Multimodal and Interactive Micro-Biomanipulation:
From Sensors Development, Mind-controlled Interface to
Network-enabled System Integration

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ABSTRACT

Micro-biomanipulation is an advanced technology that aims at the development and application of advanced sensing/imaging and automation technologies to improve processes involving the manipulation (injection, alignment, separation, patch clamp, etc.) and in-vitro mechanical or electronic characterization of biological entities such as individual cells, early embryos, and tissues. In this thesis, we describe a cost-effective, highly efficient, multi-degree-of-freedom, and multi-modal micro-biomanipulation research platform that is in a symbiotic relationship with human operators to improve processes of micro/nano biomechanical characterization and its automation level. As a first step, several important sensors and interfaces for our multi-modal and interactive micro-biomanipulation system are developed, custom designed, and tested, including a position sensitive detector (PSD) based micro/nano position sensing system, a non-invasive Electroencephalography (EEG) interactive interface, and hybrid piezoresistive (HP) based highly sensitive 1-D and 3-D microforce sensors with self-decoupling functions. Beyond that, relying on these developed sensors and interface, a network-enabled system architecture is established and three system applications consisting of (1) musical tuning enhanced micro palpation of biological entities; (2) brain-driven micro-biomanipulation; and (3) a portable radial artery pulse sensing system are successfully conducted and demonstrated. Extensive simulation and experimental results validate that our work is a major step toward a multi-modal and interactive micro-biomanipulation system for varied biomedical applications.
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TABLE OF CONTENTS

LIST OF TABLES ............................................................................................................. v
LIST OF FIGURES .......................................................................................................... v

CHAPTER 1. Introduction .............................................................................................. 1
1.1 Micro-Biomanipulation Technology and Current State-of-the-art ...................... 1
1.2 Our Research in Micro-biomanipulation ............................................................. 4
1.3 Technical Components and Review ..................................................................... 5
1.3.1 Micro/nano-position Sensors ......................................................................... 5
1.3.2 Brain Computer Interface ................................................................................ 10
1.3.3 Microforce Sensors ........................................................................................ 19
1.4 Summary ............................................................................................................... 26

CHAPTER 2. High Precision Micro/Nano Position Sensitive Detector System ........... 28
2.1 Introduction .......................................................................................................... 28
2.2 PSD Interface Circuit Design and Tests ............................................................... 34
2.3 PSD Distortion Rectifying, Mapping and Verification .......................................... 37

CHAPTER 3. Emotiv EEG Based Brain Computer Interface .................................... 41
3.1 Introduction .......................................................................................................... 41
3.2 Emotiv EEG Interfacing, Programming, and Data analysis ............................... 42
3.2.1 Emotiv EEG system ...................................................................................... 42
3.2.2 Practical Strategy for Realizing a Full 2-D Mind Control ............................... 44
3.2.3 Mind Motion Control Analysis Using BCI 2000 ............................................ 46

CHAPTER 4. Durable and Highly Sensitive Micoforce Sensors .............................. 51
4.1 Introduction .......................................................................................................... 51
4.2 Tests on Hybrid Carbon/Ploymer Based Piezoresistive Film ............................ 51
4.3 1-D Microforce Sensors Design, Modeling, and Testing .................................... 57
4.3.1 Design and Dynamic Modeling .................................................................... 57
4.3.2 Static Testing .................................................................................................. 62
4.4 Design and Testing of 2-D and 3-D Microforce Sensors ..................................... 69
4.4.1 3-D Microforce Sensors Design and Simulation ........................................ 69
4.4.2 Parallel Structured and Self-decoupled 3-D Microforce Sensor .................... 74
4.5 Summary ....................................................................................................... 89

