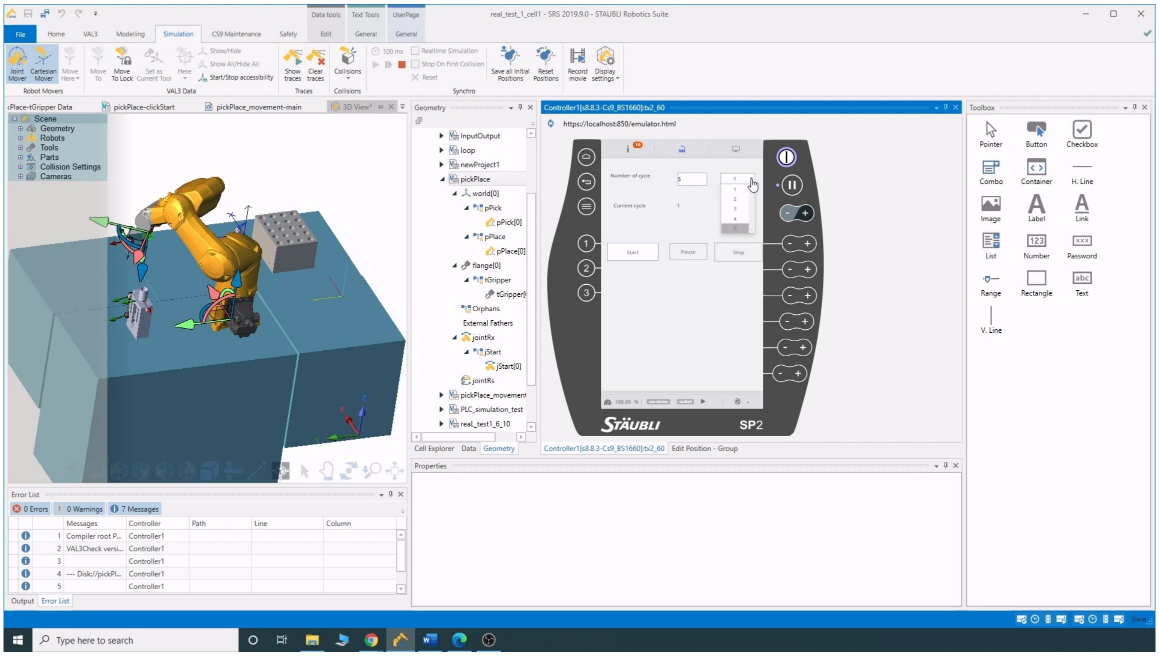


Figure 3.2: User Interface in SRS

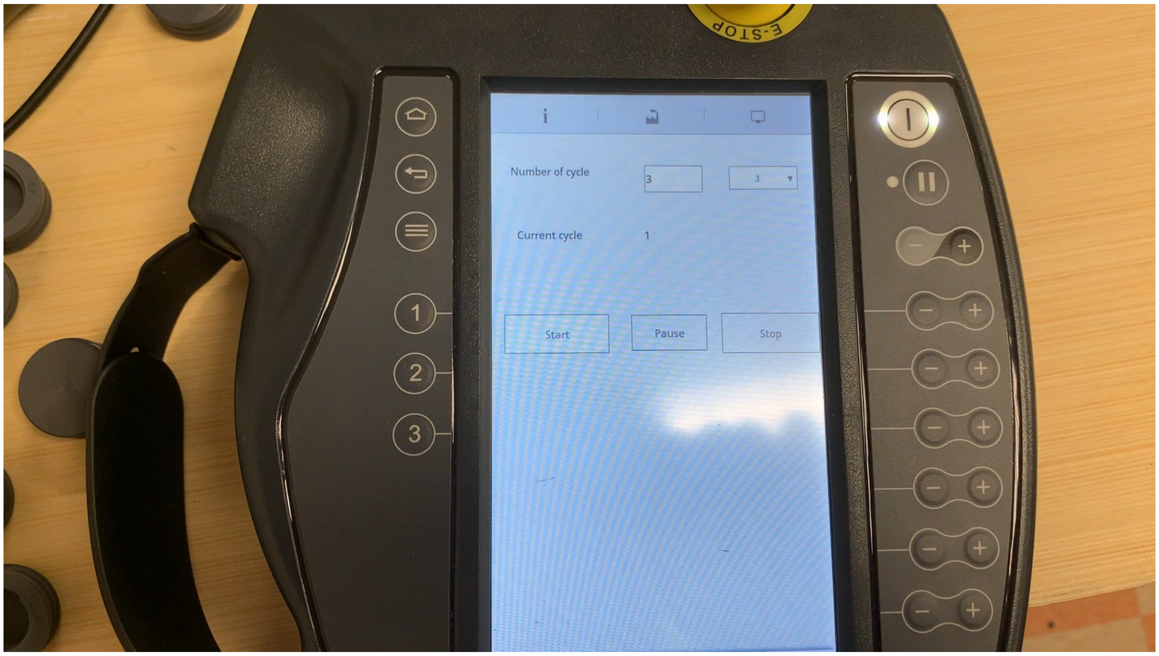
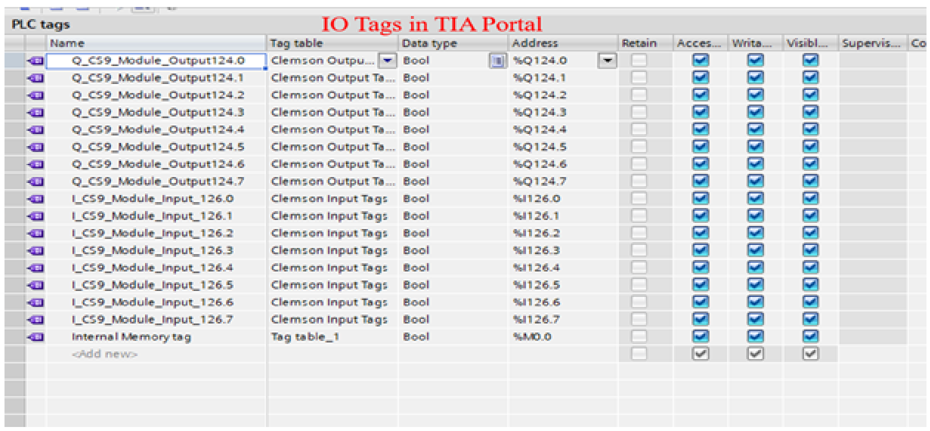


Figure 3.3: User Interface in Teach Pedant

3.1.3 Emulation Connection

The advances in the manufacturing industry have paved way for a systematical deployment of Cyber-Physical Systems (CPS) [14], within which information from all related perspectives is closely monitored and synchronized between the physical factory floor and the cyber computational space[19]; The operation of the emulation is one of the advances that separated into two parts for this specific project. The connection between the robot and the PLC that including the installation of the CS9 emulation version with the process of matching the corresponding IP address which represents the SRS emulator programming environment that including the Stäubli robotic language practice (VAL3) as well as built-in emulator features. In Fig 3.4 and Fig 3.5, shows the IOs



Name	Tag table	Data type	Address	Retain	Acces...	Writa...	Visibl...	Supervis...	Co
Q_CS9_Module_Output124.0	Clemson Outpu...	Bool	%Q124.0						
Q_CS9_Module_Output124.1	Clemson Output Ta...	Bool	%Q124.1						
Q_CS9_Module_Output124.2	Clemson Output Ta...	Bool	%Q124.2						
Q_CS9_Module_Output124.3	Clemson Output Ta...	Bool	%Q124.3						
Q_CS9_Module_Output124.4	Clemson Output Ta...	Bool	%Q124.4						
Q_CS9_Module_Output124.5	Clemson Output Ta...	Bool	%Q124.5						
Q_CS9_Module_Output124.6	Clemson Output Ta...	Bool	%Q124.6						
Q_CS9_Module_Output124.7	Clemson Output Ta...	Bool	%Q124.7						
I_CS9_Module_Input_126.0	Clemson Input Tags	Bool	%I126.0						
I_CS9_Module_Input_126.1	Clemson Input Tags	Bool	%I126.1						
I_CS9_Module_Input_126.2	Clemson Input Tags	Bool	%I126.2						
I_CS9_Module_Input_126.3	Clemson Input Tags	Bool	%I126.3						
I_CS9_Module_Input_126.4	Clemson Input Tags	Bool	%I126.4						
I_CS9_Module_Input_126.5	Clemson Input Tags	Bool	%I126.5						
I_CS9_Module_Input_126.6	Clemson Input Tags	Bool	%I126.6						
I_CS9_Module_Input_126.7	Clemson Input Tags	Bool	%I126.7						
Internal Memory tag	Tag table_1	Bool	%M0.0						
<Add new>									

Figure 3.4: IOs in TIA portal

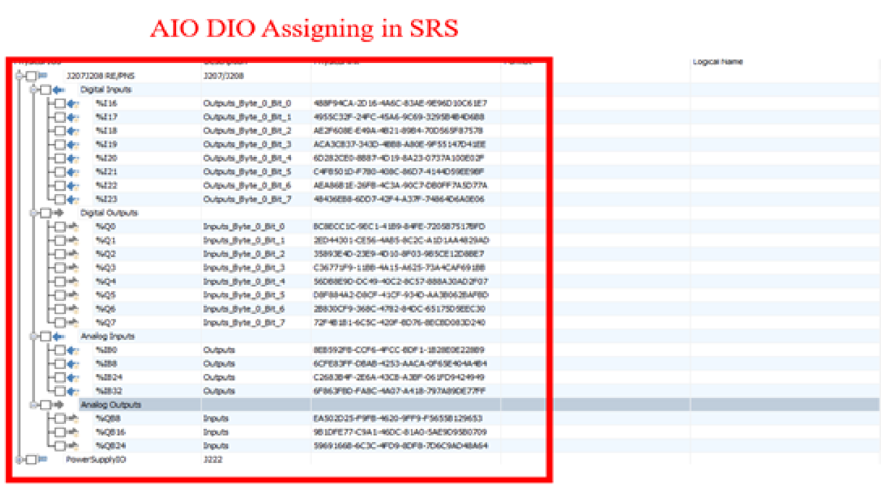


Figure 3.5: IOs in SRS

are connected throughout the devices. The industrial connection protocol uses PROFINET which gives you new ways to boost the productivity with four decisive advantages – openness, flexibility, efficiency, and performance. Even simulation provides the easier way to do the virtual environment automated test within the SRS software environment, the emulated process takes the process further by emulating the automated process as well as physical configuration. Either simulator or emulator in SRS is useful, yet depends on the specific situation, however, neither is a complete substitute for real-device testing.

3.1.4 Emulation Process

The first step of the emulation process is to create the virtual representation of the physical components in SRS shown in Fig 3.6. The robotic arm model of Tx2-60 is a built-in model in SRS, the Cartesian gantry robot is drawn in Solidworks and imported to SRS as .stl file. After all the IOs are connected throughout the devices, by following the algorithms 2.1.3.2, the emulation process representation is shown in Fig 3.7. As it is observed that the emulation process shows that the

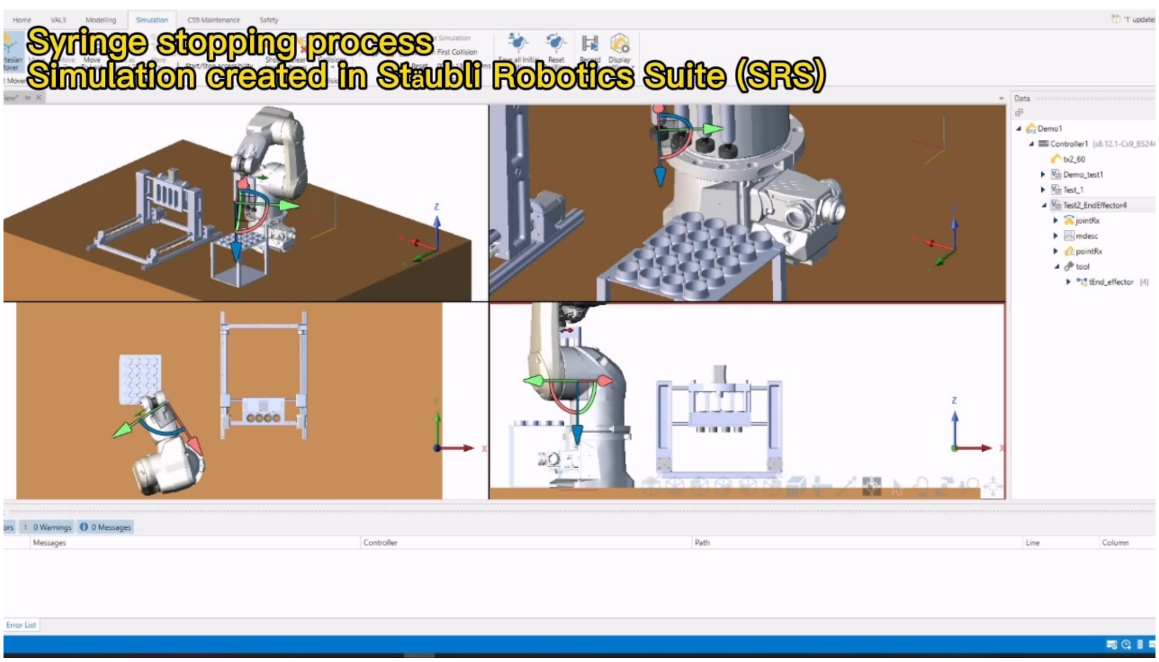


Figure 3.6: Virtual representation in SRS

motion of the Cartesian gantry robot and Tx2-60 robotic arm in virtual environment matches the motion in reality due to IO communication is real-time communication. For the suction cup behavior

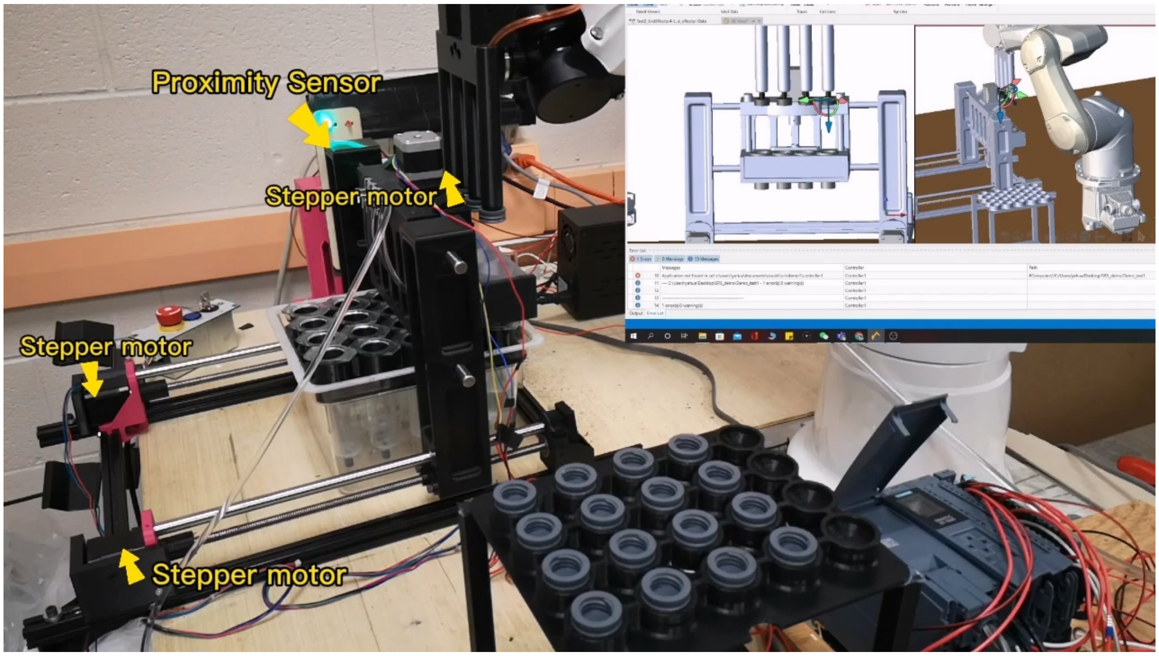


Figure 3.7: Emulation Process

in SRS, the behavior is controlled by the IOs from the PLC side shown in Fig 2.23, basically, under the PROFINET protocol, the virtual motion is controlled by the IOs from the PLC in milliseconds which achieves the real-time emulation although complexity of computing, physical dynamics and industrial connection protocol speed bring a lot of challenges due to the real-time delay [16].

