Pin Transfer Robot for Chemical Screening

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***Abstract* — Chemical screening is a modern means of novel drug discovery. For large amounts of chemicals, it is critical to automate the process for high throughput screening. However, accessing such machines can be cost prohibitive for many research laboratories. This paper presents the design of a low-cost option for automated chemical screening. The Pin Transfer Robot for Chemical Screening consists of a combination of consumer-grade parts for the construction and operation of the robot and a scientific-grade pin tool for the chemical screening process.**

***Index Terms* — Automation, DC motors, medical robotics, robot control, microcontrollers, servomotors.**

I. Introduction

Pin transfer operations are used in chemical screening experiments to transfer extremely small volumes of small molecules, chemical compounds, or drugs (typically nanoliters) from a chemical library source microplate into a cell culture recipient microplate. Pin transfer operations allow for many cell culture wells to be treated at the same time which enables high throughput screening for "hit" compounds that have a desired effect on the cell population of interest. We categorize the currently available systems on the market at three different levels of pin tool system capability and complexity. The simplest and cheapest option, typically around $3000-6000, is a manual pin tool. These devices are mounted with a handle and must be manually held by the operator. This takes an acquired skill to use properly and is impossible to guarantee repeatability or accuracy between experiments.

Liquid handling station adaptation kits are a more advanced alternative to manual pin tools which independent labs can purchase [3]. These devices transform a liquid handling robot, which usually automatically pipet liquid volumes into different reservoirs and conical tubes, into a pin transfer robot. Because these robots were not initially designed for the pin transfer application, without additional robotics to load/offload microplates they cannot handle multiple microplates at the same time. These platforms can cost anywhere from $10,000 and upwards depending on the capabilities required and auxiliary robotics used. Lastly, there are high throughput screening facilities whose entire purpose is to conduct screens with millions of compounds to identify drug candidates for disease such as cancer. These facilities can be found at the National Institutes of Health and other large biomedical research facilities. These robotic systems can require an entire laboratory of space and are expensive and exclusive to use. Advanced robotic screening systems can cost millions of dollars to build.

Our goal in this senior design project is to make a robotic system specifically designed for pin tool operation that is cheaper and more effective than a liquid handling adaptation system. The robot should ease the workload on laboratory scientists and most importantly provide more reliable and reproducible results than manual operation. Our system should be affordable enough that it will grant new labs access to this kind of equipment, which would allow them to conduct small scale chemical screening experiments on novel disease models that cannot justify the use of more expensive screening laboratories and equipment, enabling new scientific discoveries.

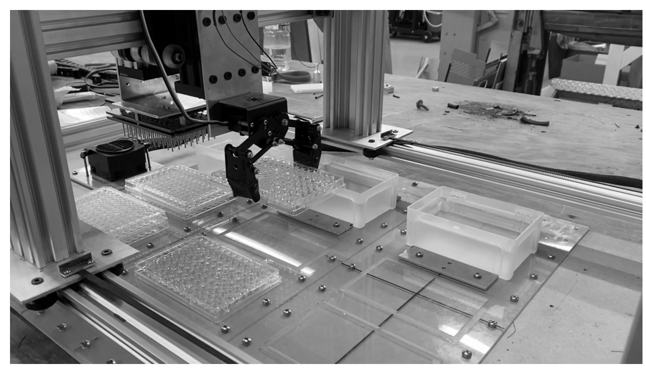

Fig 1. Picture of the Pin Transfer Robot for Chemical Screening

II. Operation

The operation of the pin tool robot can best be described in cycles where at the beginning of a cycle one source and one recipient microplate are transported into the operating workspace and at the end of the cycle a successful liquid transfer from source to recipient plate has occurred, these plates are moved out of the operating arena, and the pin tool has been cleaned and dried and thereby prepared for its next operation.

The robot requires limited operator input which includes placing source and recipient microplates into their respective stacks, as well as defining operation variables using the mounted touchscreen LCD which will modify motor parameters and cleaning profiles to best suit their needs. During robot operation, the current progress is displayed on both the LCD as well as the Pin Tool cellular application to allow for remote work while the pin transfer completes.