CHAPTER 5. Multi-Modal System Integration and Applications ........................... 89
5.1 System Integration and Components ............................................................... 89
5.2 Network-Enabled Communication and Programming ...................................... 90
5.3 Application 1: Musical Tuning Enhanced Micro Palpation System ................. 92
5.4 Application 2: Brain Driven Micro-Biomanipulation ...................................... 97
5.5 Application 3: Portable Radial Artery Pulse Sensing System ....................... 110

CHAPTER 6. Conclusion and Future Work .......................................................... 116
6.1 Conclusions ...................................................................................................... 116
6.2 Future Work ..................................................................................................... 116

REFERENCES ........................................................................................................ 118
### LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 4.1 Self-decoupling Strategy of 3-D microforce Sensor with Parallel Structure</td>
<td>77</td>
</tr>
</tbody>
</table>
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 2.1</td>
<td>Schematic illustration of PSD device</td>
<td>28</td>
</tr>
<tr>
<td>Figure 2.2</td>
<td>Schematic illustration of segmented PSD device</td>
<td>31</td>
</tr>
<tr>
<td>Figure 2.3</td>
<td>Photograph of lateral-effect PSD device</td>
<td>33</td>
</tr>
<tr>
<td>Figure 2.4</td>
<td>Spectral response curve of the lateral-effect PSD device</td>
<td>34</td>
</tr>
<tr>
<td>Figure 2.5</td>
<td>Schematic illustration of 2-D lateral PSD</td>
<td>34</td>
</tr>
<tr>
<td>Figure 2.6</td>
<td>Schematic and Prototype of PSD processing circuit</td>
<td>36</td>
</tr>
<tr>
<td>Figure 2.7</td>
<td>Calibration set-up of PSD sensor</td>
<td>36</td>
</tr>
<tr>
<td>Figure 2.8</td>
<td>PSD 2-D raw output with Pincushion-type radial distortion</td>
<td>36</td>
</tr>
<tr>
<td>Figure 2.9</td>
<td>PSD 2-D mapping result after the distortion rectifying</td>
<td>38</td>
</tr>
<tr>
<td>Figure 2.10</td>
<td>PSD 2-D mapping traces following three laser circles</td>
<td>39</td>
</tr>
<tr>
<td>Figure 2.11</td>
<td>PSD software interface</td>
<td>40</td>
</tr>
<tr>
<td>Figure 3.1</td>
<td>Photograph of Emotiv EEG headset</td>
<td>42</td>
</tr>
<tr>
<td>Figure 3.2</td>
<td>EEG SDK interface</td>
<td>43</td>
</tr>
<tr>
<td>Figure 3.3</td>
<td>EEG headmap</td>
<td>43</td>
</tr>
<tr>
<td>Figure 3.4</td>
<td>Cognitiv control interface</td>
<td>44</td>
</tr>
<tr>
<td>Figure 3.5</td>
<td>Gryo sensor output interface window</td>
<td>45</td>
</tr>
<tr>
<td>Figure 3.6</td>
<td>BCI2000: signal interface</td>
<td>46</td>
</tr>
<tr>
<td>Figure 3.7</td>
<td>BCI2000: Mu and Beta rhythm brain signal map interface</td>
<td>47</td>
</tr>
<tr>
<td>Figure 3.8</td>
<td>BCI2000: Channel frequency signal</td>
<td>47</td>
</tr>
<tr>
<td>Figure 3.9</td>
<td>BCI2000: Mu and Beta rhythm brain signal map for real motion</td>
<td>50</td>
</tr>
<tr>
<td>Figure 4.1</td>
<td>Photograph of hybrid piezoresistive sensing film</td>
<td>51</td>
</tr>
<tr>
<td>Figure 4.2</td>
<td>Thermal drift test of sensor film</td>
<td>52</td>
</tr>
<tr>
<td>Figure 4.3</td>
<td>Environmental exposure test of sensor film</td>
<td>53</td>
</tr>
<tr>
<td>Figure 4.4</td>