3.2 Experiments and Discussion

3.2.1 Individual Syringe Stoppering

The emphasis of this paper was to develop a proof-of-concept automation platform that enables a research outcome addressing the requirement to increase US pharmaceutical manufacturing capacity in response to the ever-growing pharmaceutical demands that hospitals have [13]. Prefilled syringes are in high demand due to their ease of use and flexibility. Therefore, a benchtop robot with automated filling and stoppering mechanisms is highly relevant for manufacturing prefilled syringes.

Demonstration of the key components begins with the venting tube depicted in Figure 2.4. An experimental setup was created by mounting a syringe filled with 50mL of water on a 3D printed fixture that was secured to a table. The vent tube was placed inside the syringe barrel and was fixed in place utilizing another 3D printed fixture. A simple end-effector with one pushrod was created that mounted to the TX2-60 robot. A stopper was attached to this end-effector with a suction cup so that it was effectively manipulated by the robot. The experimental setup, including the pushrod and the syringe stand, are displayed in Figure 3.8. The venting tube is contained by the white 3D printed fixture and feeds directly into the CoC syringe (contained by the bright pink fixture).

Figure 3.8: Customized pushrod for forcing stoppers through venting tube (left), and experimental syringe stand (right).

The syringe was partially filled with 25mL of water and was inserted into the fixture for the experiment. Half the value of the full 50mL was used in order to determine how far the stopper could reliably be positioned in the barrel. The robot was then programmed to move the stopper above the entrance to the vent tube, and force it through vertically, until it was placed inside the syringe above the waterline. The positioning of the stopper as it entered the venting tube and is inserted into the syringe is shown in Figure 3.9.

Figure 3.9: Angle of stopper entering the venting tube.

The stopper was successfully compressed as it was forced through the compression funnel inside the vent tube, allowing it to be deposited in the syringe. Simultaneously, the air existing in the syringe was forced out, leaving the syringe cap intact. The stoppered syringe is shown previously in Figure 3.9. The experiment was sucessful, with the vent tube correctly compressing the stopper and allowing it to enter the barrel of the syringe. The stopper was pushed below the required fluid line for a full 50mL syringe, proving the process capability. Lastly, the syringe remained intact, and the cap stayed affixed. The next validation experiment was to confirm proper gantry movement and coordination with the Stäubli TX2-60 robot for filling and stoppering a full syringe tray.

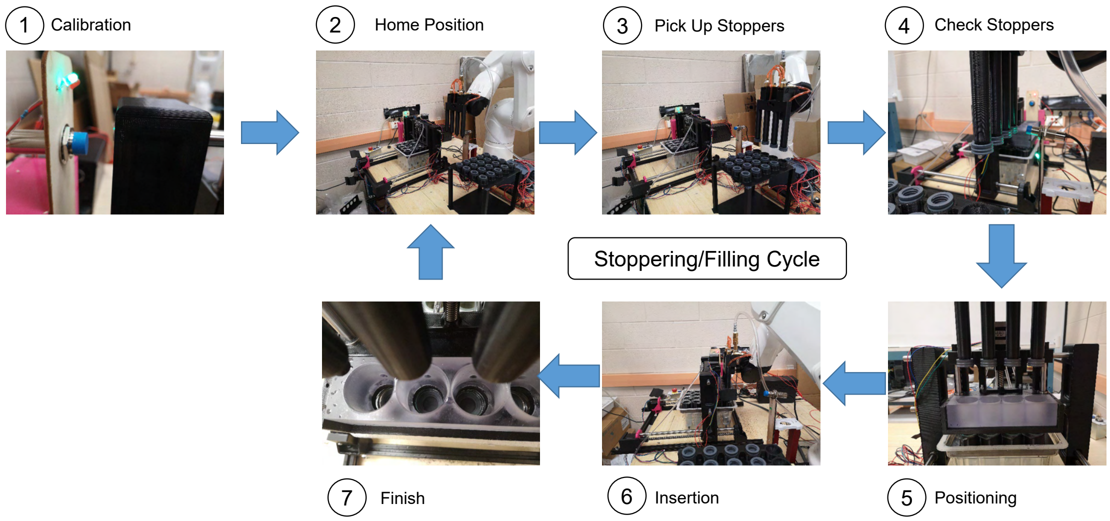


Figure 3.10: Full cycle of filling and stoppering "dry run."

3.2.2 Overall System Demonstration

The Cartesian gantry robot and end-effector are key components of the system. The overall motion planning and control strategy is based on simultaneous control of the robot end-effector in coordination with the external stepper motor and a peristaltic pump. A queue of Cartesian space waypoints is constructed through VAL3 languages and the robotic motion controlled is based upon the order of robot tasks to be performed and stored in the ladder logic of the PLC for the filling and stoppering tasks. As described in Section 2.1.1, the gantry and the end-effector must work in sync to function properly. This requires the utilization of a PLC, which can allow the system to communicate with both the TX2-60 and the gantry Nema motors. Additionally, calibration of the motors must be performed, and any slippage of the lead screws must be examined and addressed. A "dry run" of positioning the gantry and the end-effector was performed to address these concerns. The venting tubes were removed, and the stoppers were simply placed on the surface of the syringes. This was performed to prevent repeated stress on the gantry while positioning "dry runs" were performed so that deformation of any plastic components did not occur.

The process is detailed in Figure 3.10 and is cyclic in nature. As shown in Step 1, a proximity sensor is used in order to check if the gantry is set in the correct home position. This position ensures that it is in front of the first row of syringes and is ready to move the set distance required to engage in the first operation. A green light indicates that the gantry carriage is in the correct position, which turns red when it moves away.

Step 1 in 3.10 shows that the Cartesian gantry robot moves away from the calibration position and toward the first row of syringes, the proximity sensor 1 2.14 will be energized if the Cartesian gantry robot reaches the starting position where is aligned to the first row of the syringes tray. Step 2 shows the robotic arm moving to the stopper holder and starts picking up the stoppers, proximity sensor 2 is used to detect all four stoppers are picked up, if one of the stoppers is missing from the robotic end-effector, the indicator would have a red light on shows in 22, the robotic arm goes back to the stopper holder and redo the pick-up process. Once the robotic end-effector reaches the top of the first row of the syringes tray, the filling nozzles are over the first syringe row start filling them using the separate repeater pump, that the repeater pump is controlled by a solenoid valve. It then is moved further ahead so that the venting tube block is directly above the first row of syringes. The central arm is lowered so that the venting tubes will be inserted into the barrel of the syringes. Meanwhile, the end-effector begins its cycle in the home position, as shown in Step 2, when the PLC indicates that the gantry is in place. The TX2-60 moves the end-effector above the stopper plate and then vertically down to press the suction cups on the inner surface of the stoppers, as shown in Step 3. At this point, the one-way solenoid valve for the vacuum pump is automatically opened, allowing for the suction force to grip the stoppers.

Step 4 shows the TX2-60 moving the end-effector and stoppers in front of a mounted proximity sensor to determine if the stoppers are properly attached to the end-effector. In Step 5, the end-effector is positioned directly over the venting tube mounting points in preparation for the inserting action. Step 6 shows the TX2-60 moving the end-effector directly downward through the venting tube mounting points and depositing the stoppers at the entrance of the syringe barrel. According to the dry-run protocol, the end-effector releases the stoppers when they have barely inserted into the syringes by automatically sealing the one-way solenoid valve. Step 7 shows the finalized product, with all four stoppers evenly deposited in the top of the syringe barrels. The cycle repeats with the end-effector raising and returning to its home positioning, leaving the stoppers placed barely within the barrels of the first four syringes. The Cartesian gantry robot will repeat its process by moving a designated amount toward the next row of syringes, without repeating the calibration process.

After the end-effector is returned to its home positioning, the cycle repeats again with the next row of syringes until the entire tray is successfully stoppered. This experiment is crucial to ensuring the manufacturing process has the correct positioning during operation and is proven sucessful with the stoppers resting in the correct locations relative to each syringe. Combined with the proven capability to stopper a single syringe to the correct depth, the proof-of-concept benchtop robot and automation system for manufacturing filled CCC syringes is deemed valid.

For the whole automated process, there is some potential improvement could be done by upgrading the cyber-physical architecture. Jay Lee presents Cyber-Physical Systems (CPS) as the interconnection between the physical assets and the computational capabilities[19]. He proposed concept for the 5-level CPS structure shows in Fig 3.11. For the 5-level CPS structure, it provides a 4.0 industry system which gives out a leading guidance to lots of automation application. Our prefilled syringes automated production currently fit into the smart connection level and data-to-information conversion level of the structure, the rest of the levels of the system could be guidance for future development. The smart connection between the robot and the PLC, as it is observed in Fig 3.11, the smart connection level is the fundamental level of the pyramid system that illustrates the importance of the communication protocols that allow different network devices to communicate with each other, it not only ensure the security level of the network but also provides a great way to organize and manage data. The CS9 controller of the robot comes with a wide range of industrial connection types such as real-time Ethernet Fieldbus, OPC UA, and PROFINET. On the other hand, the SRS software has a smart log viewer that provides detailed IOs and connection status information. All the features and functionalities of the smart connection could lead to the next level which is smart acquisition. The advantages from the data acquisition from the PLC and the SRS shows the power of tracking the operations. Siemens S7-1500 PLC has a data logging functionality that allows the user to save selected process values from the user program in a file which is the data log. The data log is saved on SIMATIC memory card in CSV format which secures the accuracy of the real-time data. In addition, for data monitoring, a web browser can read data through the web server. The CS9 controller also provides a powerful data-to-information conversion system, that virtual simulation combines with multiple tool behaviors and collision detection. The robot's motion in the real physical world can be converted into data and computed through the CS9 controller to evaluate the robotic arm payload and inertia. The next development of the automated process should go to the cyber level of the 5C architecture that the system could verify the quality of the data and give out real-time feedback. Then, the next development would be the cognition level which the system could have the capability to collaborate the machine and human decision. The final phase would the configuration level that the integrated system as whole is able to do self-configure for resilience, self-adjust for variation and self-optimize for disturbance [19].

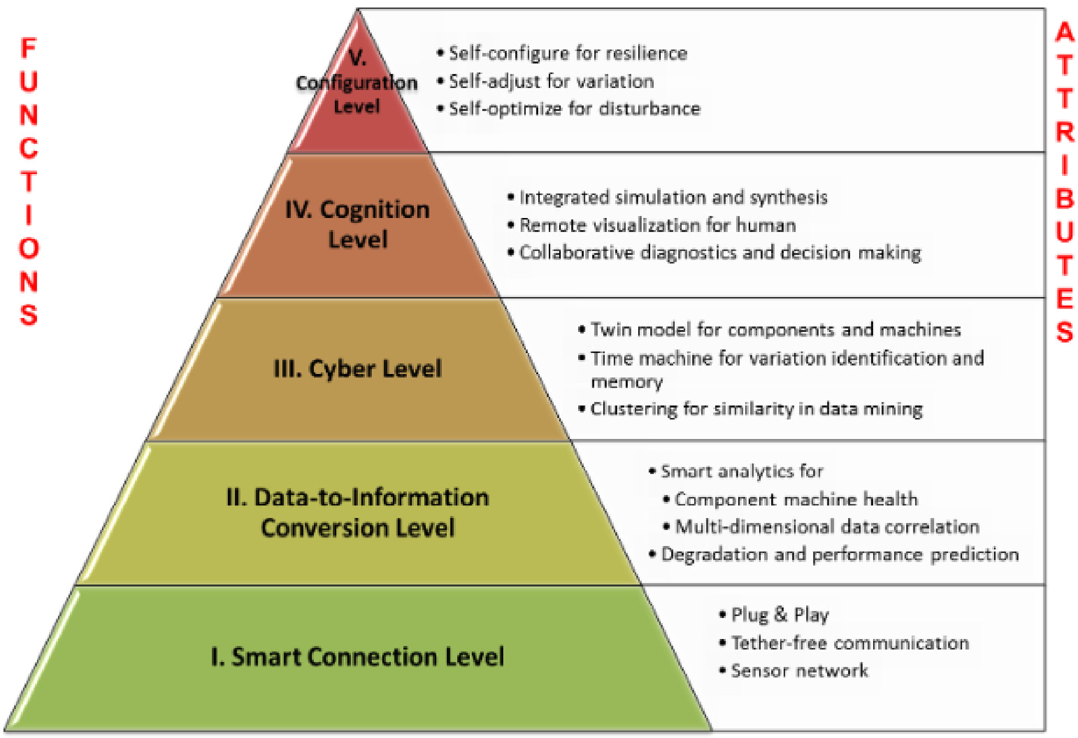


Fig. 1. 5C architecture for implementation of Cyber-Physical System.

Figure 3.11: 5C architecture in Cyber-Physical Systems

Chapter 4

Results

This paper presented a proof-of-concept robotic and automation solution that demonstrated a remote, automated, and rapidly deployable approach for manufacturing prefilled syringes. The goals were to enable an automated solution to achieve the filling and stoppering of COC syringes with a cycle time comparable to humans using readily available common-off-the-shelf components. However, the risk of contamination is localized inside the working area of the robot. Cleaning procedures of the working area are to be further investigated. An effective decontamination procedure for the working area of the robot and automated capping of filled syringes should be developed to further minimize occupational risk due to the cleanroom standard that the surface contamination in the working areas of the robotic system ranged from 0.4 to 114 pg/cm^2 for Pt and from 1.3 to 1,250,000 pg/cm^2 for 5-FU [18]. Reliable production was achieved as demonstrated by 300 seconds cycle time and 20 out of 20 batches run success rates for 50 mL volume COC syringes, wherein only one human correction intervention was required. While the average cycle time on our system is currently slower than humans, the production rate may be increased in future work through 1) filling and stoppering multiple syringes simultaneously, 2) performing concurrent processing of system commands, and 3) reducing the delay between system actions. Similarly, as robotic systems have shown the introduction of few contaminants and greater consistency over time compared to humans, prolonged production runs (compared to the 30-minute runs currently enabled) are expected possible and are the subject of future research.

Chapter 5

Conclusions and Discussion

The emergence of automation makes a huge difference from traditional robotic application. Modern robots like KUKA, FANUC, Stäubli have the built-in language and functions that can be operated independently from a centralized PLC. That means the PLC can continuously monitor the information received from devices (sensors, transducers, transmitters), but the PLC can trigger the robot to perform the tasks that have been built in its own language. It not only increases the reliability of the machinery operation but also the efficiency of the integrated process. This paper presented a proof-of-concept robotic and automated system as a solution for benchtop COC syringe manufacturing. It demonstrates an automated and rapidly deployable approach for manufacturing prefilled syringes using common components and 3D printed design. The hardware design and control approaches were described with a systems approach, and the design validation experiments were detailed. To achieve automatic filling and capping of the COC syringes while remaining lightweight and modular. The architecture comprises wireless and wired components to empower toleration to remote operators while keeping cable management requirements low, both of significance when operating within cleanroom environments. The network's wireless component comprises an industrial router exchanging data packets between the PC and robot controller. The framework allows for easy integration with existing in-house data management systems to aid in the compliance of requirements such as the US FDA Code of Federal Regulations (CFR) Part 11, which establishes the rules on electronic signature records, authentication, integrity, and confidentiality. The automatic solution will reduce human-related tasks to decrease the contamination and tedium of syringe manufacturing and utilizes a design that can be built and maintained in-house. In addition, the emulator in SRS software could be a part of the cloud-based cyber-physical architecture to leverage the Sensing as-a-Service (SenAS) model, where patient's health data could be stored and shared through a cloud-based twin cyber process [1], furthermore, the wireless and battery-free sensor has been popular in automation manufacturing which provides the great advantage and convenience to make the production even in harsh environment [20]. Experiments validated the idea of using a 3D printed venting tube to successfully insert a stopper into a syringe while simultaneously removing the air from the syringe barrel in proper accordance with standard syringe manufacturing. Additionally, the concept of filling and stoppering multiple syringes simultaneously using single fluid movements from the automation system was explored, and the positioning and programming of the manufacturing process was validated. Stericlean TX2 series robot from Stäubli meets the most demanding requirements in terms of safety, efficiency, and flexibility. The TX2-60 robot in the lab is a six-axis robot that can perform critical steps in every phase of the aseptic process. According to the current progress, the following task is to automate the filling of syringes under aseptic conditions. For a bigger picture, more sensors would be brought into the automation system, like photoelectric sensors and proximity sensors to detect the distance of the syringes location. More likely, machine vision cameras would also be an advanced option, due to the system can combine industrial cameras, lenses, and lighting to automate visual inspections of manufactured products, in addition, for defect detection, assembly checks, positioning of the robot [2]. Automation has long been awaited in parenteral drug dispensing. Pharmacists can benefit much in theory from a good automated device to handle the hazardous drugs used in pharmaceutical production [8]. To benefit the industrial manufacturing, the robotic PLC automated control is the key to harmonize and unify programming environment to support the production environment [8]. It is beneficial for pharmaceutical companies like Nephron by utilizing the automation production especially when it comes to the cleanroom environment, the specialized cleanroom robot can reduce additional contamination and are required to meet specific cleanroom standard. The ultimate goal is to have the system level up to the cognition and configuration level [19] that the automated process integrates simulation and data synthesis to the self-configure and self-adjust for the resilience and variation.

