Electronic Controller Design of a Semi-Automatic Cell Microinjection System

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***Abstract*—Cell microinjection systems are widely used in cell micromanipulation and are integral part of many useful procedures, including drug design, organ development and in-vitro fertilization. Due to the involvement of micro scale movements, manually guiding the process is error prone. This has led to the introduction of semi and fully automated cell microinjection systems. The electronic control system of a cell microinjection system is one of its most critical components. Given its significance, we present a cost-effective design of the electronic controller using off-the-shelf components in this paper. Both the hardware and software aspects of the design are presented along with the testing setup for the controller. The testing results indicate the effectiveness of the proposed controller.**

Keywords—Microbiology, Cell Microinjection, Controller, Hardware and Software.

I. INTRODUCTION

Cell microinjection [1] is a well-known technique in the domain of biological cell micro-manipulation. It is used for the delivery of a small amount of material, such as Protein, DNA, Bio-molecules, in a specific location of cells, such as Nucleus. A holding pipette is used to hold the target cell and an injection/suction pipette is used to pierce the target cell and then insert the considered substance in the cell. Due to the micro scale nature of the whole experiment, it is observed under a microscope. Microinjections have been used since early 1900s to facilitate micromanipulation of cells. Cell microinjection is used in many applications, ranging from delivering drugs to a single cell for the treatment of diseases, like Cancer, and Alzheimer's, developing organs, like heart, lungs and kidney, In-vitro fertilization (IVF) and RNA interference [2].

Due to the microscopic, delicate and safety-critical nature of the cell injection process, it is usually advocated [3] to be carried under a controlled environment instead of manual manipulation. The idea is to use a microscope with a camera and project the experiment view to a computer screen and then conduct the whole experiment using the Micromanipulator/Microinjector controllers, the Micromanipulators and an interactive graphical user interface (GUI) where the operator can see the real-time video on a computer screen. As depicted in Fig. 1, the operator interacts with the system through Micromanipulator/Microinjector controllers as controlling devices. Customized controllers are usually designed as input devices that allow the operator to control the fine movements of the injection pipettes through a precise motorized control system. The jittery effect in human hands can be overcome by deploying dedicated filters. Thus, a semi-automated cell microinjection system provides higher accuracy, which enables the operator to work in delicate narrow spaces with high precision. Moreover, the interactive GUI for microinjection allows the operator to sit in a comfortable position instead of bending over the microscope all the time during the experiment.

There are various fully automated cell microinjection systems [4-6], based on image processing techniques, reported in the literature as well. The idea is to partition the real-time video acquired from a Charge Couple Device (CCD) camera into frames. Then, various digital Image Processing (DIP) techniques are used to identify the location of cell nucleus, and injection and holding pipette from the frame. These coordinates are then used by a motion control algorithm to automatically find the exact path for the cell microinjection process. However, most of the automatic cell microinjections systems are still in the development stage and to the best of our knowledge, there is no complete system that performs the whole process without human guidance. Thus, semi-automatic cell microinjection systems can still be classified as the state-of-the-art systems that are widely used to conduct the safety-critical task of cell injection.

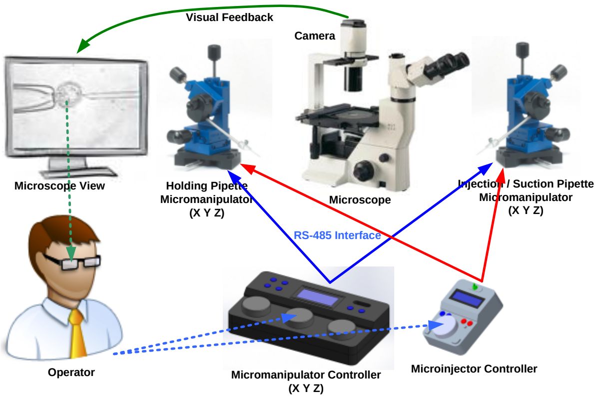

Fig. 1. Semi-Automatic Cell Microinjection System

The focus of this paper is to describe a novel semi-automatic cell microinjection system while focusing on its electronic controller design. To the best of our knowledge, there is no such detailed description of the controller design available in the literature about any semi-automatic cell microinjection system. The distinguishing features of our controller design include its cost-effectiveness, robustness and ease of manufacturing. We also present the testing setup and results for the proposed electronic controller of the cell microinjection system in this paper.