<td>Maximal defelection test of sensor film</td>
<td>53</td>
</tr>
<tr>
<td>Figure 4.5</td>
<td>Free vibration test</td>
<td>54</td>
</tr>
<tr>
<td>Figure 4.6</td>
<td>FFT of the free vibration test</td>
<td>54</td>
</tr>
<tr>
<td>Figure 4.7</td>
<td>Different OpAmp circuits tests for the circuit selection</td>
<td>56</td>
</tr>
</tbody>
</table>
Figure 4.1 Flow chart of musical tuning enhanced micro palpation system ........................................ 61
Figure 4.2 Flow chart of brain driven micro-biomanipulation system ........................................ 61
Figure 4.3 Flow chart of musical tuning enhanced micro palpation ........................................ 62
Figure 4.4 Overview of musical tuning enhanced micro/nano palpation system ............................ 63
Figure 5.1 Flow chart of integrated multi-modal manipulation system ....................................... 84
Figure 5.2 Flow chart of brain driven micro-biomanipulation system ........................................ 84
Figure 5.3 Flow chart of musical tuning enhanced micro palpation system .................................. 85
Figure 5.4 Overview of musical tuning enhanced micro/nano palpation system ............................ 88
Figure 5.5 88-key piano keyboard .............................................................................................. 88
Figure 5.6 Experimental set-up of musical tuning enhanced micro palpation ................................ 89
Figure 5.7 Software interfaces for musical tuning enhanced micro palpation ............................... 89
Figure 5.8 Results of musical tuning enhanced micro palpation ................................................. 90
Figure 5.9 Force profile when adding Ethanol to the surface of bio-sample .................................. 91
Figure 5.10 Overview of brain driven micro-biomanipulation system.......................... 100
Figure 5.11 System architecture of brain-driven micro-biomanipulation ................... 102
Figure 5.12 Mind controlled 2-D motion ...................................................................... 104
Figure 5.13 Errors of mind controlled 2-D motion....................................................... 104
Figure 5.14 Mind controlled 2-D path tracking ............................................................. 105
Figure 5.15 Experimental set-up for brain driven micro-biomanipulation............... 106
Figure 5.16 Results of brain driven micro-biomanipulation ................................. 108
Figure 5.17 Gyro sensor output signals from head movement .............................. 109
Figure 5.18 Full 2-D mind motion control triggered by Gyro sensor signals......... 109
Figure 5.19 Portable radial pulse sensor design............................................................ 112
Figure 5.20 Portable radial pulse sensor prototype.................................................... 112
Figure 5.21 Radial pulse sensor signals ...................................................................... 113
Figure 5.22 Radial pulse sensor signals analysis ....................................................... 113
Figure 5.23 Referenced pulse signal ......................................................................... 114
Figure 5.24 Radial pulses signal form our sensor ...................................................... 114
CHAPTER 1