The materials used to construct the robot are able to be completely sanitized with 70% ethanol and just one 120 volt AC outlet is required to power all of the components making it suitable for operations within most biosafety cabinets. An emergency stop button is included which if pressed will instantly cut power to the microprocessor thereby stopping all stepper motors and gripper actions. If this button is pressed it can be reset by powering off the robot, resetting the button by twisting the knob, and turning the power supply back on.

III. Mechanical

A. Pin Tool

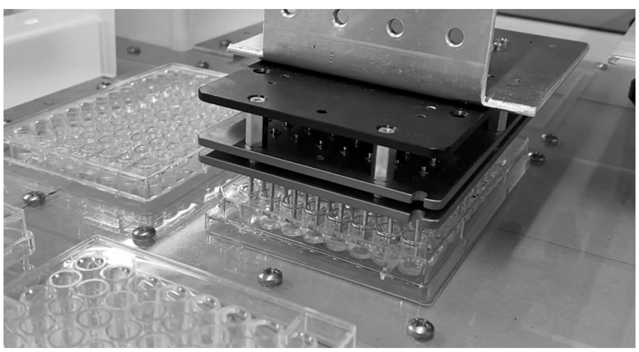

Figure 2: Pin transfer tool. Transfers ~0.2uL/well [2]

The pin transfer tool transfers extremely small volumes of liquid in a high-throughput manner for the purposes of chemical screening or microplate replication procedures. Pin transfer tools come in both manual or robot variants. For manual operation the pin transfer tool is handheld and slowly lowered onto a source microplate. The manual tool is typically aligned using a guide plate that allows for key pins on the manual pin transfer tool to be aligned so that each pin on the tool enters its respective well in the microplate. Robotic pin transfer tools eliminate the need for a key plate by using very precise NEMA motors on a linear belt driven actuator platform. This sensitively calibrated system ensures the pin tool is correctly inserted into the microplate.

The pin transfer tool transfers liquid by cleverly manipulating liquid to surface adhesion on the pins. The pins are calibrated so that each transfer makes a very precise dilution ratio in the destination microplate. The two main parameters that can be controlled which affect the amount of liquid that is transferred is the depth at which the pin tool is dipped into the microplate wells and by the speed of the pin transfer tool as it withdraws from the liquid in the microplates and moves to deliver into the destination microplate.

In our design, the pin transfer tool hangs from a gantry that can operate in three degrees of freedom (X, Y, and Z axis) so that it can span the entire workspace. An example scenario would be a simple pin transfer process from a source chemical plate to a destination cell culture microplate. The input source and recipient microplate stacks are unloaded into their respective workspace positions using the parallel gripper. The pin transfer tool will first dip into the source chemical microplate at a user specified depth and speed before raising out of the microplate at a specified speed. The pin transfer tool translates directly above the recipient microplate where it then descends into the plate at a user specified depth and speed. After the liquid is transferred into the recipient microplate, the pin tool is washed at different cleaning reservoirs and finally dried. The processed microplates are deposited at the two output microplate stacks.

B. Mechanical Designs

Throughout the semester, many different parts were 3D printed, laser cut, and printed in the design of the robot. When limit switches were still being tested, a couple of limit switch mount designs were 3D printed and another was laser cut out of acrylic 3mm in thickness. In early iterations of the robot, a number of custom gantry carts were designed and laser cut for the v-slot linear rails in acrylic when they were used to carry microplates to the center of the gantry. However, restricting the pin tool and plate gripper to two degrees of freedom proved to be an inefficient way of automating the robot due to its incompatibility with stacking microplates and wasting usable space. For example, using gantry carts to move a stack of microplates to the parallel gripper and pin tool for processing meant that custom L-brackets were necessary to keep the stack from falling over. It also meant that the timing belt was to go through two carts on one linear actuator since the parallel gripper would have to move one plate from the stack to an empty gantry cart for a pin transfer operation.