Appendices

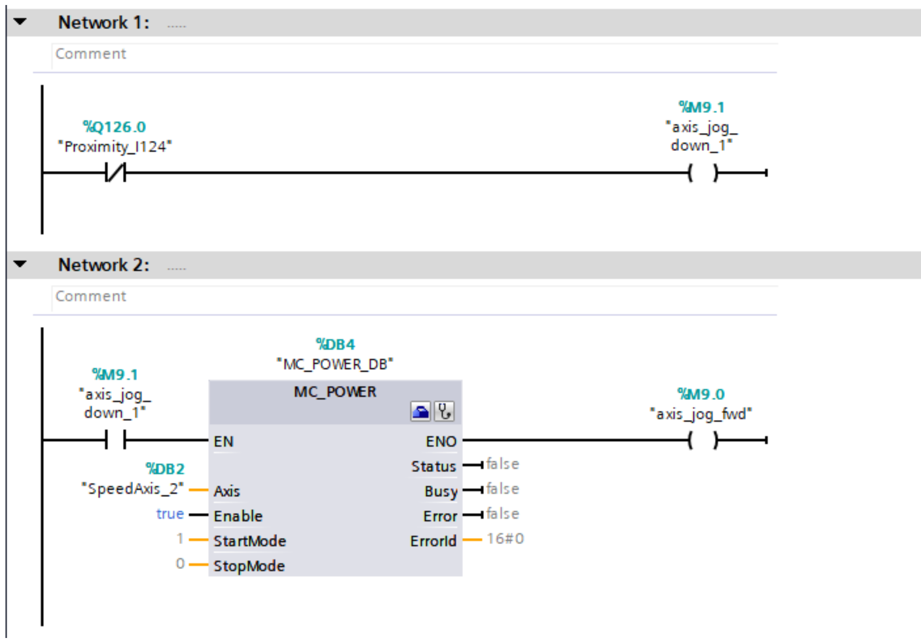


Figure 1: Ladder Logic 1

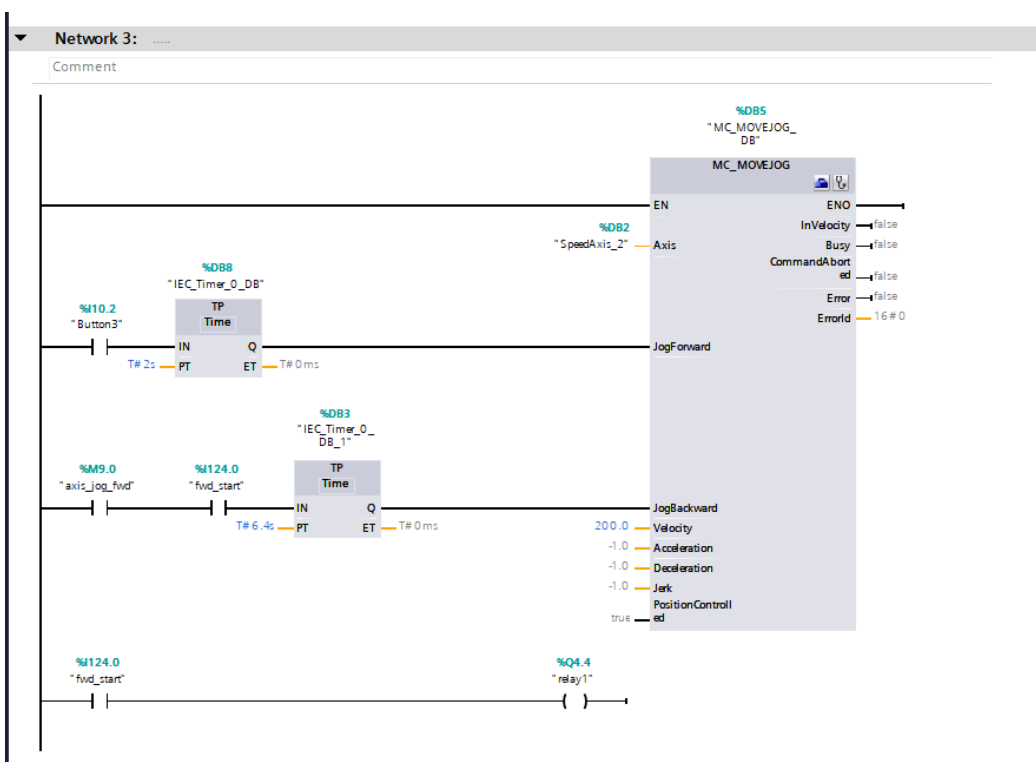


Figure 2: Ladder Logic 2

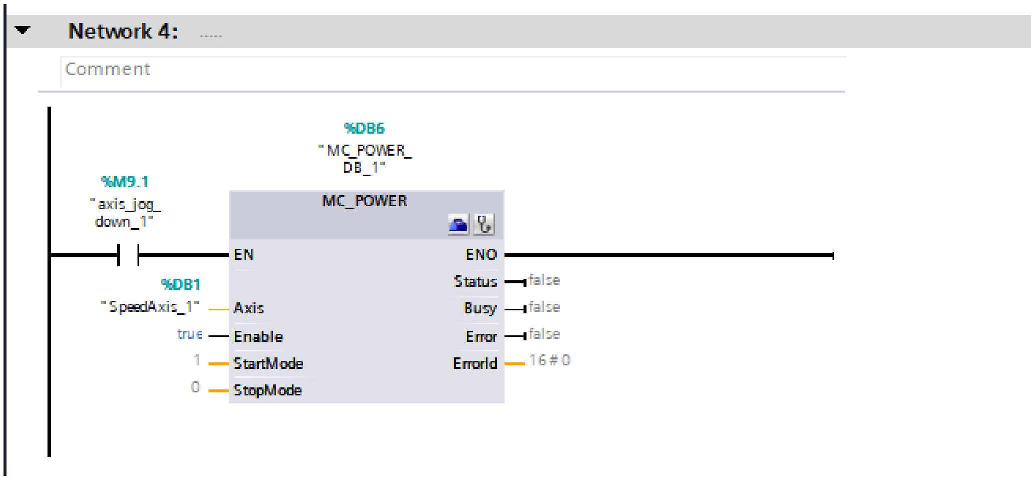


Figure 3: Ladder Logic 4

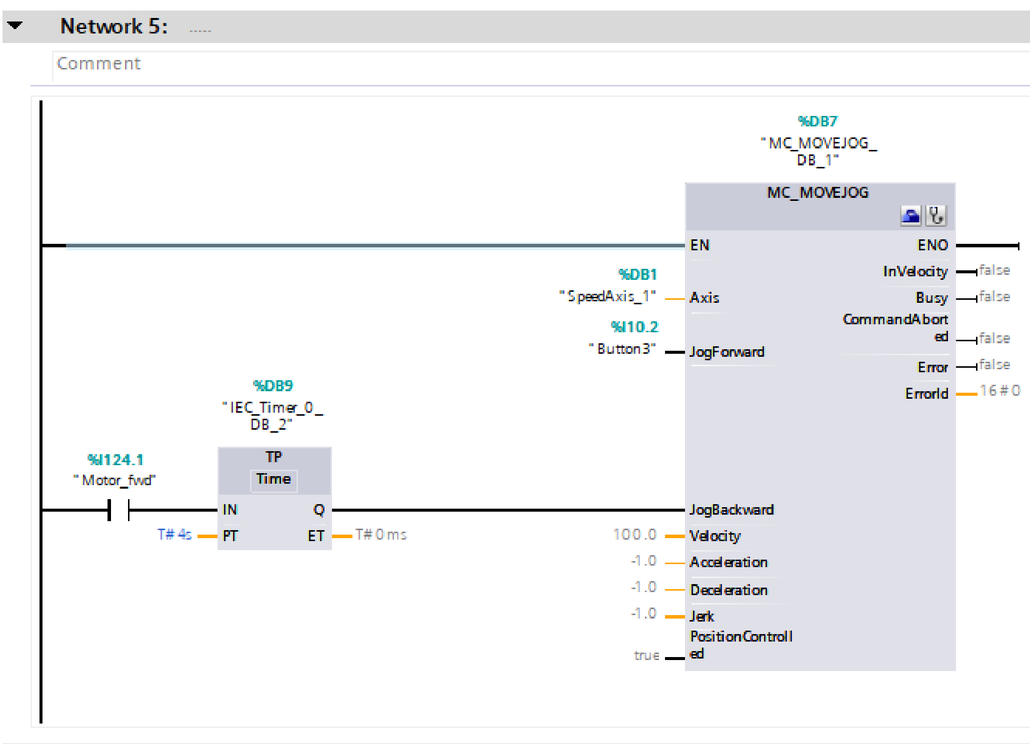


Figure 4: Ladder Logic 5

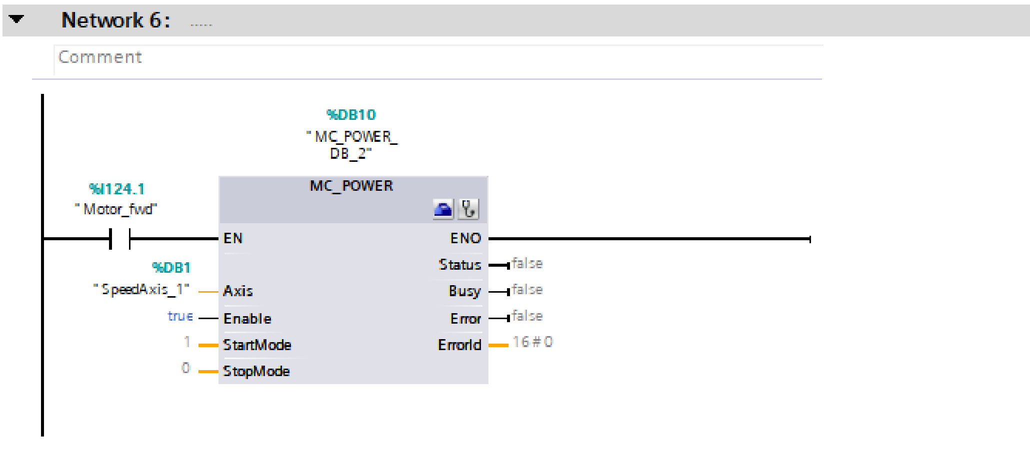


Figure 5: Ladder Logic 6

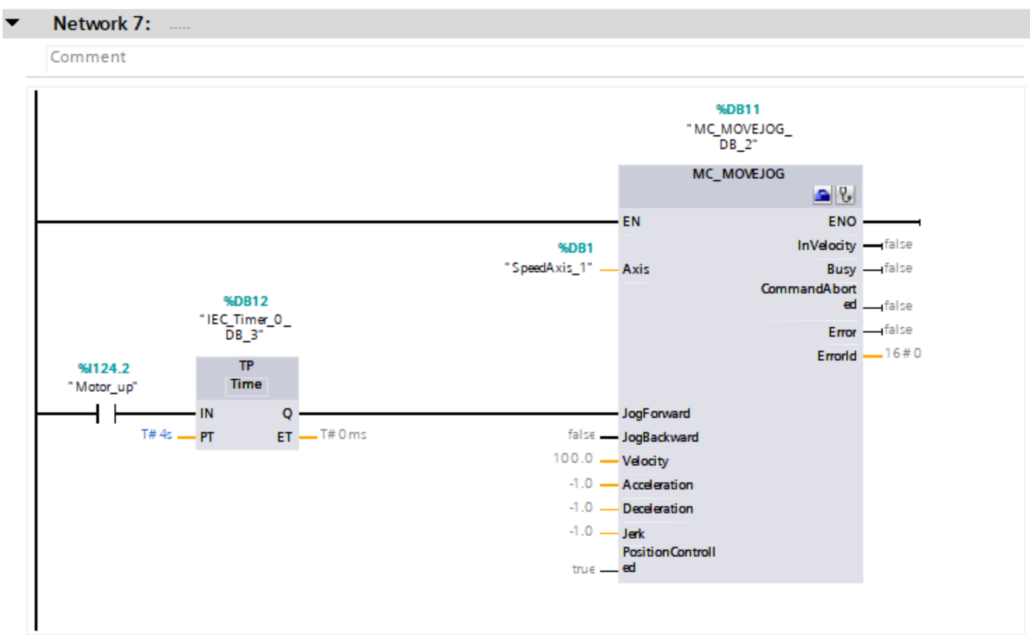


Figure 6: Ladder Logic 7

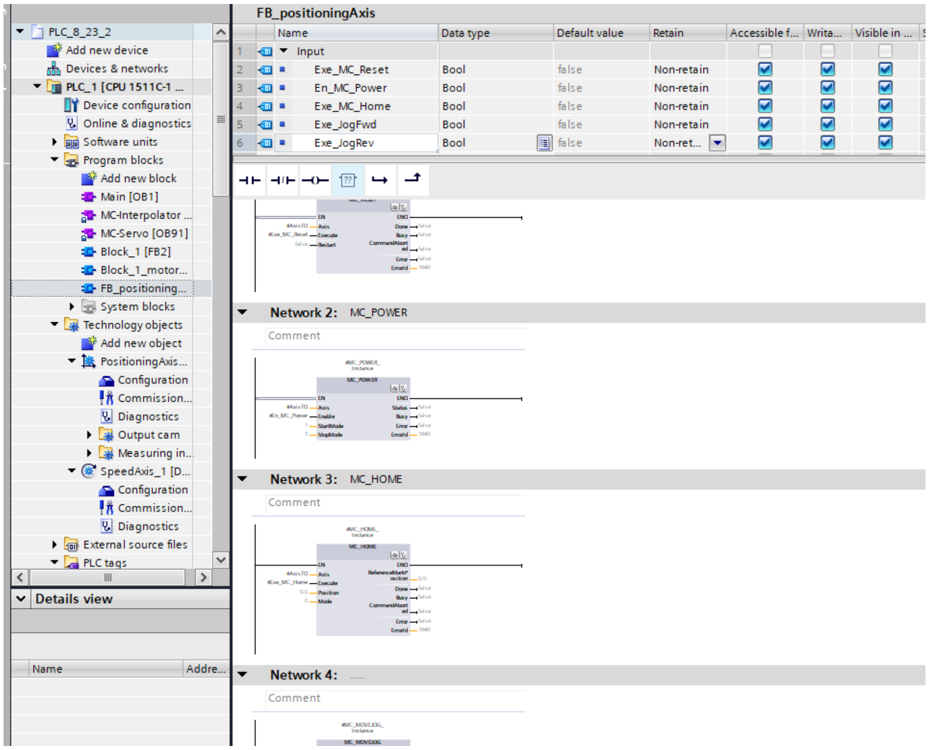


Figure 7: Functional Block in TIA

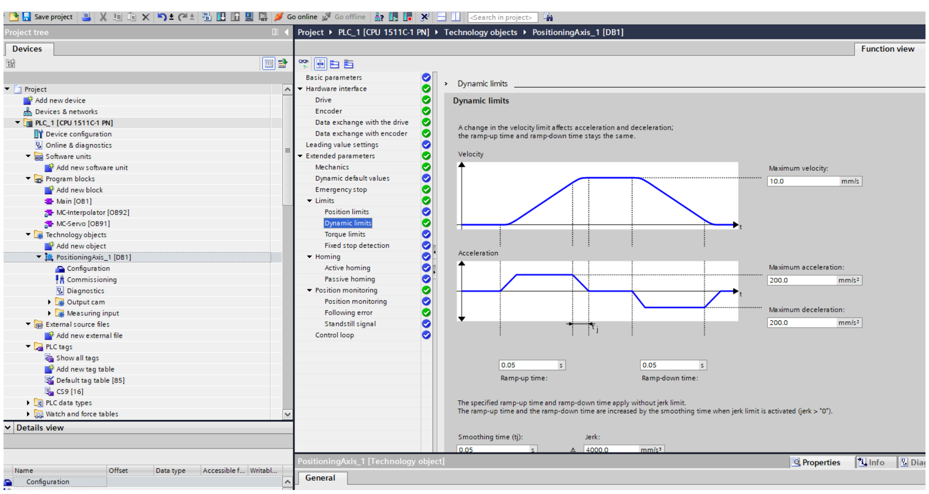


Figure 8: Speed Axis Function in TIA

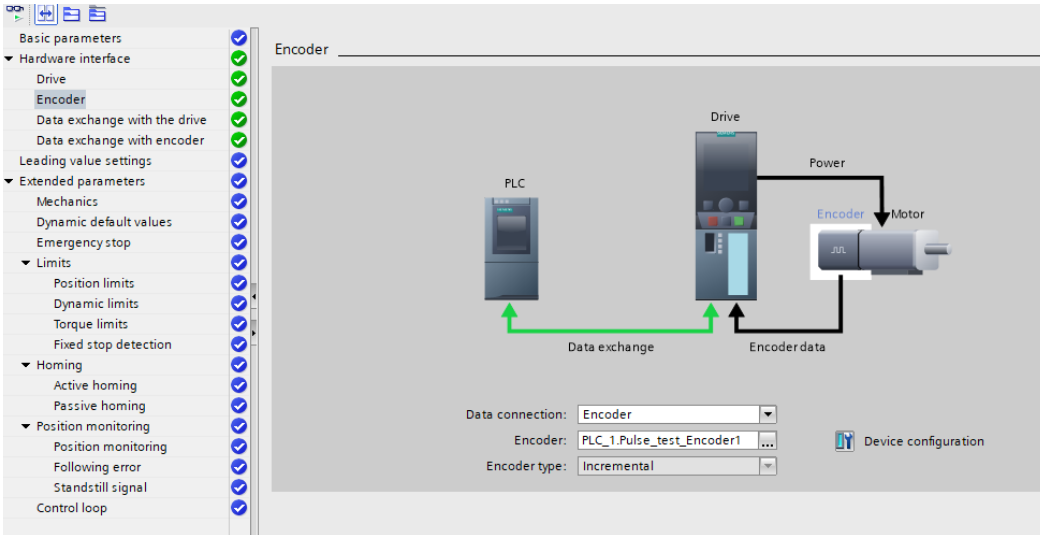


Figure 9: Encoder Configuration in TIA

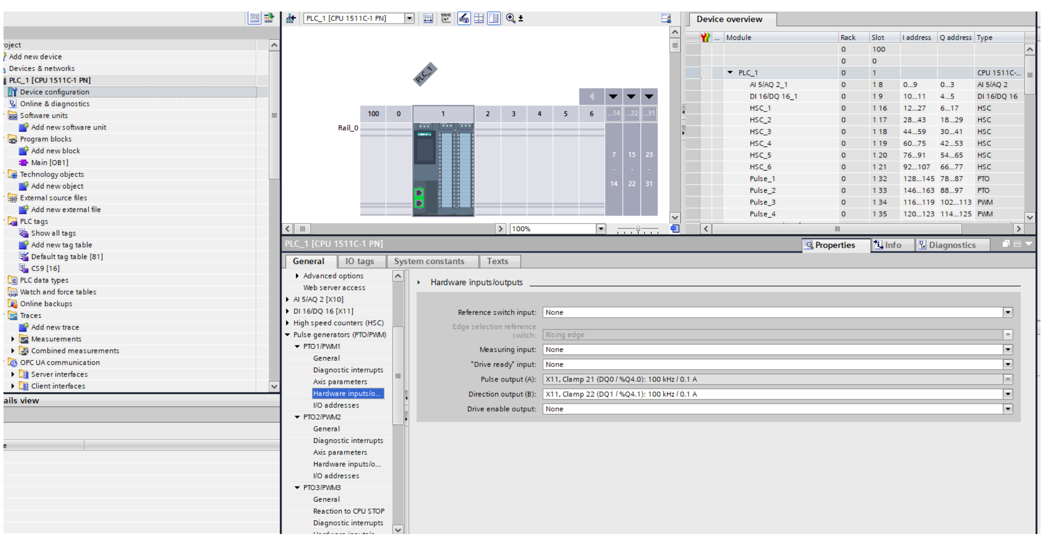


Figure 10: PWM Mode in TIA

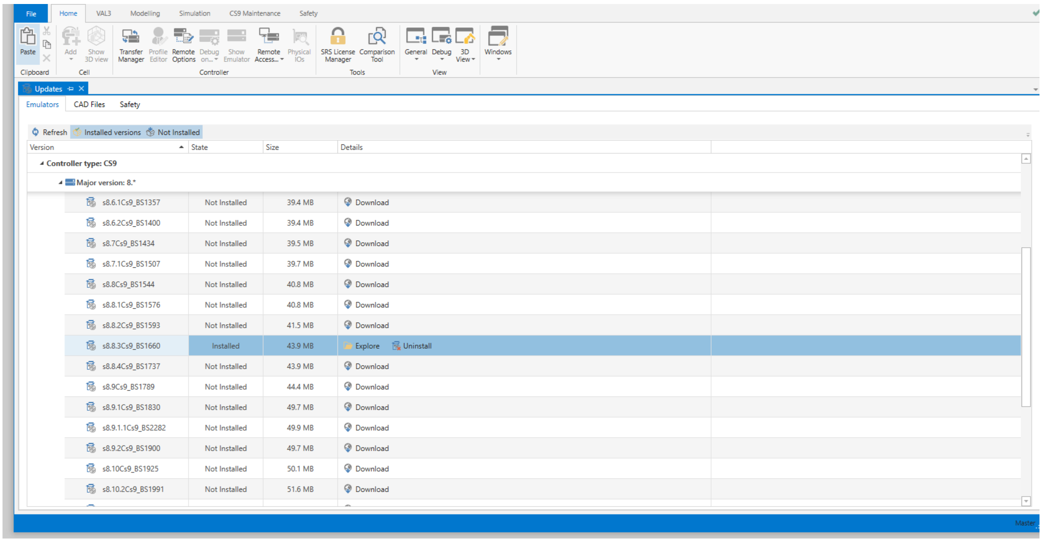


Figure 11: CS9 Controller Version in SRS

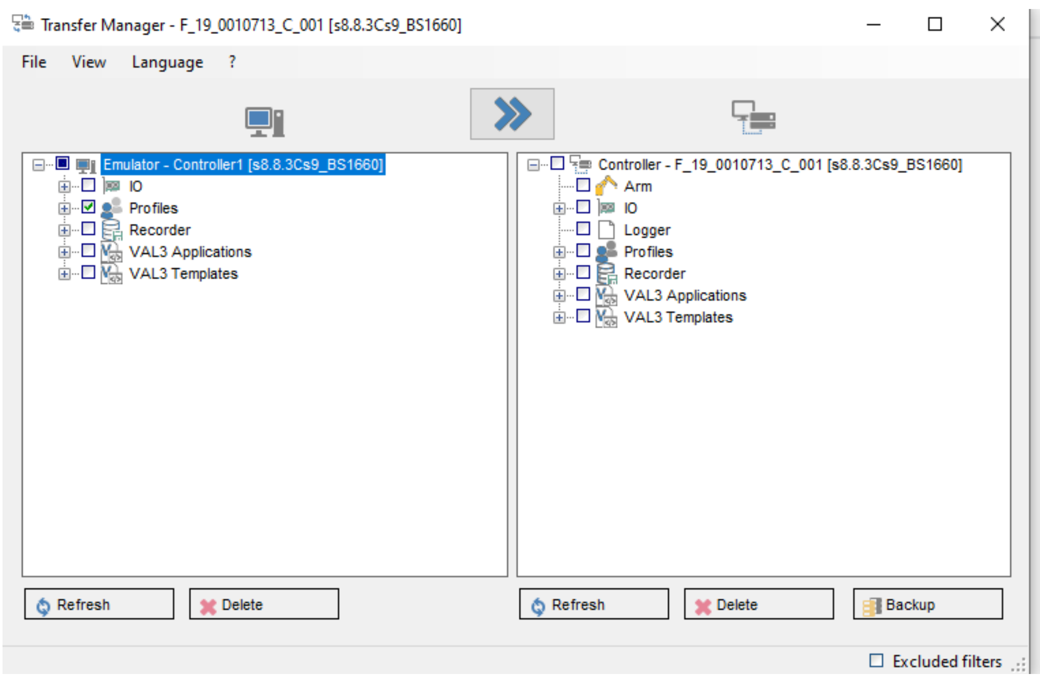


Figure 12: Emulator in SRS

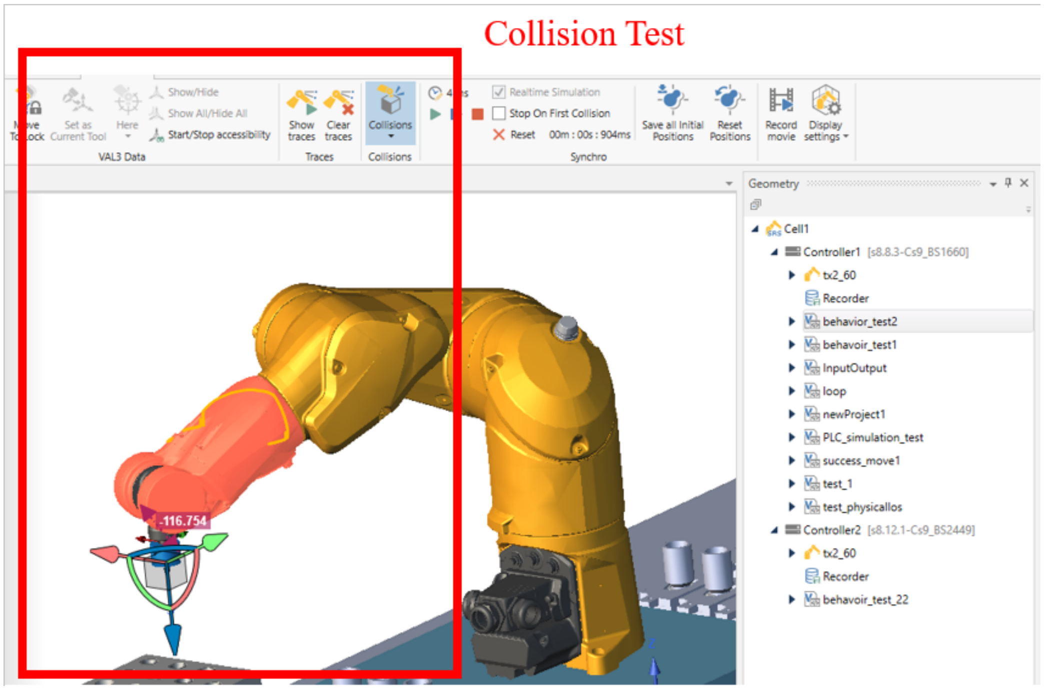


Figure 13: SRS Collision Test

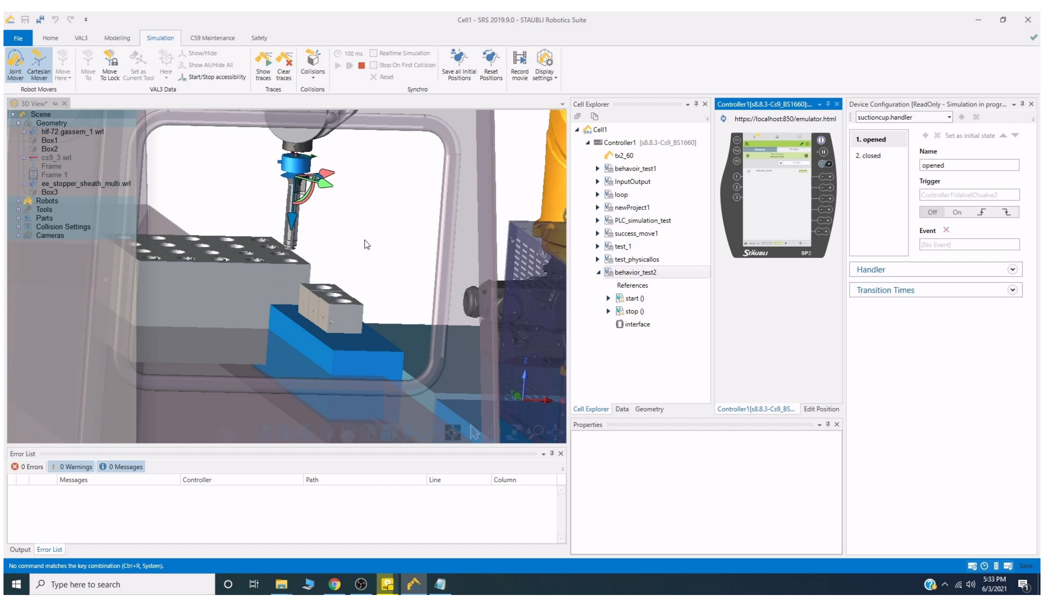


Figure 14: Tool Behavior Control in SRS

Figure 15: Robot Test

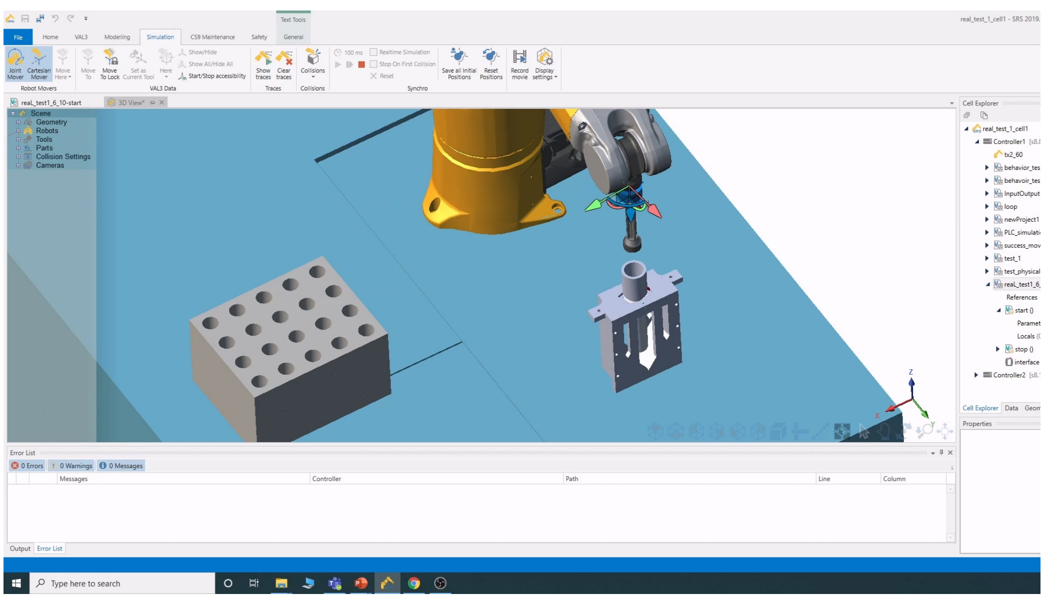


Figure 16: SRS Simulation Test

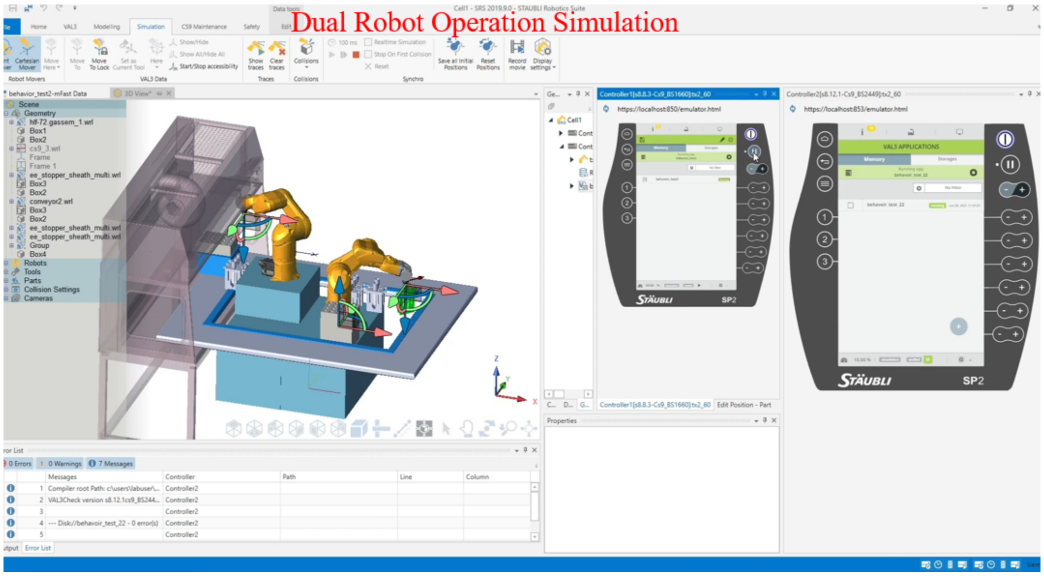


Figure 17: Dual Robot Operation Simulation

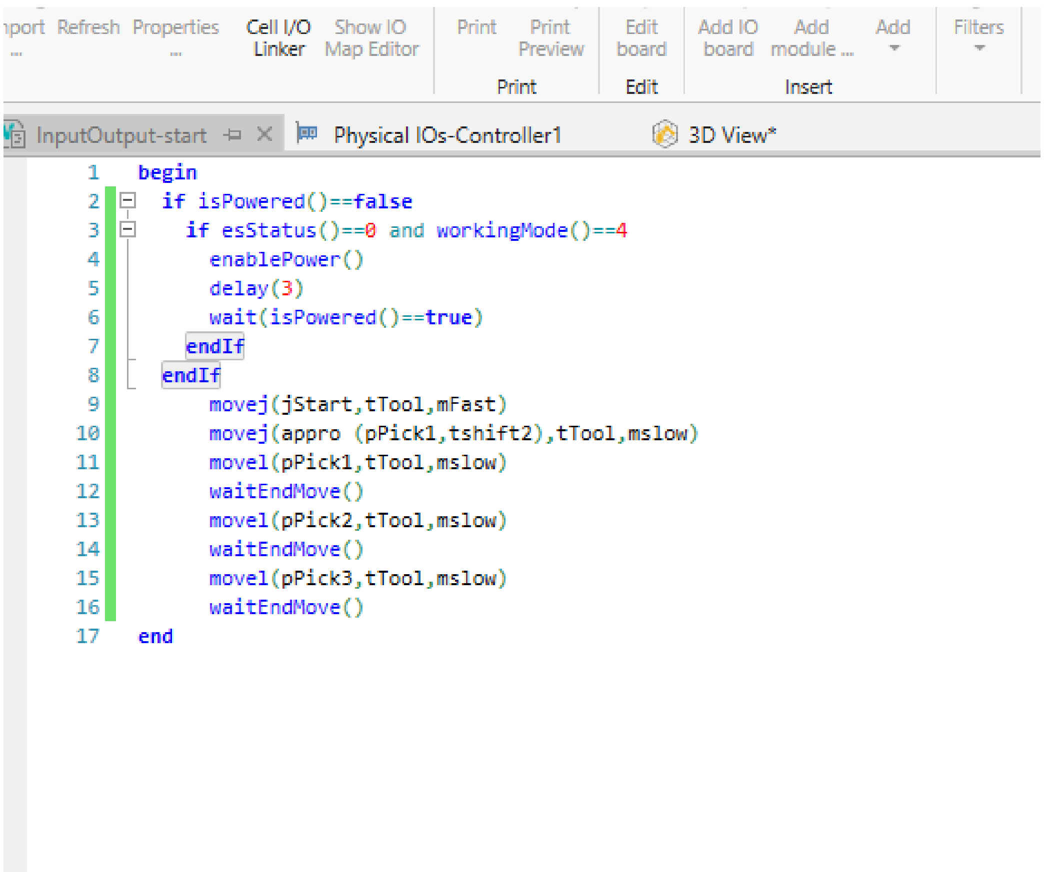


Figure 18: SRS Auto-start code

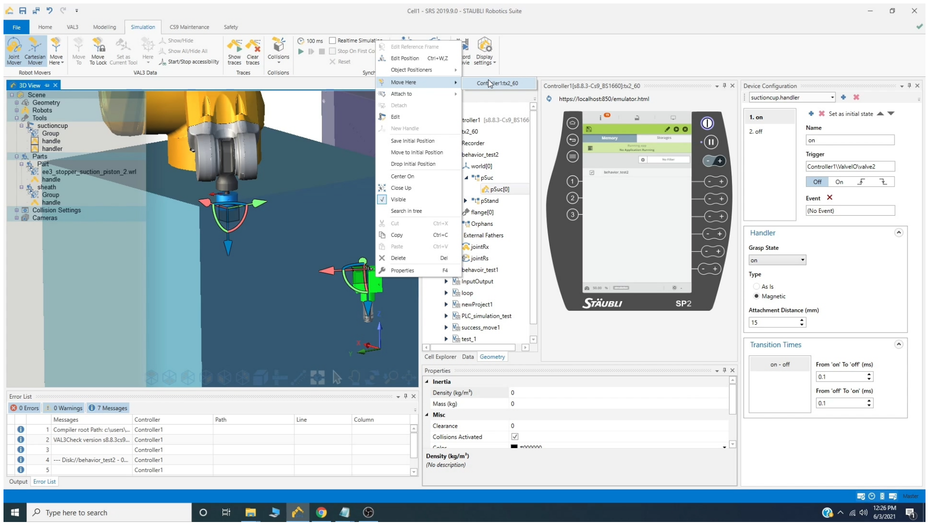


Figure 19: Suction Cup Behavior in SRS

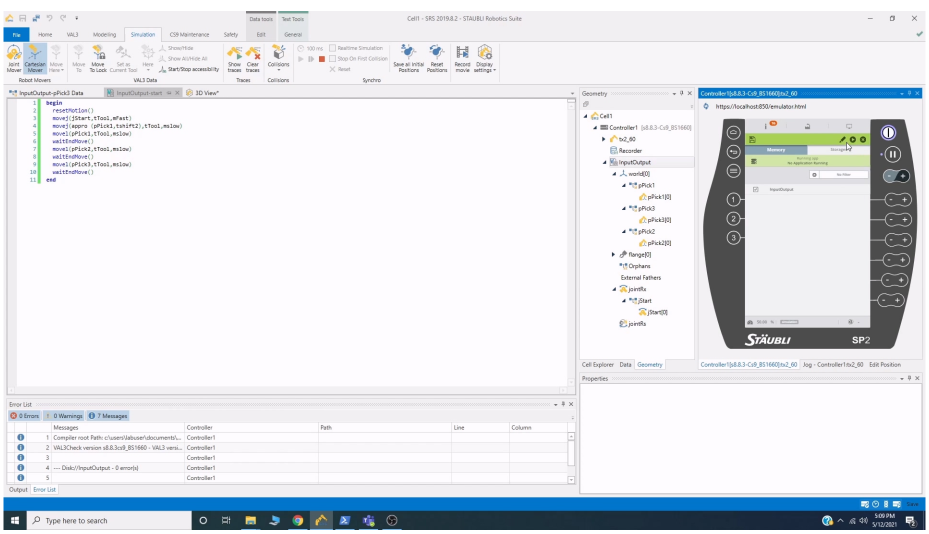