The rest of the paper is organized as follows: Section II provides an overview of the proposed design of the

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electronic controller of a semi-automatic cell microinjection system. Section III describes the hardware design details of the proposed micromanipulator's electronic control module. This is followed by the description of the speed control algorithm of the motor drive unit in Section IV. We describe the test strategy and results of the proposed micromanipulator's electronic control module in Section V. Finally, Section VI concludes the paper.

II. PROPOSED DESIGN METHODOLGY

The main components of a semi-automated cell microinjection system are depicted in Fig. 1. In this section, we describe the proposed methodology to develop the electronic controller of such a system while considering the exact requirements and functionalities of a semi-automated cell microinjection system.

The manipulator interface module is a part of Micromanipulator Controller (MC), which continuously tracks the operator hand movements while simultaneously updating the drives in the manipulator in real-time. The main objective of this module is to sense motion for each degree of freedom (DoF) and transmit them via a RS-485 communication link to the manipulator's electronic control module, which further drives the micromanipulators.

Fig. 2 represents the proposed methodology for the design of the micromanipulator's controller using the dashed boundary. It generally obtains the position coordinates from the operator through rotary knobs that are coupled to optical encoders. The desired parameters can be selected using a set of selection buttons then processes these input commands and sends them to the manipulator via a RS-485 interface. Manipulator interface module also allows the operator to adjust the parameters, like step size, micromanipulator speed and response time. Furthermore, the communication and connectivity link diagnosis checks are performed to ensure the system connections stability and reliability. This module not only provides the inputs to the manipulator, but it also serves as a fault diagnostics system.

A custom-built incremental encoder based system with rotary knobs is developed as an input controlling device for generating the motion commands to move the micromanipulator. These motion sensing devices are directly connected to the controller circuit board that comprehends the commands. The Liquid Crystal Display (LCD) displays the micromanipulator's exact position (x,y,z) and allows the operator to select the operating parameters. There are six buttons, i.e., select, set, zero, home, up and down, in the keypad for dedicated tasks based on their naming.

The input low pass and noise suppressor filters are used to eliminate the unwanted high frequency noise spikes from sensitive signal lines caused by electromechanical inductive loads, such as DC servos or actuators. This unwanted noise may lead to false readings and may even stop the controller operation so it must be suppressed at an early stage. Usually this noise is of high frequency, which can be eliminated by deploying passive low pass filter comprising of a resistor and a capacitor.

CMOS technology based dedicated quadrature decoding chips are specially designed for error free encoder reading and to minimize the computational effort or processing power of the microcontroller/computer. Quadrature clocks derived from optical or magnetic encoders, when applied to the A and B inputs of the chip, are converted to a Clock and an Up/Down direction control. The line filters on the input side of the chip suppresses any unwanted noise coming from the encoder.

The dedicated microcontroller receives the input position commands, corresponding to the (x,y,z) coordinates, from the rotary encoders and transmits them to the manipulator via RS-485 channel. The supervisory microcontroller is responsible for supervising all the tasks ranging from connectivity checks to parameter settings. It has its own operating system, which allows the operator to interact with the micromanipulator controller parameter settings.

The RS-485 bus standard is one of the most widely used communication highways in industrial and instrumentation