INTRODUCTION

1.1 Micro-Biomanipulation Technology and Current State-of-the-art

Manipulation is an important action to move, arrange, operate or control a target by human hands or electronic/mechanical tools. Micro-biomanipulation is a technology that aims at the development and application of advanced sensing/imaging and automation technologies to improve processes involving the manipulation (injection, alignment, separation, etc.) and in-vitro mechanical or electronic characterization of biological entities such as individual cells, early embryos, and tissues. Such processes are currently depending on labor-intensive operations that suffer from low consistency, low efficiency, and the need for extensive operator training. For instance, most embryonic injections are performed manually. Geneticists often require at least one year of training to become proficient at skills required for injection and such manual techniques are very time consuming. Furthermore, the average success rate of a manual injection is disappointingly low. The reason for this is that successful microinjection is greatly dependent on moderate injection forces, specific injection speeds, and accurate localization methodology during manipulation [1]. Several recent studies have addressed how to improve microinjection performance on varied cells or embryos with automated force and position feedback. Nelson et al. introduced their work on the development of a microrobotic cell manipulation system, which employs a multi-axis capacitive force sensor with a tip diameter of 5-µm to characterize the mechanical properties of murine Zona Pellucida [2]. In another project, the mechanical behavior of the Zebrafish embryo...
chorion was quantified using an un-modeled piezoelectric force sensor with a resolution of 14.5 \( \mu \text{N} \). The attached injection pipette had a radius of 14.6 \( \mu \text{m} \) and measured force ranged from 100 to 800 \( \mu \text{N} \) with an average penetration force of 737 \( \mu \text{N} \) [3]. Zhang et al. [4] presented a micrograting-based force sensor integrated with a surface micromachined silicon-nitride probe for effective and efficient penetration and injection of Drosophila embryos. In Zhang’s work, they found an average penetration force of 52.5 \( \mu \text{N} \pm 13.2\% \) with a 30-\( \mu \text{m} \) diameter silicon tip. In addition, Shen et al. have developed a minimally invasive sensing system to improve injection efficiency and to evaluate the force profiles during microinjection of Drosophila embryos [5]. The system consists of an \textit{in-situ} polyvinylidene fluoride piezoelectric microforce sensor with a resolution in the range of micro newton. The sensor can be integrated with a glass pipette with an ultra-sharp injecting tip diameter of 1.685-\( \mu \text{m} \) and 0.0147\( \pi \) in tip conical angle. Using this novel-sensing system, close monitoring of the behavior of micro force during the injection is achieved. The measured force profiles have been used for rapidly optimizing injection performance using Drosophila embryos.

In addition, recent developments in micro-biomanipulation technologies have greatly promoted micro/nano mechanical characterization on multi-scale biological entities such as cells, embryos, tissues, and organs. These technologies deepen our understanding of biomechanical properties and mechanical bio-markers as well as allow us to mathematically model the physical character or growth, morphology, interaction functions that relate to development, disease, pathological and physiological functions. Lanero et al. [6] have studied the mechanical properties of encapsulated Saccharomyces cerevisiae yeast cells by performing force measurements through atomic force
microscopy [7]. These measurements have helped to quantitatively evaluate cell rigidity with and without encapsulation [6]. It has been shown that there are links among the structure, mechanical properties, the phenotype behavior, and the function of cells or embryos in their microenvironments [8]. A better understanding of these processes could have far-reaching implications. Additional studies have shown that mechanical properties can affect cell growth, differentiation, locomotion, adhesion, signal transduction, and gene expression [9]. The key to addressing all of these issues is to study the motion and force-induced conformational changes of biological material by precision measurements through micro-biomanipulation processes [9]. Additionally, Janmey and McCulloch [10] surmised that biomechanical forces should be viewed as major regulators of cell structure and function. They also found that mechanical properties of cells are essential to the mechanisms by which cells sense external forces and transmit information to the cell interior or other cells. Lim et al. [11] experimentally investigated the structure-mechanical property–function relationship of cells and biomolecules to understand their important physiological implications as well as to establish possible connections to human diseases. They found that biomechanical measurement and characterization could provide quantitative insight to the physical changes of cells and biomolecules with the progression of certain human diseases such as cancer.

Currently, the most popular ways to conduct micro/nano mechanical characterization of biological entities are to use atomic force microscopy (AFM) or fragile silicon based microforce sensors and position detectors to limitedly quantify measurements and process results offline. However, these high-cost micro-biomanipulation systems usually lack
degrees of freedom and have low efficiency during manipulation. Moreover, they lack intelligence and are not user-friendly systems for complex biomedical research.