Figure 20: Emulator Programming

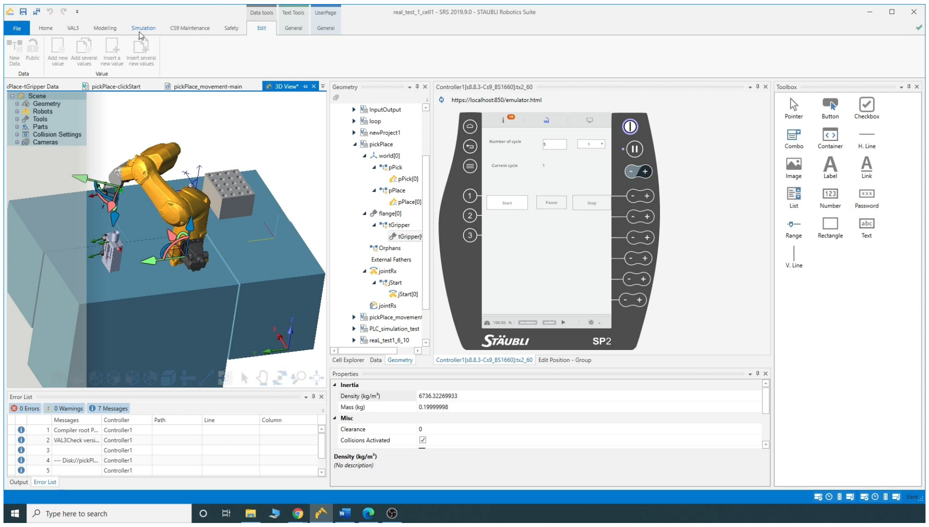


Figure 21: Customized User-Interface in SRS

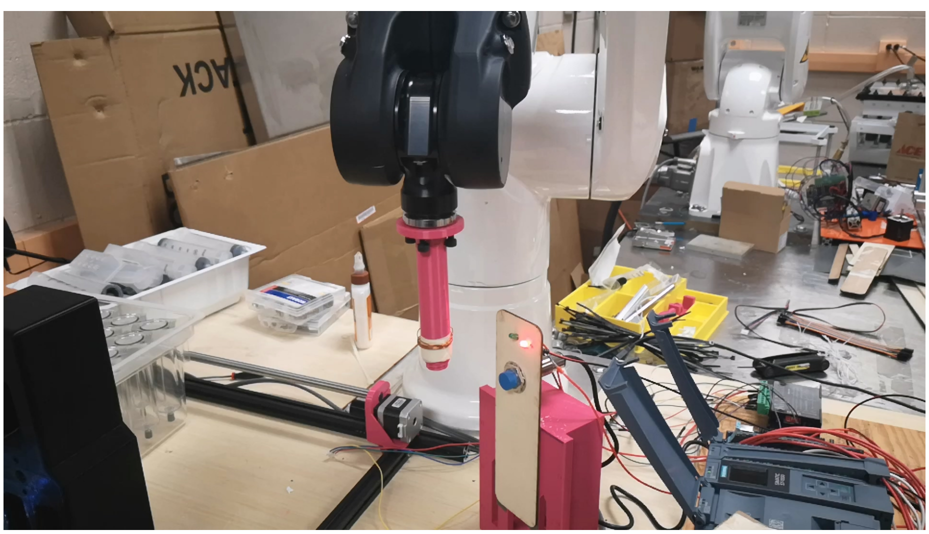


Figure 22: Capacitive Proximity Sensor Detection

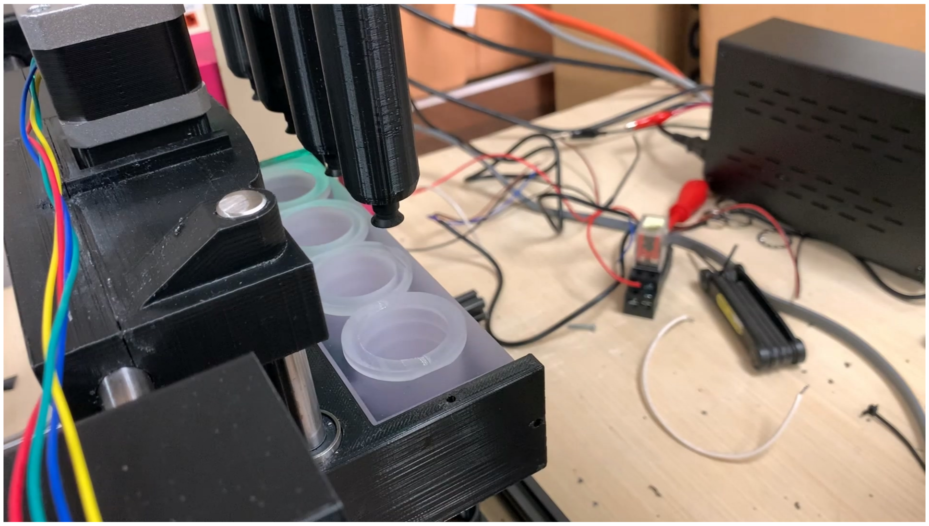


Figure 23: Alignment for the Syringes Row

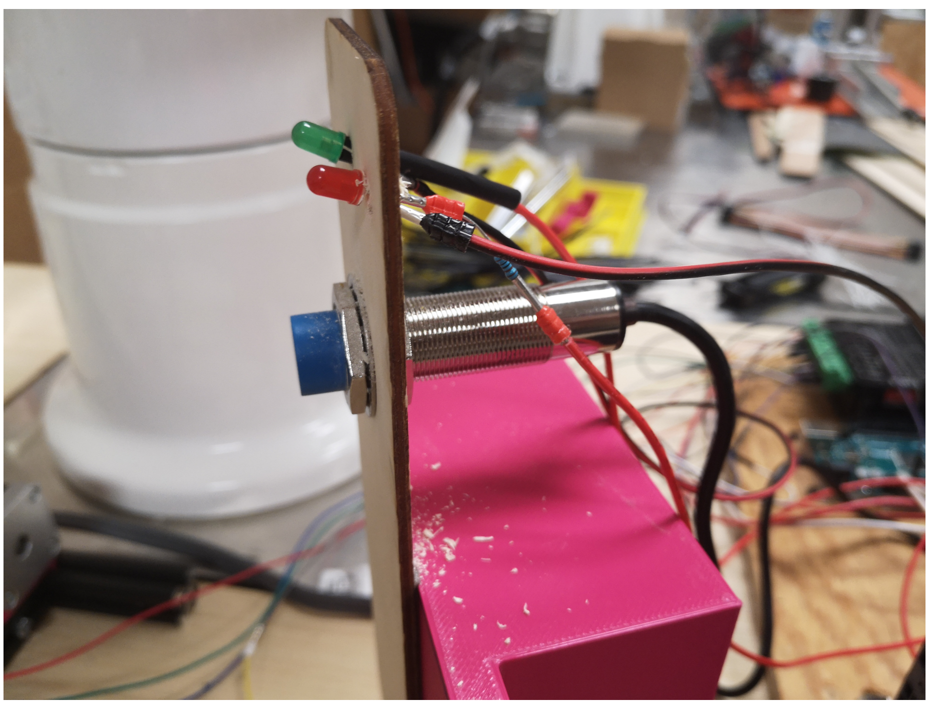


Figure 24: Proximity Sensor Wiring

Figure 25: Pump

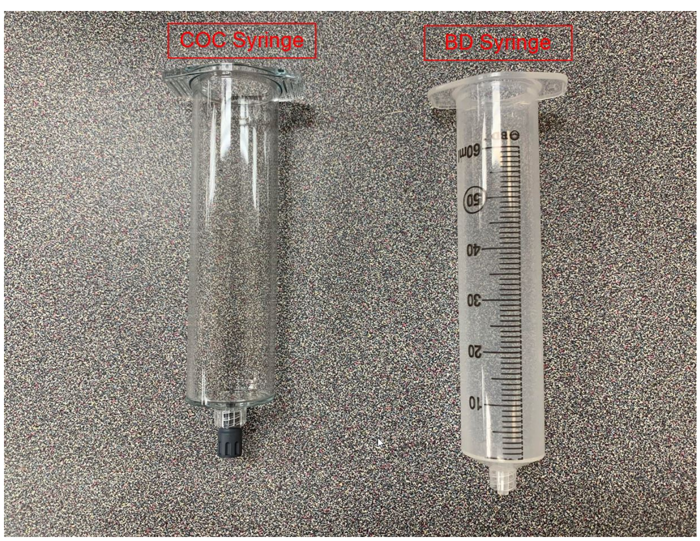


Figure 26: Syringes Comparison

Figure 27: Pneumatic System

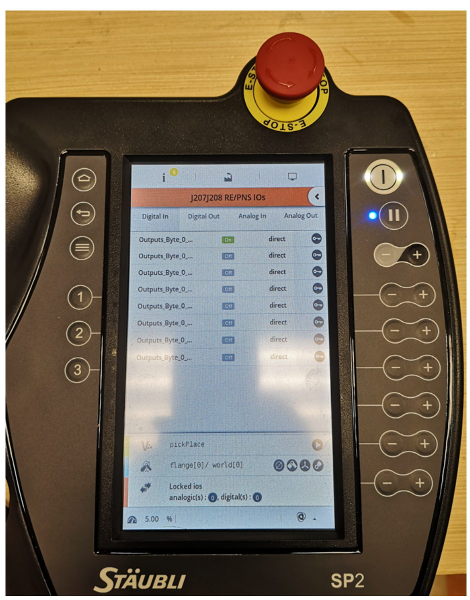


Figure 28: IO in Teach Pendant

Figure 29: Power Supply

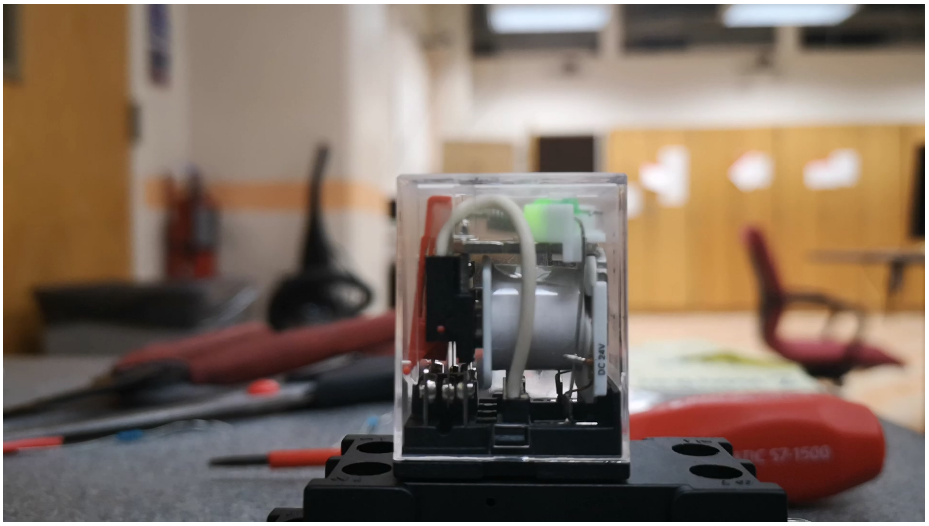


Figure 30: 24VDC 8 Pin Relay

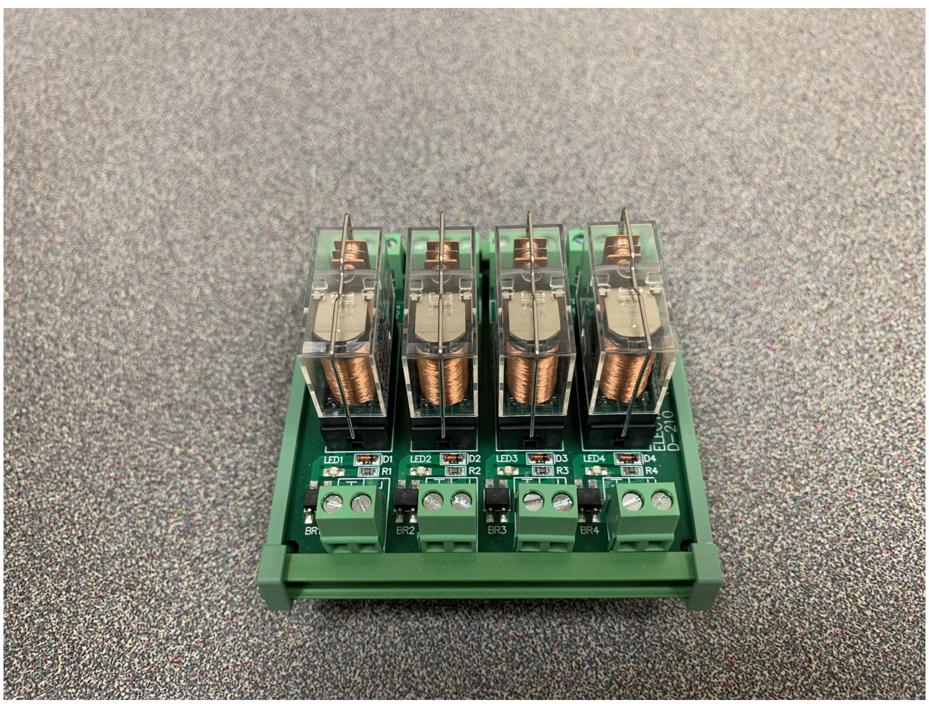


Figure 31: Omron 5-pin Relay

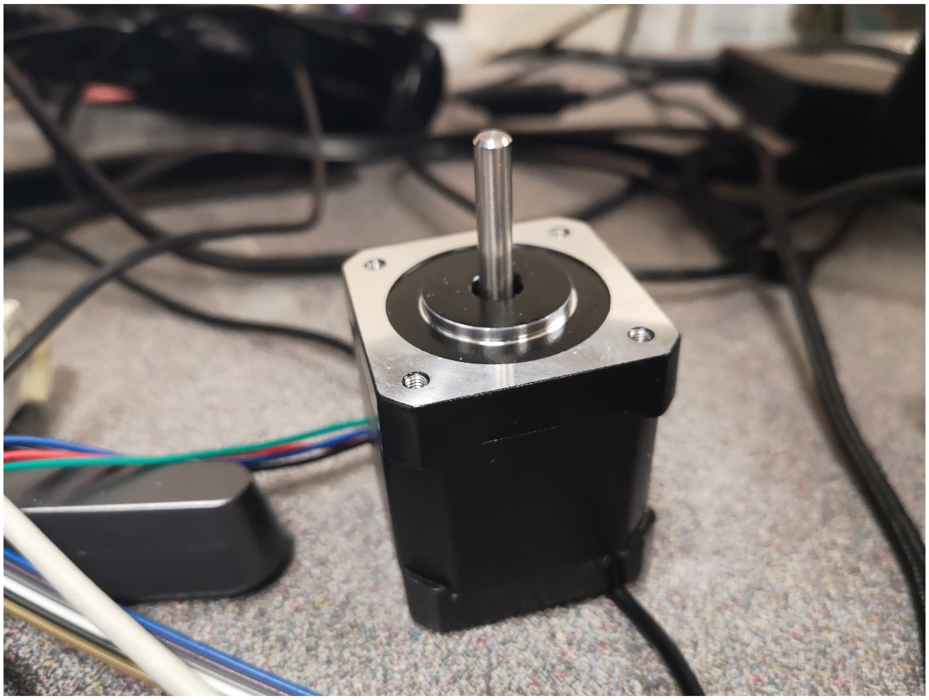


Figure 32: Stepper Motor

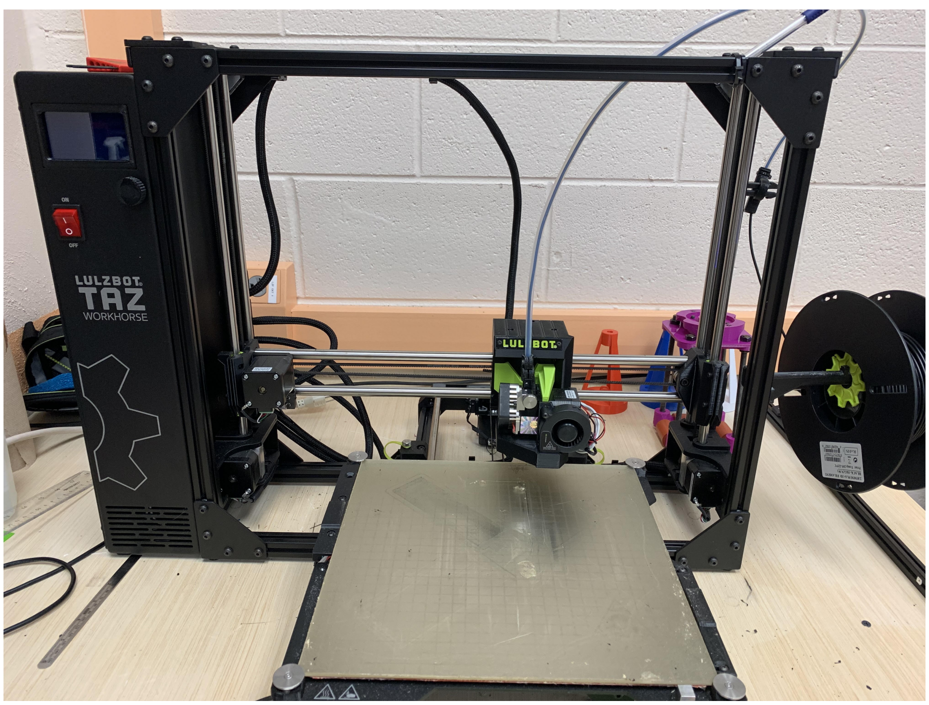


Figure 33: WorkHorse 3D Printer

Figure 34: Stopper Holder

Figure 35: Venting Blocks Comparison

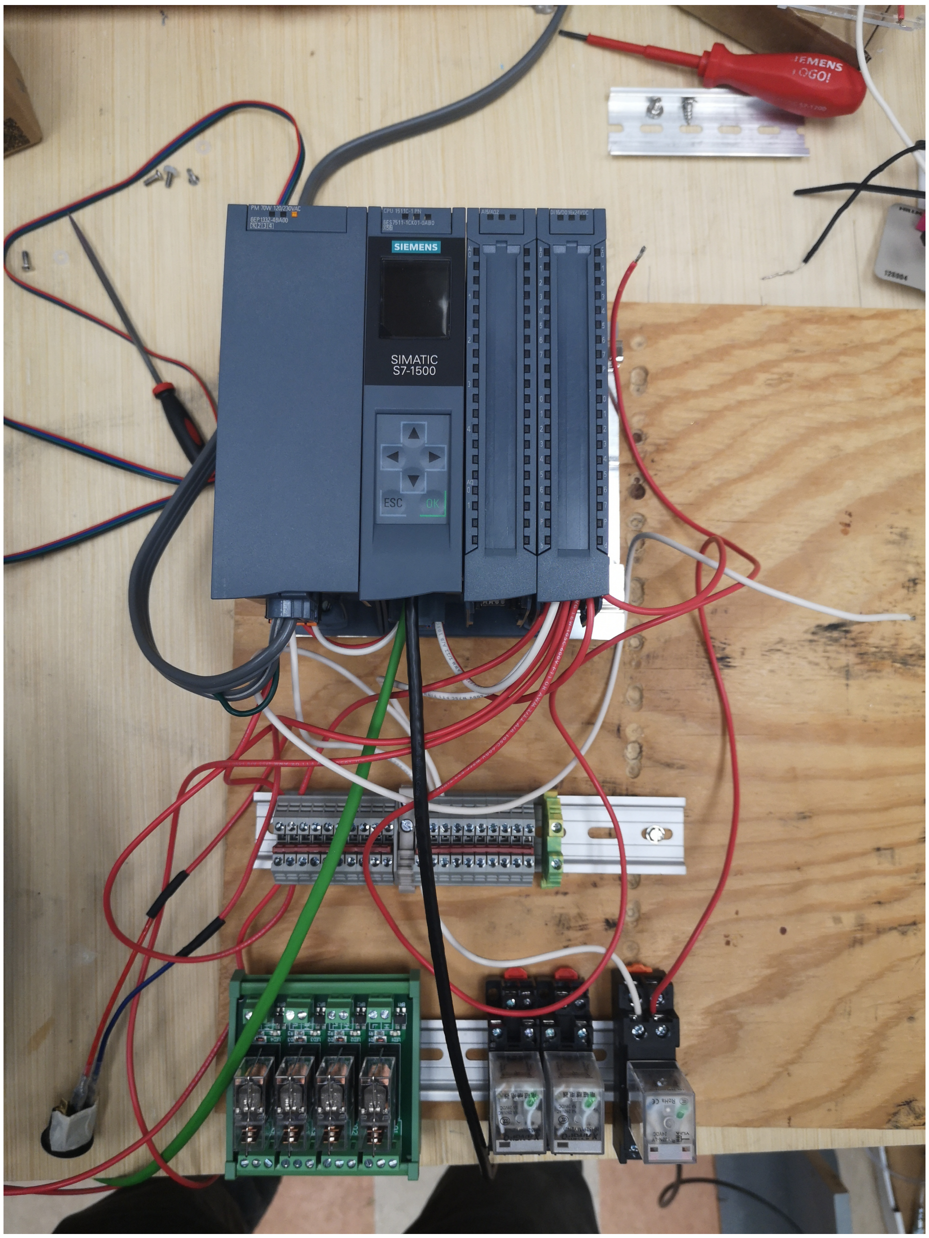


Figure 36: Electrical Panel

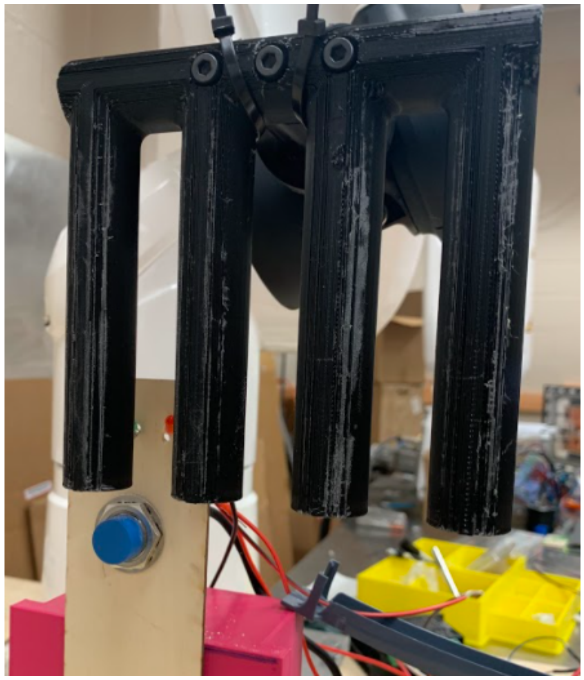


Figure 37: End-effector Design

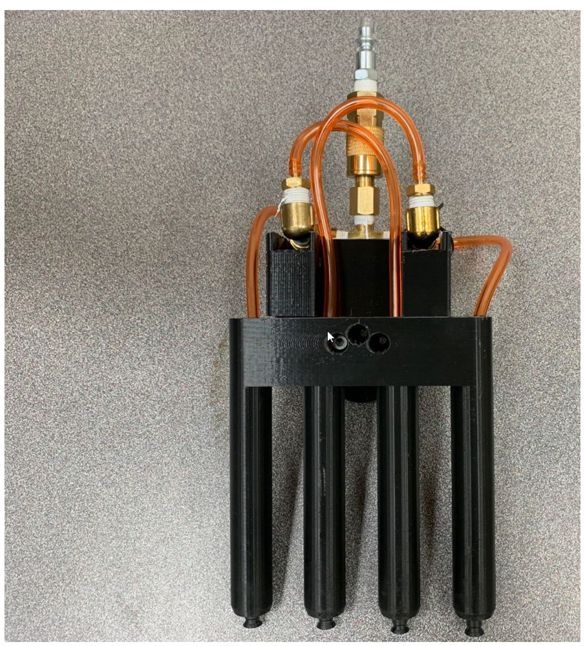


Figure 38: Updated End-effector

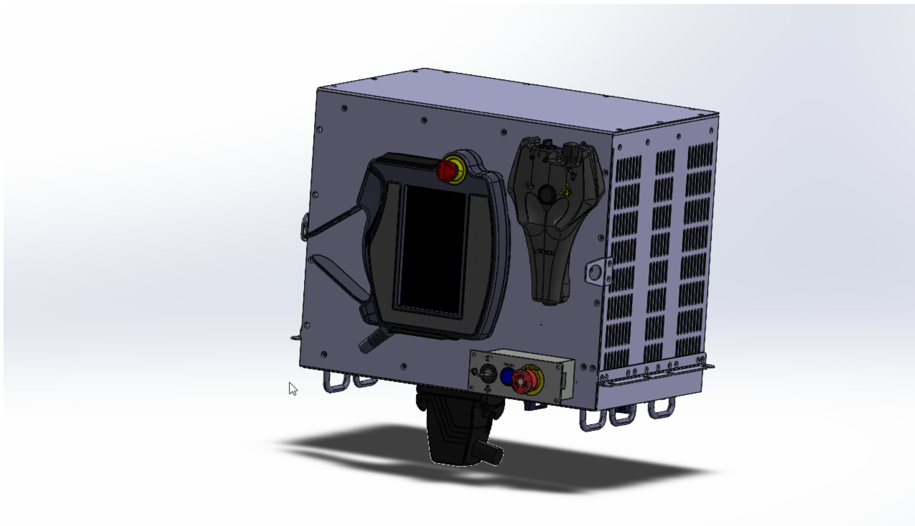


Figure 39: CS9 Controller CAD

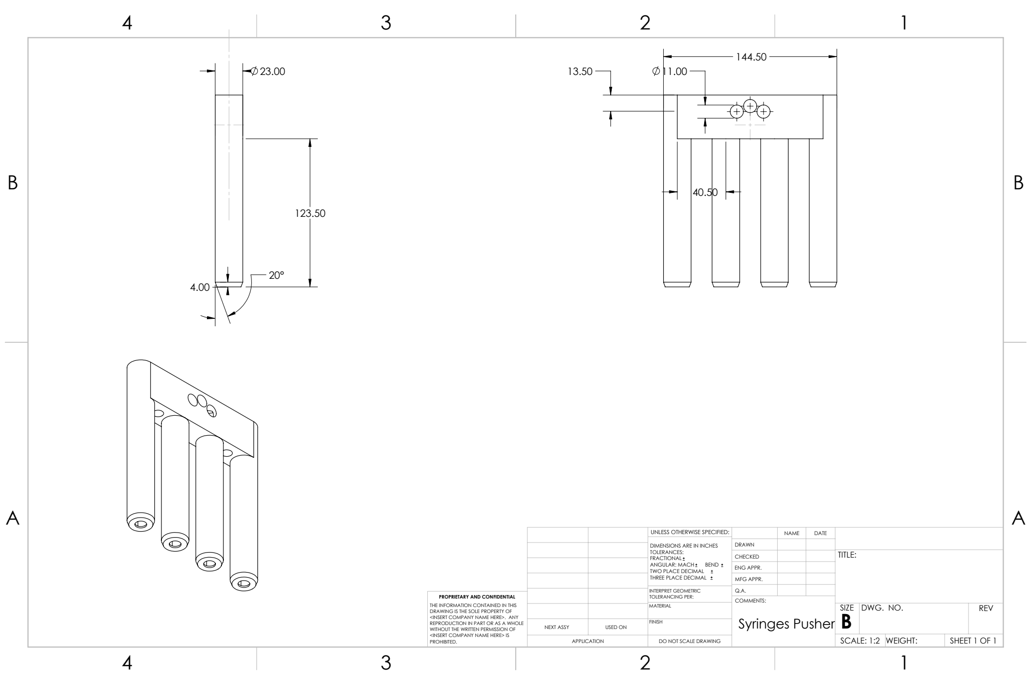


Figure 40: Push Rod Design

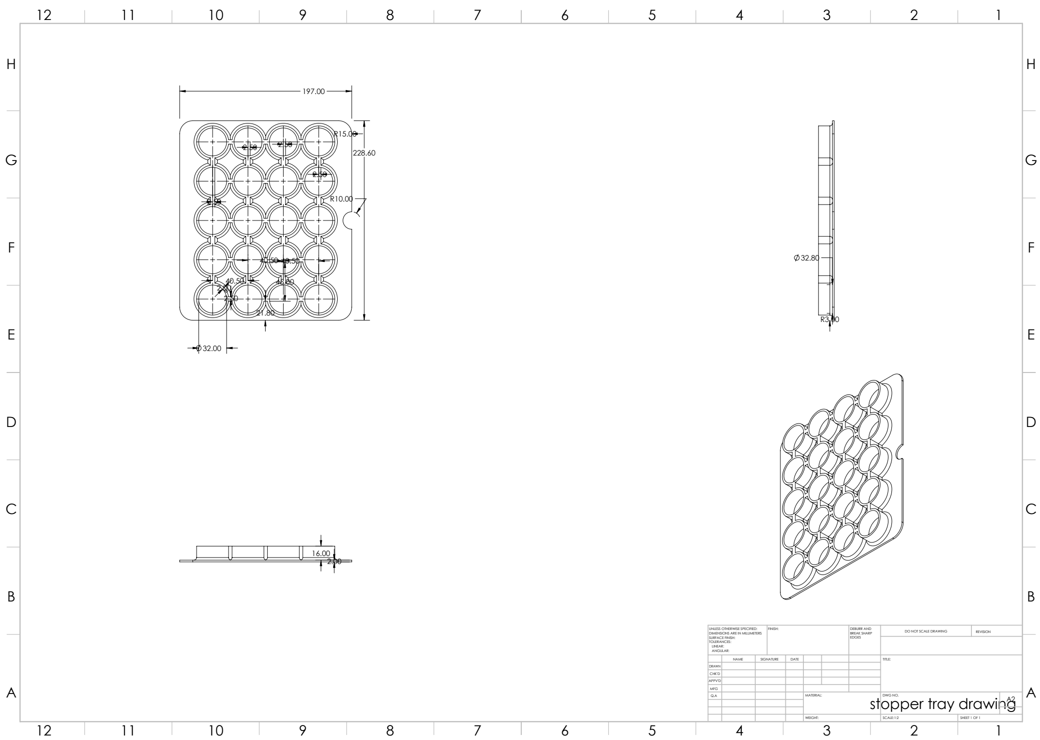


Figure 41: Stopper Tray Drawing