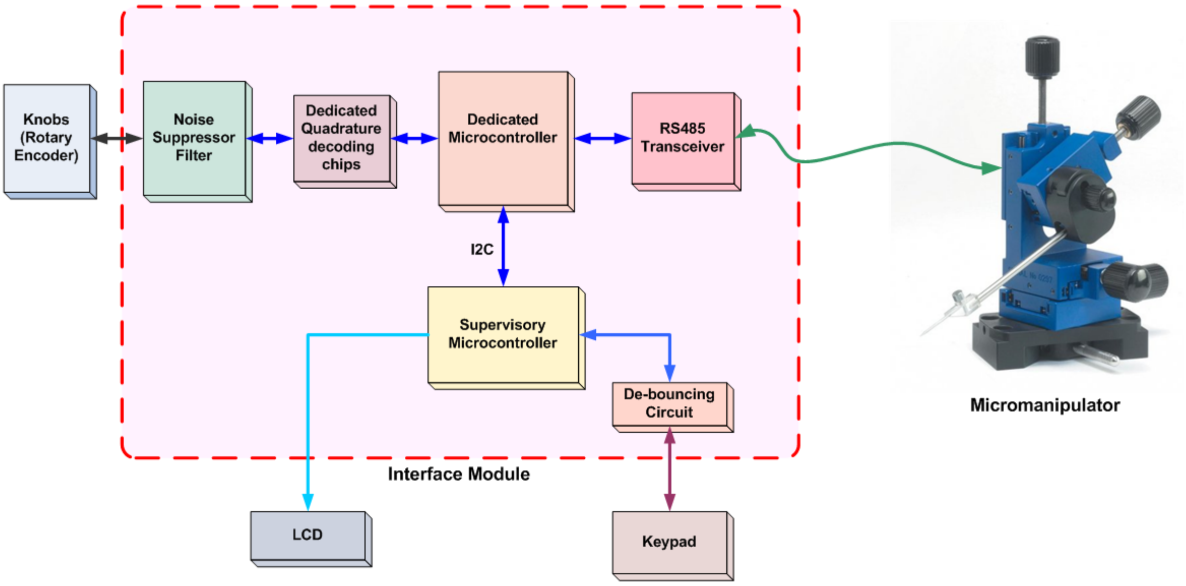

Fig. 2. Proposed Design Methodology

applications. Thus, the differential transmission ability of RS-485 increases noise immunity and ensures a reliable link. The long distance bidirectional communication over a single pair of twisted cables makes the communication more feasible and reliable. It also allows multiple transmitters and receivers to be connected on a single bus in the master-slave topology.

III. HARDWARE DESIGN DETAILS

As depicted in Fig. 3, the electronic control module of the micromanipulator cell injection system mainly comprises of the following main sub-modules:

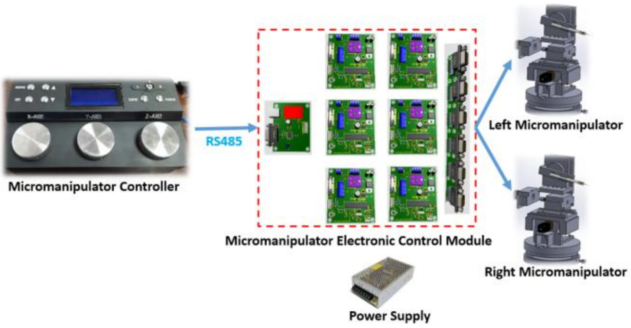

Fig. 3. Electronic Controller of Cell Microinjection System

A. *Motor Drive Unit*

The Motor Drive Unit (MDU) is one of the foremost components of the micromanipulator cell injection system. This is mainly responsible to drive the Micromanipulator motors with high precision. The unit performs the following key tasks:

- Drives the stepper motor.
- Regulates the current flow to the motor.
- Gets inputs from the proximity switches.
- Executes the command instructions and sets the motor speed and position accordingly.
- Communicates with other micromanipulator drive units.

The Motor Drive Unit (MDU) is primarly responsible for driving the actuators of the Micromanipulators. The position coordinate commands are acquired from the Micromanipulator Controller and are forwarded to the MDU's microcontroller for further processing. The microcontroller processes the position coordinates information and calculates the stepper motor drive signals by applying the position control algorithm. The information of each stage axis limit is sent to the microcontroller through proximity sensors after filtering the noise from the signal by passing it through a schmitt trigger and a noise suppressor filter. Finally, the microcontroller sends the instructions to the motor driver to drive the stepper motor in a controlled fashsion. The feedback current of the stepper motor drive is adjusted according to the motor specification. The preferred motor can produce a maximum of 4Ncm torque at 700mA. The current limit is determined by “$I_{limit} = V_{REF} \times 2.5$” as mentioned in the drive datasheet that is used to set the stepping motor current limit. Where V_{REF} is 0.280V, hence a current limit of 700mA is achieved which is ideal to drive the specified motor at maximum performance.

The stepper motor drive can be configured in different stepping modes. A 1/16 micro stepping mode is pertained for the micromanipulation application that allows the motor to complete one revolution in 16 x 200 = 3200 steps with an angular resolution of 360^0 / 3200 = 0.1125 degree / step. The motor drive unit’s PCB artwork and fabricated circuit board is depicted in Fig. 4.