### 1.2 Our Research in Micro-biomanipulation

Aiming at research challenges and needs, the focus of this project is the development and application of durable, cost-effective, multi-degree-of-freedom, and high performance sensing and automation technologies to efficiently improve processes of micro/nano biomechanical characterization and automation level of micro-biomanipulation. Impact areas include cancer genetics and drug discovery, developmental and birth defect research, and neuroscience, which rely on manual manipulations that currently suffer from high cost, low success rate, low consistency, and low efficiency. We are developing several micro/nano scale sensors/actuators and their dynamic models with robust and adaptive control methodologies, combined with the multi-sensor feedbacks (micro-force, position, velocity, vision, audio, thermal, etc.). In addition to pursuing advanced sensing and automation technologies for micro-biomanipulation, our research also explores how micro-biomanipulation systems and designs can be enhanced by leveraging and integrating our understanding of human cognition, multi-modal perception, and action-control behavior. Finally, a novel, efficient, multi-modal micro-biomanipulation research platform that is in a symbiotic relationship with human operators will be established. The platform helps facilitate studies in micro/nano-biomanipulation and mechanosensing in a cost-effective, intelligent, and interactive manner.
Our research will be conducted in several phases. This thesis presents the first phase work of our research. In this phase, sensors and interfaces for multi-modal and interactive micro-biomanipulation system were developed, custom designed, and tested, including a position sensitive detector (PSD) based micro/nano position sensing system, a non-invasive Electroencephalography (EEG) interactive interface, and novel 1-D and 3-D hybrid piezoresistive microforce sensors. Based on the developed sensors and interfaces, network enabled system integration was finished and three system applications consisting of (1) musical tuning enhanced micro palpation of biological entities; (2) brain-driven micro-biomanipulation; and (3) portable radial artery pulse sensing system were demonstrated. Extensive simulation and experimental results validate the performance of this work, which will be a major step toward a multi-modal and interactive micro-biomanipulation system for varied biomedical applications. To introduce our work, we first review the current technical status of three major components: micro/nano position sensors, EEG based brain computer interfaces, and microforce sensors.

1.3 Technical Components and Review

1.3.1 Micro/nano Position Sensors

Due to their simplicity and low-cost, resistive strain gauges are widely used for position control of piezoelectric actuators. Resistive strain gauges can be integrated into the actuator or bonded to the actuator surface. Other application examples can be found in references [12-15]. Resistive strain gauges are constructed from a thin layer of conducting foil laminated between two insulating layers. With a zig–zag conductor pattern, strain gauges can be designed for high sensitivity in only one direction, for
example, elongation. When a strain gauge is elongated, the resistance increases proportionally. Metal foil strain gauges are the simplest and lowest cost sensor considered in this review. Due to their size, strain gauges are suitable for mounting directly on to actuators or stages with a range from 10 to 500 µm. Although strain gauges can be calibrated to achieve higher accuracy, it is reasonable to consider an error of 1% FSR (Full scale range) due to drift and the indirect relationship between the measured strain and actual displacement. [16]

In 1954, a visiting researcher at Bell Laboratories, C.S. Smith, demonstrated that ‘exceptionally large’ resistance changes occur in silicon and germanium when subjected to external strain [17]. This discovery was the foundation for today’s semiconductor piezoresistive sensors that are now ubiquitous in applications such as integrated pressure sensors and accelerometers [17]. Compared to metal foil strain gauges that respond only to changes in geometry, piezoresistive sensors exhibit up to two orders-of-magnitude greater sensitivity. In addition to their high strain sensitivity, piezoresistive sensors are also easily integrated into standard integrated circuit and MEMS fabrication processes which is highly advantageous for both size and cost. The foremost disadvantages associated with piezoresistive sensors are the low strain range (0.1%), high temperature sensitivity, poor long-term stability, and slight non-linearity (1%) [18]. The elimination of these artifacts requires a more complicated conditioning circuit than metal foil strain gauges; however, integrated circuits are now available that partially compensate for non-linearity, offset, and temperature dependence. A typical integrated piezoresistive strain sensor consists of a planar n-doped resistor with heavily doped contacts. When the sensor is elongated, the average electron mobility increases in that direction, reducing resistance
[18]. The effect is reversed during compression, or if the resistor is p type. Since the piezoresistive effect is due to changes in the crystal lattice, the effect is highly dependent on the crystal orientation. Piezoresistive sensors are smaller than metal foil strain gauges and can be bonded to actuators that are only 1 mm long with a range of up to 1 µm. Although the resolution of piezoresistive sensors is very high, nonlinearity, temperature sensitivity, and inexact matching limit absolute accuracy. An error budget of 1% FSR is typical. Although strain sensors require contact with the actuator or flexural components, they do not introduce forces between the reference and moving platforms. Thus, in this sense, they are considered to be non-contact. In addition to their actuating role, piezoelectric transducers are also widely utilized as high-sensitivity strain sensors [19-25]. In the flexional sensor, the applied force and resulting strain are perpendicular to the polarization vector [16].