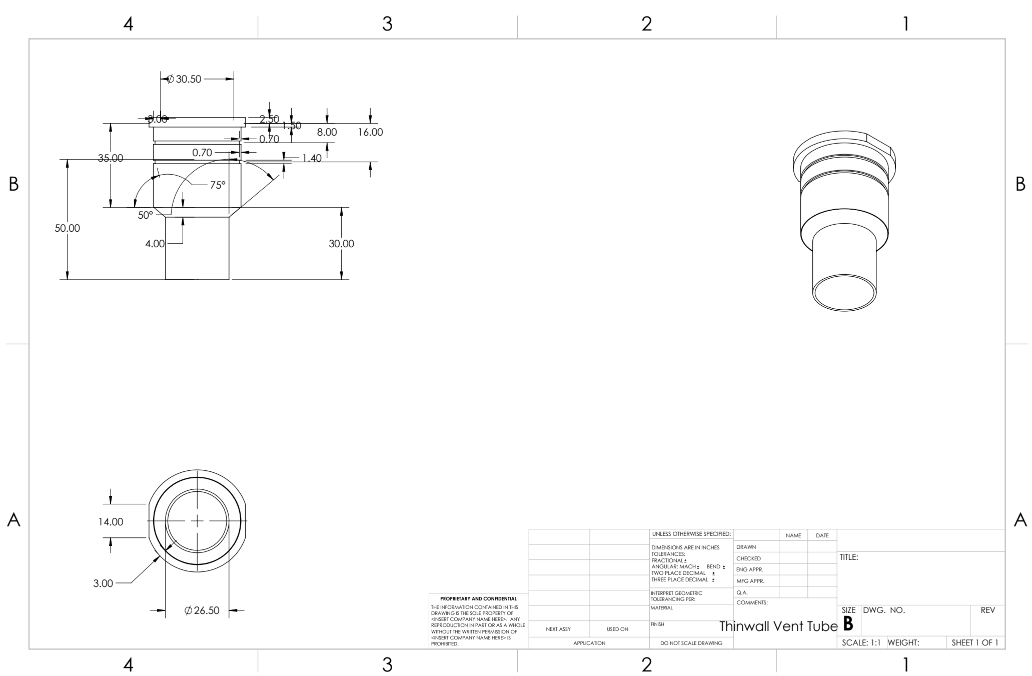


Figure 42: Thin Wall Sheath

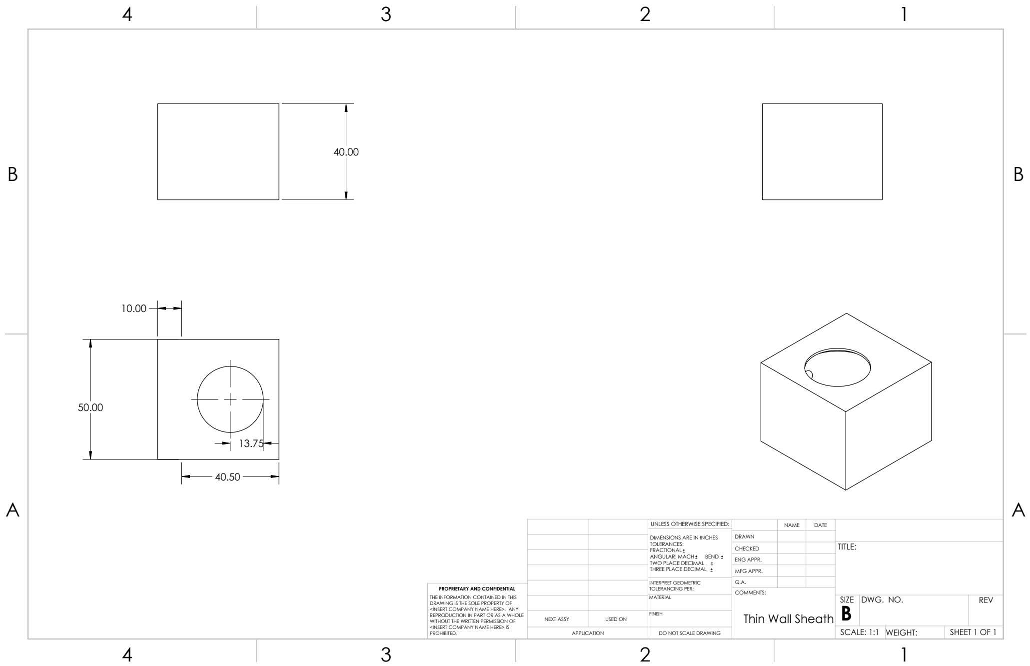


Figure 43: Thin Wall Sheath Edge

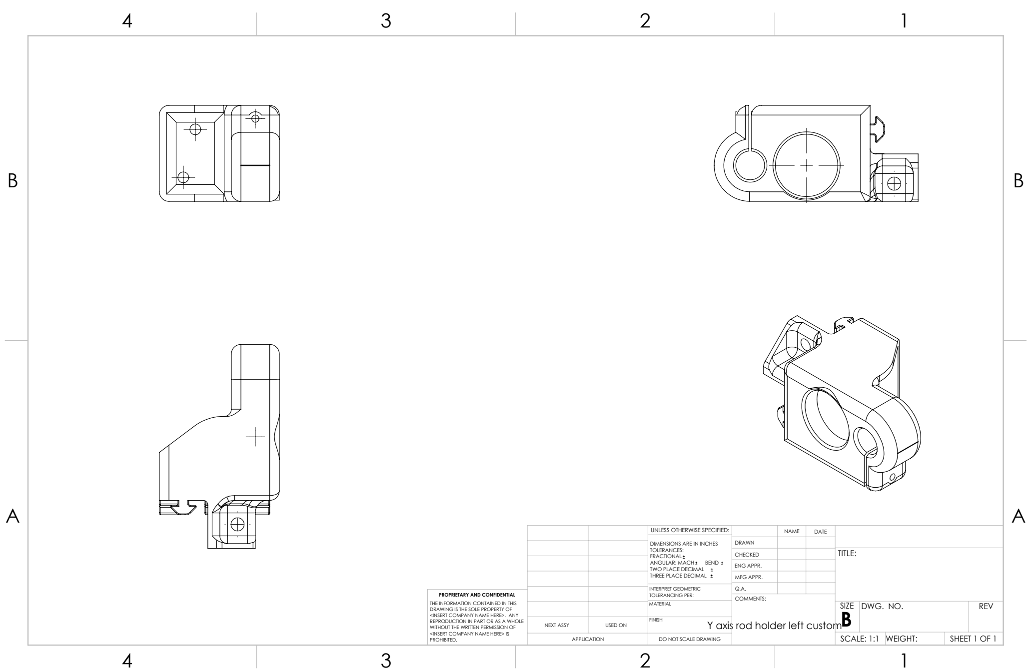


Figure 44: Y axis rod holder

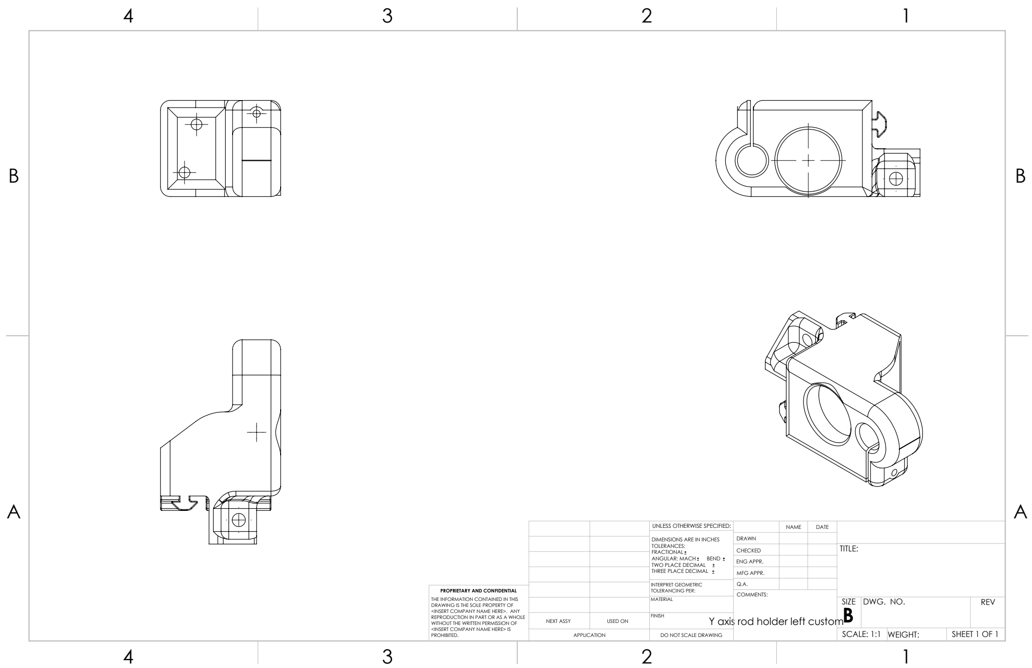


Figure 45: Y axis rod holder

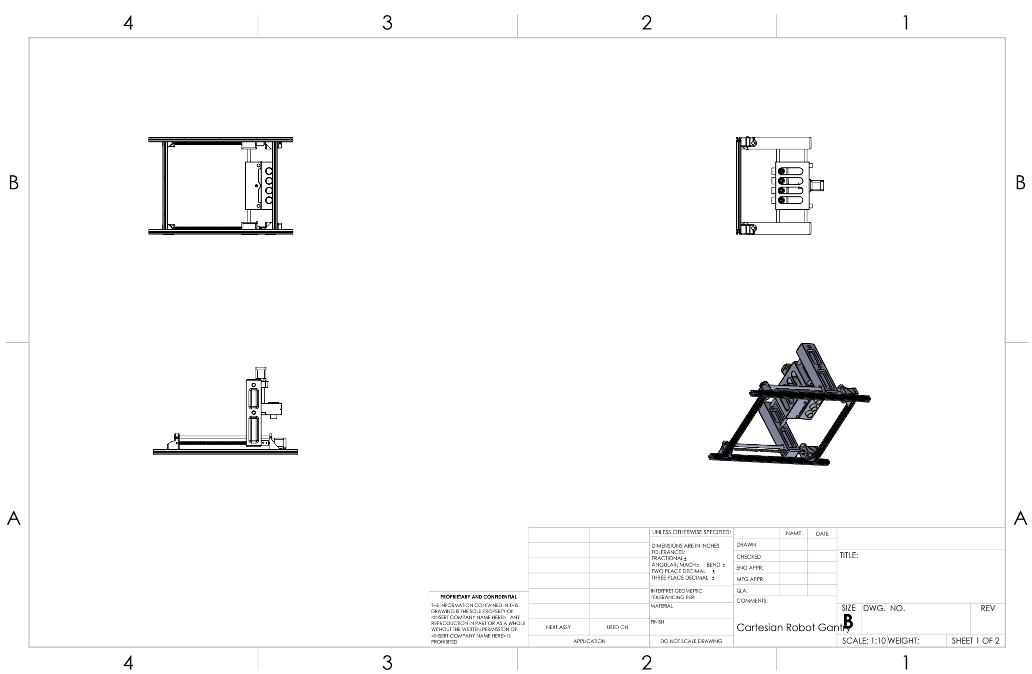


Figure 46: Cartesian Gantry Robot Design Drawing

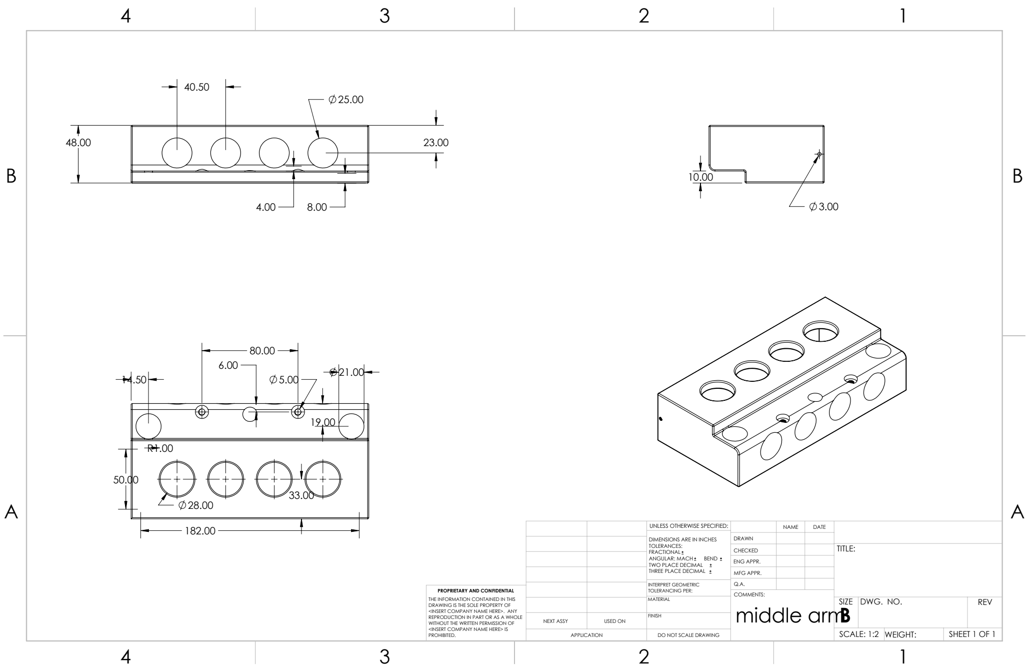


Figure 47: Middle Arm Design Drawing

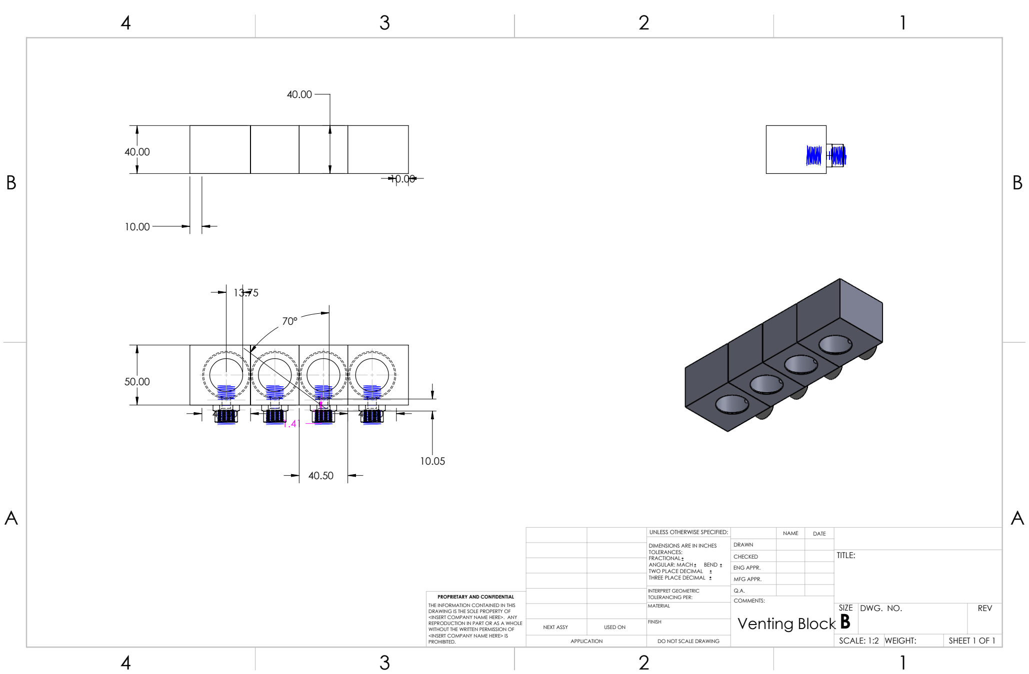


Figure 48: Vent Tube Design

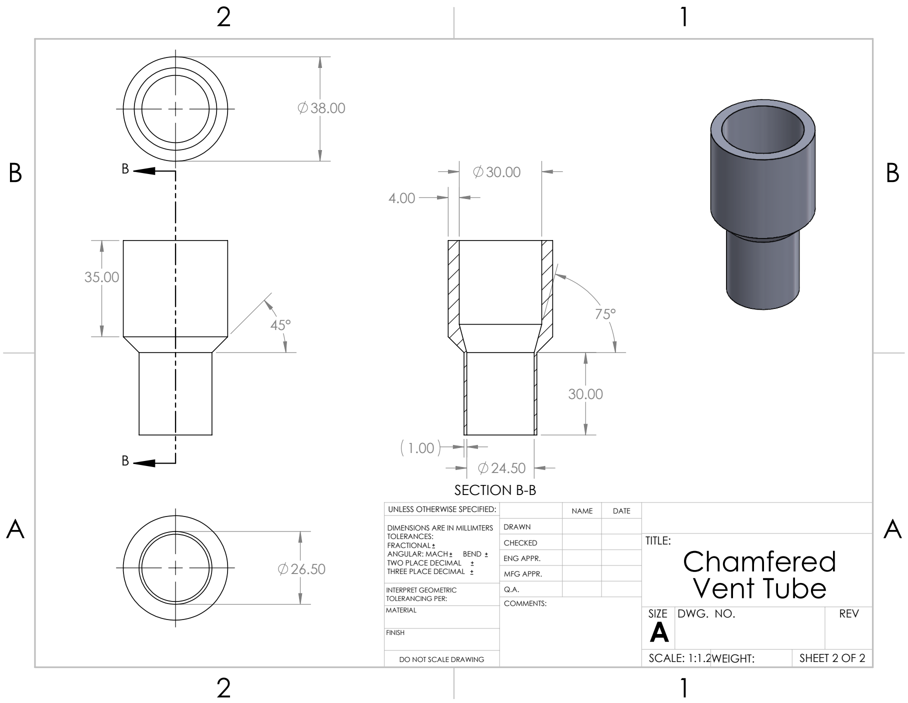


Figure 49: Machined Chamfered test rig

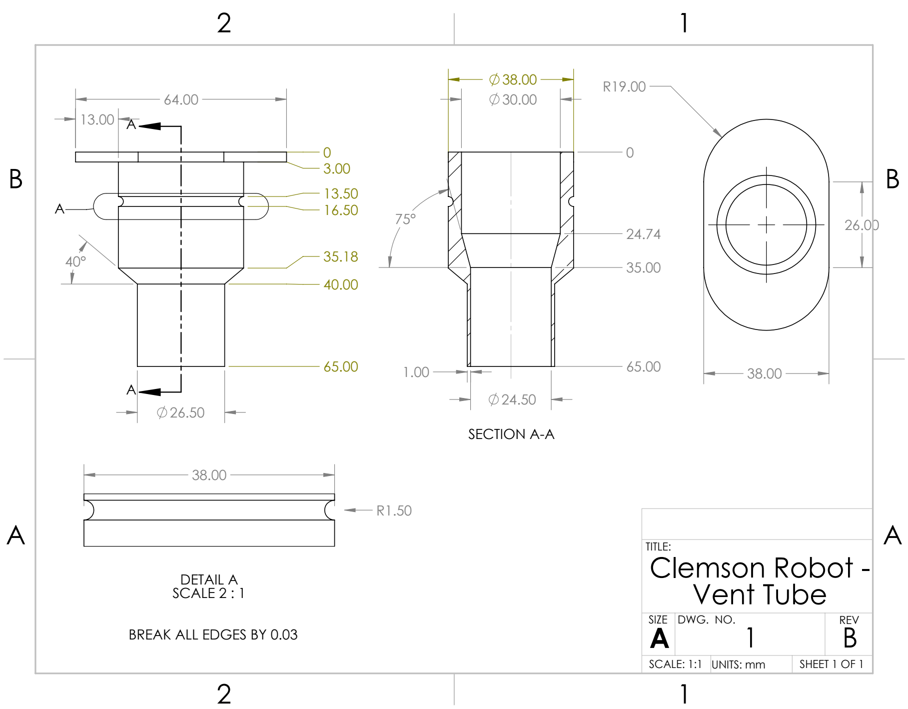


Figure 50: Vent Tube Final Draft oblong

Bibliography

[1] Kazi Masudul Alam, Alex Sopena, and Abdulmotaleb El Saddik. Design and development of a cloud based cyber-physical architecture for the internet-of-things. In *2015 IEEE International Symposium on Multimedia (ISM)*, pages 459–464, 2015.

[2] Michal Alexovič, Yannis Dotsikas, Peter Bober, and Ján Sabo. Achievements in robotic automation of solvent extraction and related approaches for bioanalysis of pharmaceuticals. *Journal of Chromatography B*, 1092:402–421, 2018.

[3] AST. Bench-top syringe and cartridge closing system, 2020.

[4] AST. Container Filling System (CFS): Tabletop vial, Syringe and Cartridge Filling Machine, 2020.

[5] Nikodem Bartnik. DIY Dremel CNC, 2022.

[6] Bausch-Stroebel. KCP series, 2020.