Fig. 4. Motor Drive Unit 3D animated view and fabricated board

B. *Communication Board*

The communication board, depicted in Fig. 5, acts as a communication bridge between the motor drive units and the micromanipulator controller. It mainly converts the RS-485 differential voltage level to the UART TTL voltage level, which is compatible with the microcontroller and vice versa.

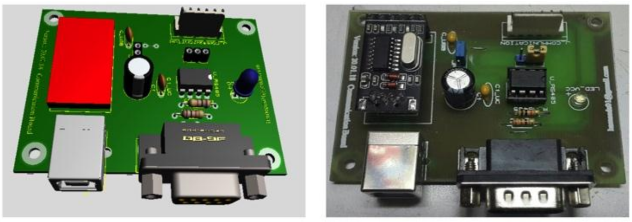

Fig. 5. Communication Board 3D animated view and actual fabricated board

C. *DB9 Connector Board*

A separate connector board, shown in Fig. 6, is used to mount all the six DB9 connectors and the board is fixed inside an enclosure with multiple M3 x 10mm screws for structural strength. Each connector is responsible for driving a micromanipulator stage, which in turn comprises of one precision stepper motor and two proximity switches to sense the extreme points and for system initialization. The DB9 connector has a total of 9 pins, out of which 4 pins are used for motor, 3 pins for proximity switches and thus 2 pins are spare. The purpose of using the DB9 connector is because of its rigid nature and local availability.

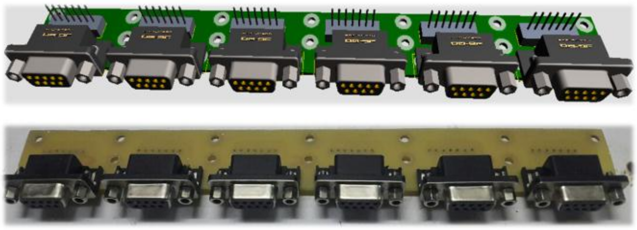

Fig. 6. Connector Board 3D animated view and fabricated board

D. *Micromanipulator Electronic Control Module Enclosure Assembly*

A two-stage enclosure is designed to accommodate all the circuit boards. The enclosure is made with acrylic plastic sheets and painted in a matt black color for a finished look. The communication board, buck converter module and a connector board are housed in the bottom stage as well as all the boards interconnecting wiring harness reside in this stage as depicted in Fig. 7.

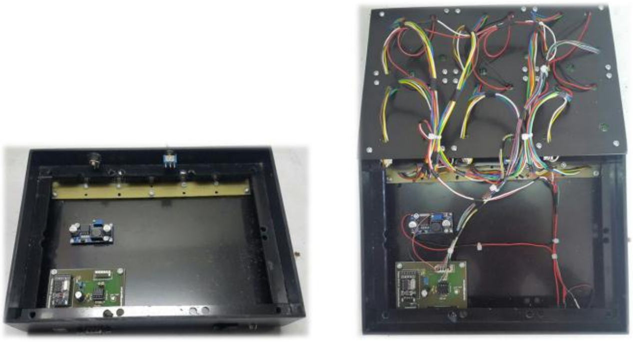

Fig. 7. Bottom Stage of the Microinjector Electronic Control Module Enclosure

The top stage of the enclosure mainly accommodates the motor drive units and interconnecting wiring harness. There are six independent Motor Drive Units (MDUs), out of which 3 MDUs are dedicated for the cell holding pipette micromanipulator and remaining 3 MDUs are dedicated for the cell injection/suction pipette micromanipulator. Each MDU represents a degree of freedom (DoF) of the micromanipulator. All of them share the same communication highways (UART and I2C) as depicted in Fig. 8.