Capacitive sensors are the most commonly used sensors in short-range nanopositioning applications. They are relatively low cost and can provide excellent linearity, resolution and bandwidth [26]. However, due to the electronics required for measuring the capacitance and deriving position, capacitive sensors are inherently more complex than other sensors such as resistive strain gauges. Larger ranges can be achieved with the use of an encoder-style electrode array [27]. All capacitive sensors work on the principle that displacement is proportional to the change in capacitance between two conducting surfaces. Capacitive sensors can be constructed relatively simply, provide the highest resolution over short ranges, are insensitive to temperature, and can be calibrated to an accuracy of 0.01% FSR. However, during general purpose applications where the sensor is not calibrated after installation, alignment errors may limit accuracy to 1% FSR [16].
MEMS capacitive sensors operate on a similar principle to their macro scale counterpart discussed in the previous section. However, due to their small size, a more complicated geometry is required to achieve practical values of capacitance. The comb type sensor is a common variety found in a number of nanopositioning applications, for example [28, 29]. In this configuration, the total capacitance is approximately proportional to the overlap area of each electrode array.

The basic comb sensor can be improved by employing a differential detection. Here, two sets of excitation electrodes (terminals 2 and 3) are driven 180 degrees out of phase. Thus, at the central position, the potential at terminal 1 is zero. This configuration provides a higher sensitivity than the basic comb sensor and is used extensively in devices such as accelerometers and gyroscopes [26, 30]. To increase the range of motion beyond a single inter-electrode spacing, the configuration uses withdrawn electrodes to form a capacitive incremental encoder [31–33]. The slider can move freely in either direction, limited only by the length of the excitation array. As the slider moves horizontally, the induced voltage at terminal 1 alternate between the phase of terminals 2 and 3. A second array is typically used to create a quadrature signal for ascertaining the direction of travel. This approach can provide a large travel range with high resolution but the decoding electronics is more complicated and performance is sensitive to the separation between the arrays. If the two arrays can be overlain vertically, the capacitance can be increased while difficulties with array separation are reduced [34, 35].

Since 1960, the meter length standard has been defined by optical means. This change from a physical standard arose after Michelson invented the interferometer, which improved the accuracy of length measurements from a few parts in$10^7$, to a few parts
in $10^9$ [36]. The operating principle of a Michelson interferometer is split a laser beam into two paths, one that is reflected by a moving mirror and another reflected by a stationary mirror. The movement of the mirror is measurable by observing the fringe pattern and intensity at a detector. If the distance between the paths is an integer number of wavelengths, constructive interference occurs. The displacement of the moving mirror, in wavelengths, is measured by counting the number of interference events that occur. The phase of the interference, and hence the displacement between interference events, can also be derived from the detector intensity. Duke and Gordon from Hewlett-Packard based modern displacement interferometers on the Heterodyne interferometer developed in 1970 [37]. Although similar in principle to a Michelson interferometer, the heterodyne interferometer, overcomes many of the problems associated with the Michelson design. Most importantly, the phase sensitivity remains constant regardless of path length. Compared to other sensor technologies, laser interferometers provide an unprecedented level of accuracy. Stabilized interferometers can achieve an absolute accuracy exceeding 1 pm, or in other words, better than 1 μm.