[7] Bennett Brumson. Robots in the lab, 2012.

[8] Elaine Chen. Drugmakers Race to Build Covid-19 Vaccine Supply Chains, 2020.

[9] Colanar. Modular Syringe, Vial and Cartridge Filling System – FSM, 2020.

[10] Brandon DelSpina, Yu Zhang, and Yue Wang. A benchtop robot and automation solution for prefilled syringes in pharmaceutical manufacturing. In *IEEE 17th International Conference on Automation Science and Engineering (CASE)*, 2021.

[11] FDA. *Drug Shortages: Root Causes and Potential Solutions 2019*. Food and Drug Administration, 2019.

[12] Jean-Eudes Fontan, Philippe Arnaud, and Françoise Brion. Laminar-airflow ceiling in a hospital pharmacy cleanroom. *American journal of health-system pharmacy*, 55(2):182–183, 1998.

[13] Rob Godfrey. Nephron partners with Clemson to Meet Hospitals' Growing Pharmaceutical Demands, 2019.

[14] Adam Hahn, Aditya Ashok, Siddharth Sridhar, and Manimaran Govindarasu. Cyber-physical security testbeds: Architecture, application, and evaluation for smart grid. *IEEE Transactions on Smart Grid*, 4(2):847–855, 2013.

[15] RJL Heron and FC Pickering. Health effects of exposure to active pharmaceutical ingredients (APIs). *Occupational Medicine*, 53(6):357–362, 2003.

[16] Liang Hu, Nannan Xie, Zhejun Kuang, and Kuo Zhao. Review of cyber-physical system architecture. In *2012 IEEE 15th International Symposium on Object/Component/Service-Oriented Real-Time Distributed Computing Workshops*, pages 25–30, 2012.