Ultimately, the designs that remained relevant to our final iteration of the robot were the mount for our parallel gripper and the custom V-slot gantry plates shown in Fix X. This new design features five M5 holes near the center to fasten a C-beam rail and was made so that the X-axis linear actuators could move the YZ-axis linear actuators, turning the Pin Transfer Robot from a 2-axis cartesian manipulator with a third axis for moving gantry carts into a 3-axis cartesian manipulator robot.

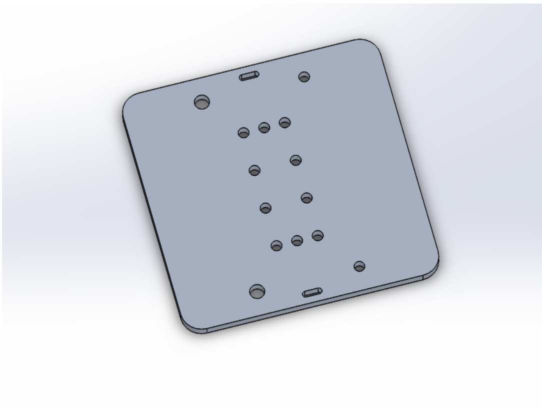

*Fig. 3. CAD Model of the Custom V-slot Gantry Plate with M5 holes for C-beam moun*t

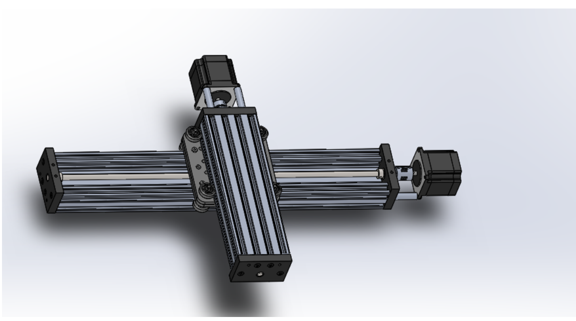

Fig. 4. CAD Model of the YZ Axis Linear Actuators

IV. Hardware

The robot consists of a multitude of different devices working together. In this section, the notable devices for delivering proper functionality will be discussed.

A. Power Supply

To sufficiently power the stepper motors, fan/heater and the microcontroller, a relatively high power output power supply unit is required. Since all of the electrical components of this robot operate at least 24V, a suitable power supply that can output 24V is necessary.

After analyzing the power requirements for all of the components of the robot including the NEMA 17 and NEMA 23 motors which require 4.8W and 8.96W respectively, the fan with a heat which requires 250W and a 2W parallel gripper. The Meanwell 24V power supply was chosen to suit the power delivery needs of the robot.

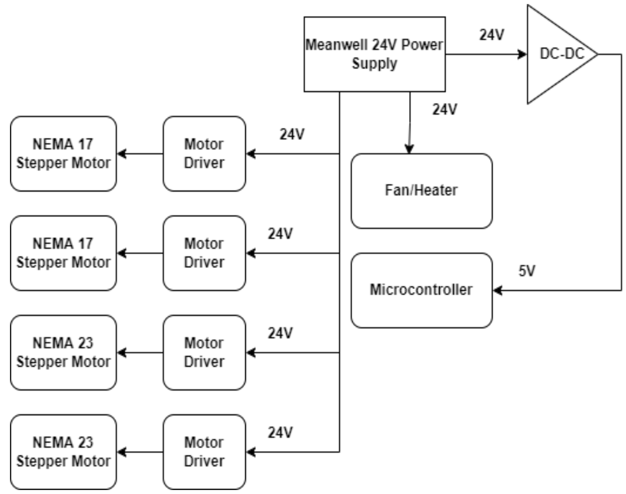

Fig 5. Block diagram of power delivery to different components powered directly by the Meanwell 24V power supply.