A linear encoder consists of two components, the reference scale and the read-head. The read-head is sensitive to an encoded pattern on the reference scale and produces a signal that is proportional to position. Either the scale or the read-head can be free to move; however, the scale is typically fixed since the read-head is usually lighter. Light from a laser diode is selectively reflected from the scale onto a photodetector. As the read-head is moved relative to the scale, peaks in received power correspond the distance between the reflective bars. In between the peaks, the position can be estimated from the received
power. Rather than partial reflection, other gratings contain height profiles that modulate the proximity and thus received power [38].

1.3.2 Brain Computer Interfaces

A brain computer interface (BCI), also referred to as a brain machine interface (BMI), is a hardware- and software-based communications system that enables humans to interact with their surroundings, without the involvement of peripheral nerves and muscles, by using control signals generated from electroencephalographic activity. Less than a decade ago, hardly anyone could have predicted that attempts to build direct functional interfaces between brains and artificial devices, such as computers and robotic limbs, would have succeeded so readily, and in the process has led to the establishment of a new area at the frontier of systems neuroscience. Born as a highly multidisciplinary field, basic research on brain–machine interfaces (BMIs) has moved at a stunning pace since the first experimental demonstration in 1999 that ensembles of cortical neurons could directly control a robotic manipulator [39]. Since then, a continuous stream of research papers has kindled an enormous interest in BMIs among the scientific community and the lay public [40]. BCI research, which was confined to only three groups 20 years ago and only six to eight groups 10 years ago, is now a flourishing field with more than 100 active research groups all over the world studying the topic [41]. The number of articles published regarding neural interface technology has increased exponentially over the past decade [42]. This interest stems from the considerable potential of this technology for restoration of motor behaviors in severely handicapped patients [40].
A BCI is an artificial intelligence system that can recognize a certain set of patterns in brain signals. This is usually performed in five consecutive stages: signal acquisition, preprocessing or signal enhancement, feature extraction, classification, and control [43].

The signal acquisition stage captures the brain signals and may perform noise reduction and artifact processing. The preprocessing stage prepares signals in a suitable form for further processing. The feature extraction stage identifies discriminative information in recorded brain signals. Once measured, signals are mapped to vectors containing effective and discriminant features from the observed signals. The extraction of such information is a very challenging task. Brain signals are mixed with other signals coming from brain activities that overlap in both time and space. Moreover, the signal is not usually stationary and may be distorted by artifacts such as electromyography (EMG) or electrooculography (EOG). The feature vector must also be of a low dimension, in order to reduce feature extraction stage complexity, but without relevant information loss. The classification stage classifies the signals considering the feature vectors. The choice of good discriminative features is therefore essential to achieve effective pattern recognition, in order to decipher the user’s intentions. Finally, the control interface stage translates the classified signals into meaningful commands for any connected device, such as a wheelchair or a computer.

BCIs use brain signals to gather information to determine user intentions. To that effect, BCIs rely on a recording stage that measures brain activity and translates the information into tractable electrical signals. Two types of brain activities can be monitored: (i) electrophysiological and (ii) hemodynamic. Electro-chemical transmitters exchanging information between neurons and generate electrophysiological activity. The neurons
generate ionic currents, which flow within and across neuronal assemblies. The large variety of current pathways can be simplified as a dipole conducting current from a source to a sink through a dendritic trunk. These intracellular currents are known as primary currents. Conservation of electric charges dictates that the primary currents are enclosed by extracellular current flows, which are known as secondary currents [44].