[17] Inas S. Khayal and Amro M. Farid. An architecture for a cyber-physical healthcare delivery system with human agents. In *2017 IEEE First Summer School on Smart Cities (S3C)*, pages 126–131, 2017.

[18] Irene Krämer, Matteo Federici, and Rudolf Schierl. Environmental and product contamination during the preparation of antineoplastic drugs with robotic systems. *Pharmaceutical Technology in Hospital Pharmacy*, 3(3):153–164, 2018.

[19] Jay Lee, Behrad Bagheri, and Hung-An Kao. A cyber-physical systems architecture for industry 4.0-based manufacturing systems. *Manufacturing Letters*, 3:18–23, 2015.

[20] Gaël Loubet, Alexandru Takacs, and Daniela Dragomirescu. Implementation of a battery-free wireless sensor for cyber-physical systems dedicated to structural health monitoring applications. *IEEE Access*, 7:24679–24690, 2019.

[21] Sagar Makwana, Biswajit Basu, Yogita Makasana, and Abhay Dharamsi. Prefilled syringes: An innovation in parenteral packaging. *Int J Pharam Investig*, 1(4):200–206, 2011.

[22] Fred Massoomi and FASHP David A Kvancz. USP 800 requirements for engineering controls. 2016.

[23] H. D. Mills, M. Dyer, and R. C. Linger. Cleanroom software engineering. *IEEE Software*, 4(5):19–25, 1987.

[24] Pharma Manufacturing. Six steps to part 11 compliance, 2002.

[25] PROFIBUS PROFINET International (PI). PROFINET specification, 2021.