A Meanwell 24V power supply supplies 24V at 14.6 A delivering ~350W. Such power delivery is necessary to support the 4 NEMA stepper motors and the drying fan. The block diagram of the power delivery to the robot is shown in Fig 1. above.

Below in Fig 6, the power draw of the robot is shown.

Component	Power produced	Total
Power Supply	Power Supply	+350W
NEMA 17	-(2 motors x 4.8W/motor)	340W
NEMA 23	-(3 motors x 8.96W/motor)	313.5W
Fan/Heater	-250W	63.5W
Parallel Gripper	-2W	61.5W

Fig 6. Power delivery and consumption for each device on the robot.

As per Fig 6 above, the Meanwell power supply can support the power draw of all of the components at the same time. However, it is important to note that the fan and heater unit will not be active at all times. It will only be drawing its power requirements during a single stage in the pin transfer process.

B. *Motors and Motor Drivers*

The approach taken to automate the chemical screening process includes the use of linear actuators controlled by stepper motors to accurately position the pin tool and the parallel gripper at any position in the workspace. Stepper motors are highly accurate DC motors that can be controlled by a stepper motor driver to precisely take a series of small steps towards a given position on the motor shaft. In the case of this robot, it is necessary to have high accuracy to perform repeated pin transfers in succession.

There are many stepper motors on the consumer market that are suitable for this robot, however, NEMA stepper motors are highly reliable and well-documented motors used in similar applications, thus NEMA stepper motors were chosen to be used. NEMA stepper motors come in different configurations to satisfy the needs of different projects, however, for this robot, NEMA 17 and NEMA 23 stepper motors were chosen. The difference between the two motors is the amount of torque each can output. Below in Fig. 7, the specification of NEMA 17 and NEMA 23 motors are provided.

	NEMA 17	NEMA 23
Face plate area	(1.7 x 1.7) in^2	(2.3 x 2.3) in^2
Holding Torque	3.2 kg-cm	19 kg-cm
Phase draw	1.2A @ 4V	2.8A @ 3.2 V

Fig 7. Specifications of NEMA 17 and NEMA 23 stepper motors [1]

Due to the design of the robot, it was decided to use both NEMA 17 and NEMA 23 stepper motors. The NEMA 17 motors are used to move the entire gantry of the robot in the X axis while the NEMA 23 motors are used to move the pin tool and parallel gripper in the Y and Z axes. The reason for using NEMA 23 in the Y and Z axes is due to the weight of the pin tool and the configuration of the linear actuators for the Y and Z axes as seen in Fig. 4. NEMA 17 stepper motors are suitable for moving the gantry across the X-axis since much less torque is needed as compared to the NEMA 23 motors.

It is common to control NEMA stepper motors with a motor driver to simplify the programming necessary to use the motors. For this robot, the DM542T stepper motor drive is used. In Fig 8 below, the block diagram of a NEMA motor, a DM542T stepper motor driver and a microcontroller is shown.

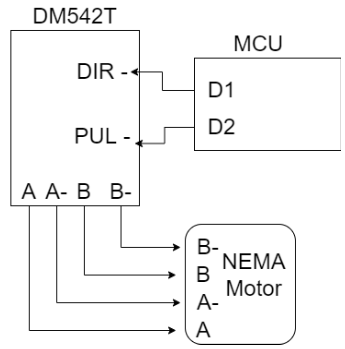

Fig 8. Block diagram for connections between Microcontroller interfacing a NEMA motor with a DM542T stepper motor driver.

Interfacing the NEMA motors with the DM542T stepper motor driver is quite simple. Later in this paper, the AccelStepper C++ library will be discussed. This software library is used to control a stepper motor driver, such as the DM542T, with a microcontroller through only 2 digital GPIO pins.