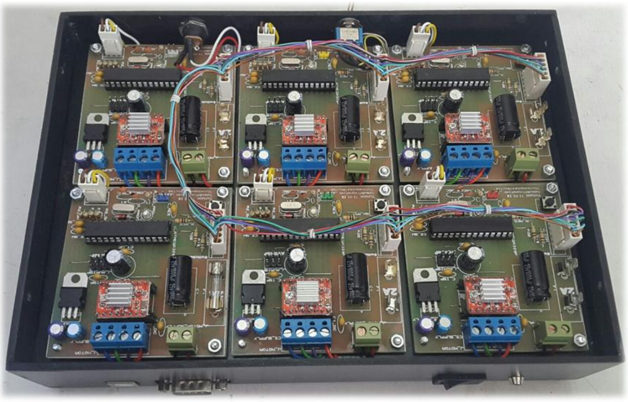

Fig. 8. Top Stage of the Micromanipulator Electronic Control Module Enclosure

The front end of the enclosure has two input communication ports (RS-485 and USB interface), an ON/OFF button and a power indication LED. The RS-485 bus communication standard is used to connect the Micromanipulator Controller directly whereas a USB interface is used to operate the micromanipulator via a PC in case of a fully automatic operation. The backside of the enclosure has six ports, which are directly connected to the left and right micromanipulators. A toggle switch acts as an input selector and allows the operator to switch between the RS-485 and USB interface. A 12V/2A power supply is connected to this enclosure via a DC jack as shown in Fig. 9.

Fig. 9. Front Side of the Micromanipulator Electronic Control Module Enclosure

IV. SPEED CONTROL ALGORITHM

The Matlab Simulink model of the speed control of the motor drive unit is given in Fig. 10. The error or position difference is calculated by subtracting the reference position from the actual or previous position. The time period to complete one complete revolution is computed by multiplying the pulse width with the steps per revolution. Finally, the rotations per minute (RPM) of the motor is obtained by taking the inverse of the time period and multiplying it by sixty seconds.

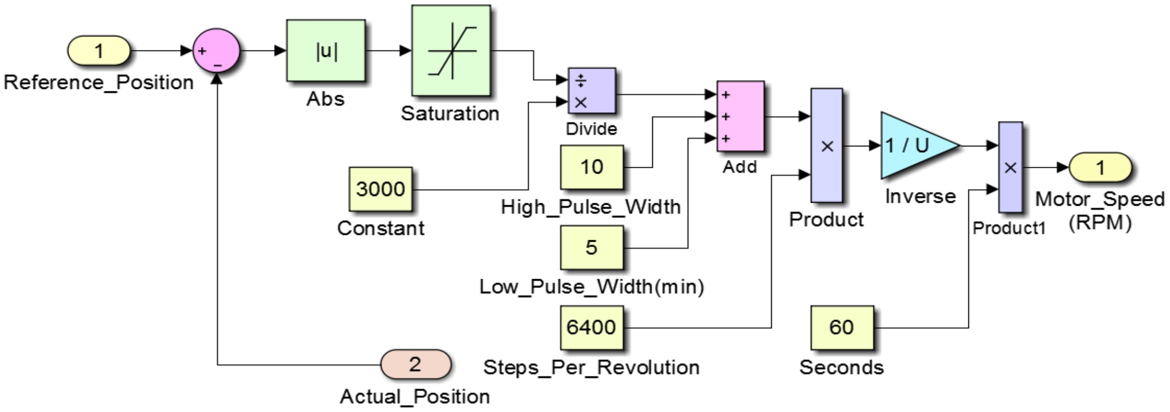

Fig. 10. Speed Control Algorithm

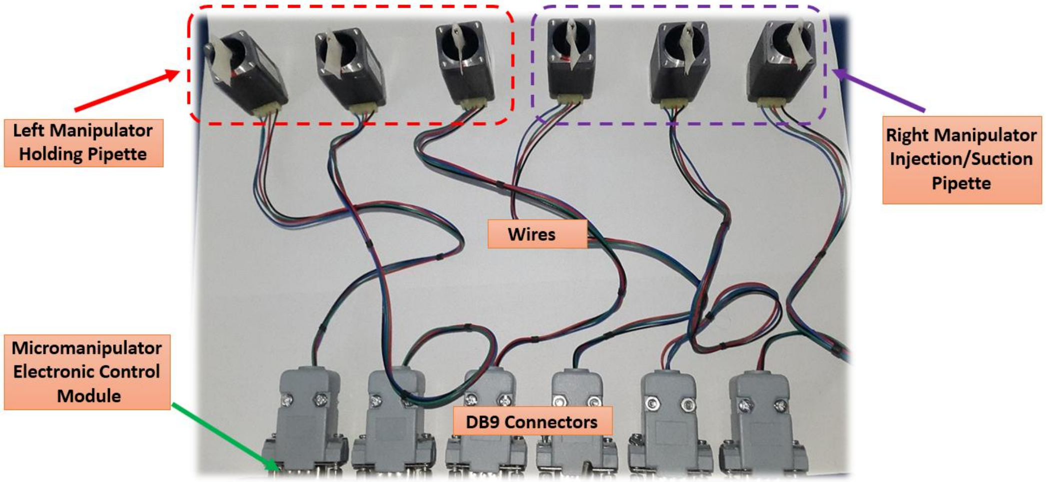

Fig. 12. Test Setup for the Micromanipulator Electronic Control Module

The MDU motor speed control algorithm is given below. The motor speed goes to the maximum value when the position difference is maximum and the motor speed reduces to zero as the motor reaches the desired reference position. The proportional control motor speed algorithm ensures jerk free and smooth motor movement.