[26] PROFIBUS PROFINET International (PI). PROFINET specification, 2022.

[27] Ciprian-Radu Rad, Olimpiu Hancu, Ioana-Alexandra Takacs, and Gheorghe Olteanu. Smart monitoring of potato crop: A cyber-physical system architecture model in the field of precision agriculture. *Agriculture and Agricultural Science Procedia*, 6:73–79, 2015. Conference Agriculture for Life, Life for Agriculture.

[28] Gregory Sacha, J. Aaron Rogers, and Reagan L. Miller. Pre-filled syringes: a review of the history, manufacturing and challenges. *Pharmaceutical Development and Technology*, 20(1):1–11, Jan 2015.

[29] Ron Sender, Shai Fuchs, and Ron Milo. Revised estimates for the number of human and bacteria cells in the body. *PLOS Biology*, 14:1–14, 08 2016.

[30] Siemens. The technology objects (to) of simatic s7-1500(t), 2017.

[31] Siemens Digital Industries. Maker of prefab pharmaceutical cleanrooms standardizes on siemens technologies with huge cost, time and space savings. 2020.

[32] Sadik Tamboli, Mallikarjun Rawale, Rupesh Thoraiet, and Sudhir Agashe. Implementation of modbus rtu and modbus tcp communication using siemens s7-1200 plc for batch process. In *2015 International Conference on Smart Technologies and Management for Computing, Communication, Controls, Energy and Materials (ICSTM)*, pages 258–263, 2015.

[33] U.S. Food and Drug Administration. Sterile drug products produced by aseptic processing - current good manufacturing practice, 2004.