C. Bluetooth

A mobile app will be provided to researchers using the Pin Transfer Robot to monitor its progress throughout the chemical screening process. For this, we will use the HM-10 bluetooth module to send serial data over UART to communicate to the app on when a certain checkpoint has been reached during chemical screening. The HM-10 is a low cost, energy efficient, Bluetooth module that is amongst the most popular in embedded systems programming alongside the HC-05. It supports the modern Bluetooth 4.0 Low Energy(BLE) technology and has a range of up to 100m in open air. This is ideal for the Pin Transfer Robot since our use case involves sending short bursts of data at infrequent intervals to a researcher who could potentially be further away from the robot.

D. LCD

The robot can be interacted with through a Liquid Crystal Display (LCD) mounted on one of the support beams. The LCD is a touchscreen, so no additional components are required to interact with it. The purpose of the LCD is to take input on specific pin transfer process instructions from a user. There is also the added functionality of displaying which well plate is being processed and what step it is on.

E. Gripper

The gripper was not part of the original design of the robot. Due to size and difficulty constraints, the original stacking idea had to be changed. This new design necessitated the inclusion of a part that could pick up and move the well plates, which is why the gripper has been included in the final design.

The gripper is mounted on the Z-axis linear actuator, opposite the pin tool. During the pin transfer process, the gripper will be used to retrieve the well plates from the input stack and move them to the proper place for the pin transfer process, then move them to the output stack once the pin transfer process has concluded.

F. Limit Switches

When working with linear actuators, it is important to determine the bounds that the motor can move between. If this is ignored, then the motor may try to move past the bounds of the linear actuator which can damage the motor or the end effectors such as the pin tool or the parallel gripper. Additional hardware referred to as limit switches are necessary to stop the motor from reaching the bounds. To properly store important coordinates within the robotic workspace a calibration function is used where the end effector is placed in the desired position, then the motor hits the limit switches on each of the 3 axes, storing the steps taken to each bound in the microcontroller's memory.

Mechanical limit switches are used which are placed on either end of a linear actuator. These limit switches are supplied with three wires: power, ground, and signal. While not pressed the limit switch signal is normally high providing a 5 volt signal to the GPIO pin. Once pressed the signal goes low indicating that the limit switch has been triggered.

Limit switches are used in calibration to zero out the location of the end effector and then the robot can move to predetermined positions on the robotic workspace relative to those limit switches. While code executes, limit switches are also used as safety features to prevent out of bounds overruns on any of the 3 axes.

G. Fan / Heater

During the operation of chemical screening with the pin tool, the pin tool needs to be washed in order to not contaminate sequential runs. The robot performs up to three wash steps to rid the pin tool of any stray chemicals remaining on the pins. After washing, a 24V fan with an attached heating element is used to quickly dry the pins of the pin tool. This significantly reduces time between each cycle.

H. Board Design

In order to control the system, a 2-layer PCB was designed to house the ATMega 2560 microcontroller and the additional circuitry for proper operation of this microcontroller.

The choice to utilize the ATMega 2560 as the microcontroller to operate this robot was made due to its large number of general purpose input and output pins. The ATMega 2560 has a total of 54 digital I/O pins necessary to precisely control all of the different components making up this robot. Some of the other microcontrollers could not compete with the large number of GPIOs necessary, thus they were quickly overshadowed by the ATMega 2560 microcontroller.

Other than the ATMega 2560, the board consists of an ATMega16U2 auxiliary microcontroller to facilitate USB to serial programming of the ATMega 2560 microcontroller. This chip is commonly used in conjunction with the ATMega 2560 microcontroller to program the ATMega 2560 through the USB to Serial port.

Specification	Value
Pin Operating Voltage	5V
Input Voltage	7-12V
Digital I/O Pins	54
Program Memory	256 kB

Fig. 9. Table showing some of the specifications of the ATMega 2560.

As seen above in Fig 9. ATMega2560 necessitates 5V power input for operation as well as 3.3V for lower level logic. Thus, a NCP1117ST50T3G and a LP2985-33DBVR voltage regulators are used to maintain 5V and 3.3V respectively for the ATMega 2560 microcontroller.