Algorithm 1 Algorithm for motor speed control

```
Pulse_Width = 10
Steps_Per_Revolution = 6400
Position_Difference = Reference_Position – Actual_Position
Position_Difference = abs (Position_Difference)
if (Position_Difference > 3000)
    Position_Difference = 3000
else if (Position_Difference == 0)
    Position_Difference = 1
end
Step_Delay  = (3000 / Position_Difference) + 5
Time_Period = (Pulse_Width + Step_Delay) × 1µ × Steps_Per_Revolution
Motor_RPM = 1 / Time_Period × 60
```

The pulse signal that the MDU's microcontroller generates to drive the stepper motor drive is shown in Fig. 11. The pulse width of the pulse signal remains constant, i.e., 10 µs whereas the duration between the pulses is variable, i.e., the Step Delay which is computed through the speed algorithm.

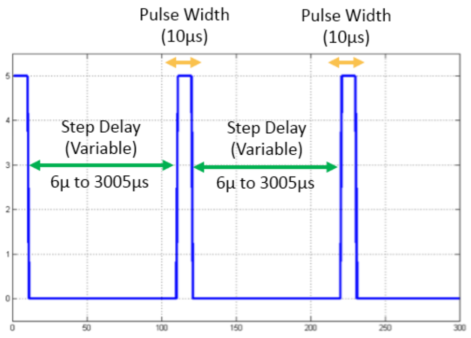

Fig. 11. Stepper Motor Drive Input Pulse Signal.

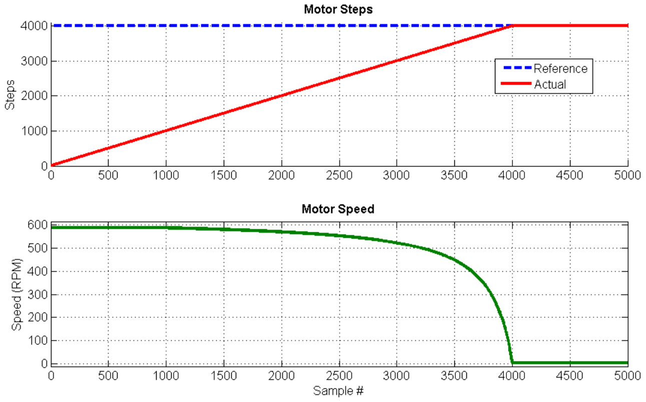

Fig. 13. Analysis of Motor Speed Control Algorithm.

V. TESTING

The test setup for the micromanipulator's electronic control module is depicted in Fig. 12. In total, six stepper motors are connected to it and the feedback current parameters are adjusted according to the motor specification in order to prevent the motor from burning and overheating.

To ensure an error free operation of the micromanipulator drive unit, certain tests have been carried out. The motor drive unit provides the provision to access real-time status of the motor that can be plotted in Matlab for analysis and fine tuning the parameters of the proportional speed control algorithm. Fig. 13 represents the actual real-time motor data plots with a sampling rate of 160Hz (Sampling time = 6.25 ms). In the first test, a constant predefined reference position profile is given to the motor drive unit to see how accurately it drives the motors to track that given profile with minimum error. In Fig. 13, the blue dotted line represents the reference position and the red line shows the actual position of the motor shaft. The green line depicts the motor speed or control effort provided by the motor drive unit to drive the motor in order to track the required reference position. It can be observed that the motor is tracking the reference position within the set time with a very few under and overshoots which demonstrates the successful design of the micromanipulator electronic control module.

VI. CONCLUSIONS

This paper presented the hardware and software design of an electronic controller of the cell microinjection system. The distinguishing features of the proposed design include its cost-effectiveness and the ability to develop it using off-the-shelf components. This makes the proposed design very useful for developing countries and small research centers to develop in-house cell microinjection systems.

ACKNOLOGYMENT

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