The ATMega 2560 has a maximum output voltage of 5V. As mentioned in Fig. 9., some components used in this robot such as the drying fan and the heating element require 24V which the microcontroller can not provide. Thus, logic level N-channel MOSFETs are included to control the 24V power supply to these components.

As shown in Fig. 9, the board can tolerate an input voltage of 7V-12V. To sufficiently supply power to this board, a DC-DC converter is connected between the 24V power supply and the microcontroller board. This converter provides the necessary power requirements to drive the microcontroller to handle all operation of the robot.

The ATMega 2560 microcontroller chip has 256kB of memory to store the code used to run the robot. The majority of the code space will be consumed by the graphics library which uses ~100kB of memory, leaving roughly another 100kB of memory for the remainder of the program. The remaining memory for the program space is more than enough for the logic and algorithms for controlling the robot.

V. SOFTWARE

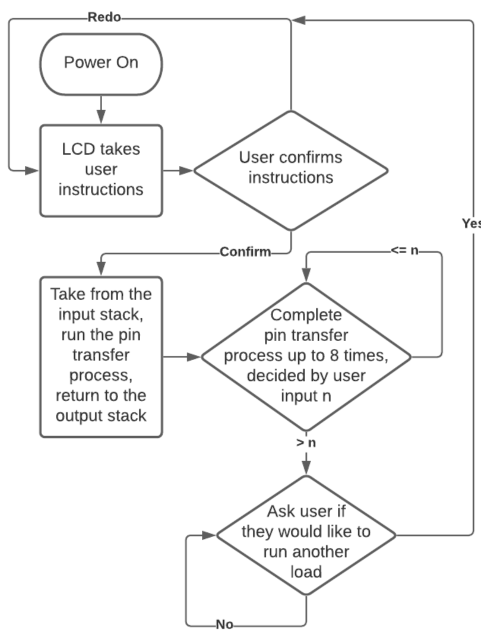

Fig. 10. Block diagram of the code

A. Language

The ATMega 2560 microcontroller can be programmed in a few different programming languages, however, for this robot, it was decided to use the C++ language. The C++ programming language provides a strong foundation for the operation of the robot since it is reliable and fast at run-time and is well-suited for embedded system applications.

B. Libraries

A myriad of different parts were used to make the robot work as intended, so a matching amount of libraries were used. This subsection will contain all the libraries used and why they were necessary.

Adafruit's Adafruit_TFTLCD library was used with the LCD. This library contains all of the functions that allow for text and images to be drawn onto the LCD, so all of the LCD interface was designed using this library.

Adafruit's TouchScreen library was also used with the LCD. This library contains all of the functions that allow a touchscreen to work, so user input is received and processed using this library.

Arduino's Servo library is used to control the parallel gripper. Basic functionality of opening and closing the gripper is all that is needed for the purposes of this robot, which is why this built-in library was used over another one that might have more features.

As mentioned in the *Motor and Motor Drivers* section of this paper, the NEMA stepper motors can be interfaced with the ATMega 2560 microcontroller through the use of a DM542T stepper motor driver. Once the DM542T stepper motor driver is connected between the NEMA motor and the microcontroller board, the AccelStepper library can be used to accurately control the steps taken by the NEMA motor with easy to use C++ function calls. Other than the LCD graphics libraries mentioned earlier in this section, the other majority of the code consists of code directly using the AccelStepper library. Functions such as motor.move(N) and motor.moveTo(N) can be used to take some amount of steps, N, either relative to the current position of the stepper motor or as an absolute position, respectively. To position the pin tool, move the gantry, and perform any other movements of the stepper motors, AccelStepper function calls are made.

For the programming of the HM-10 BLE module, the AltSoftSerial library was used. It is a simple library alternative to SoftwareSerial but uses hardware timers to allow the CPU to respond to interrupts while data transmission and reception takes place. This is useful so that the transmission of Serial data from the HM-10 does not interfere with the interrupt service routines of the limit switches.

C. User Interface

When a user turns on power to the robot, the LCD screen will display a simple interface to allow for configuring the chemical screening cycle including the number of plates used, the number of wash steps, and the depth the pin tool is inserted into the chemical tray. Other than displaying prompts and information to the user, the user is able to input to the program through the touch screen on the LCD.

The main software loop behind the user interface contains little complex logic and is instead a series of sequential function calls. The main LCD loop can be found in Figure 11 below.

```
while (true)
{
   plateNumberSetup();
   int numPlates = plateNumberInput();
   depthSetup();
   int depth = depthInput();
   washStepSetup();
   bool steps[3];
   washStepInput(steps);
   if (paramCheck(numPlates, depth, steps))
      break;
}

--- Pin Transfer Process Begins ---
progressScreen(plateNum, stepName);
--- Pin Transfer Process Ends ---

redo();
```

Fig. 11. LCD software loop.

The while-loop takes user input for the three instructions that the pin transfer process will follow. The three instructions are the number of well plates to be used in the current batch, the depth that the pin transfer tool will be dipped into the well plates, and the wash steps to complete on the pin transfer tool. Each of the instructions has a separate screen created by the respective setup function and each of the instructions receive user input from their respective input function. The while-loop is broken out of, and the robot moves on to performing the pin transfer process, through the if-statement gated by the paramCheck() function. This function displays the user's selected instructions and asks them to confirm that the instructions are correct. If the user confirms, then the if-statement is true and the while-loop is broken out of. If not, the while loop repeats and the user is asked to re-input all of the instructions.

During the pin transfer process, the current plate being used and its location in the whole process will be displayed and updated by the progressScreen() function. Once the pin transfer process is over, the redo() function is called, which creates a screen asking the user if they would like to run another batch of plates. There is no option to decline, since there is no other operation the robot can do and the robot cannot be shutdown through code. If the user decides to continue, the user will be taken back to the beginning of the instruction inputting process.

VI. *Conclusion*

To conclude, this project seeks to satisfy the existing need of research laboratories looking to conduct small scale high-throughput screens or microplate replications. The solution we offer consists of a 3D robotic gantry constructed from open sourced parts, two end effectors which are 1) a parallel gripper for mobilizing microplates 2) a robotic pin transfer tool which transfers small volumes of liquids between microplates in an expandable format, and automated pin tool washing using up to three wash reservoirs with a drying fan to expedite time between cycles.Our robot has improved capabilities over manual pin transfer operations while being more affordable than adapted liquid handling stations. In many cases this robot is more capable than systems exceeding tens of thousands of dollars in cost due to the characteristic that it can both operate the pin tool and move microplates throughout the workspace therefore making it capable of doing multiple cycles before loading/unloading is required by the operator.

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Video Demo Link:

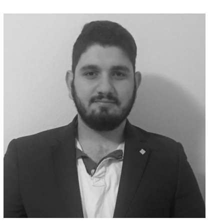
https://youtu.be/QKIKh7ecDXY?t=291

BIOGRAPHY

Chris Clifford is a 23-year old receiving his B.S. in Electrical Engineering with a Bioengineering minor. His chemical screening experience gained during an internship at the Mayo Clinic inspired this senior design project. After graduation, he plans on matriculating into a PhD program in the fall of 2022 where he hopes to continue his research of type 1 diabetes.

Brenden Morton is a 23-year old graduating Computer Engineer who plans to begin a graduate program focusing on Computer Systems and VLSI at the University of Central Florida in the Spring of 2022.

Dominic Simon is a 23-year old Computer Engineering major who will be graduating this fall. He will continue his education at the University of Central Florida in the spring when he begins working toward his doctorate, with research focus on computer vision networks and their applications.



Yousef Abdelsalam is currently a senior at the University of Central Florida. He plans to graduate with his Bachelor's of Science in Computer Engineering in Fall of 2021. Upon graduating, he intends on pursuing a Master's degree and working as a Software Engineer in industry. His interests include advanced data structures and algorithms design, mechatronics, embedded programming, and VLSI.