Electrophysiological activity is measured by electroencephalography, electrocorticography, magneto encephalography, and electrical signal acquisition in single neurons. A hemodynamic response is a process in which the blood releases glucose to active neurons at a greater rate than in the area of inactive neurons. The glucose and oxygen delivered through the blood stream results in a surplus of oxyhemoglobin in the veins of the active area, and a distinguishable change of the local ratio of oxyhemoglobin to deoxyhemoglobin [45]. These changes can be quantified by neuroimaging methods such as functional magnetic resonance and near-infrared spectroscopy. These kinds of methods are categorized as indirect, because they measure the hemodynamic response, which, in contrast to electrophysiological activity, is not directly related to neuronal activity [46].

BCI can be noninvasive can be used on severely or partially paralyzed patients to reacquire basic forms of communication and to control neuroprostheses and wheelchairs [47–49] have successfully used in Non-invasive approaches. Despite the outstanding utility of non-invasive approaches in BCI applications, motor recovery has been limited because of a need for brain signals with a higher resolution. Invasive recording methods such as electrocorticography or intracortical neuron recording were introduced in an effort to improve the quality of brain signals monitored by BCIs. Most researchers agree
that movement restoration through prostheses with multiples degrees of freedom can only be achieved through invasive approaches [40]. It is unlikely that the power of non-invasive modalities will be enhanced in the near future. Accordingly, it would appear that invasive modalities are indispensable for accurate neuroprostheses control. Nevertheless, this issue is not yet entirely clear and some researchers disagree with this conjecture. Contrary to established opinion, Wolpaw [41] suggested that performance in multidimensional control might be independent of the recording method. Further refinements of recording and analysis techniques will probably increase the performance of both invasive and non-invasive modalities. However, the latest studies in neuroprostheses control appear to indicate that invasive modalities have inherent advantages in neuroprosthesis control applications [42]. Invasive modalities require implanted microelectrode arrays inside the skull that involves significant health risks and restricts their use to experimental settings. Two invasive modalities are found in BCI research: 1) electrocorticography, which places electrodes on the surface of the cortex, either outside the dura mater (epidural electrocorticography) or under the dura mater (subdural electrocorticography), and 2) intracortical neuron recording which implants electrodes inside the cortex. Several issues had to be addressed, before such techniques become suitable for long-term applications. First, tissue acceptance of the microelectrode must be addressed. Electrodes with neurotropic media have been proposed that promote neuronal growth to improve biocompatibility [50]. Perhaps, the future of nanotechnologies would be to develop nano-detectors implanted inertly in the brain, providing a definite solution to the problems associated with long-term invasive applications. Second, a link between the microelectrode and external hardware that uses
wireless technology is needed to reduce the risks of infection. Wireless transmission of neuronal signals has already been tested in animals [51]. Third, continuous stress caused by plugging and unplugging the recording system may lead to tissue damage or system failure [48]. Many kinds of BCI are being developed.

EEG measures electric brain activity caused by the flow of electric currents during synaptic excitations of neuronal dendrites. EEG is extremely sensitive to the effects of secondary currents [52]. EEG signals are easily recorded in a non-invasive manner through electrodes placed on the scalp. For this reason, EEG is by far the most widespread recording modality. However, it provides very poor quality signals, as the signals have to cross the scalp, skull, and many other layers. This means that EEG voltages at the electrodes are weak, hard to acquire and of poor quality. This technique is moreover severely affected by background noise generated either inside the brain or externally over the scalp [46].

Magnetoencephalography (MEG) is a non-invasive imaging technique that registers the brain’s magnetic activity by means of magnetic induction. MEG measures the intracellular currents flowing through dendrites, which produce magnetic fields that are measurable outside of the head [53]. The neurophysiological processes that produce MEG signals are identical to those that produce EEG signals. Nevertheless, while EEG is extremely sensitive to secondary current sources, MEG is more sensitive to primary currents [44]. The advantage of MEG is that magnetic fields are less distorted by the skull and scalp than electric fields [54]. Magnetic fields are detected by superconducting quantum interferences devices, which are extremely sensitive to magnetic disturbances produced by neural activity [55]. The electronic equipment that measures magnetic brain
activity is cooled to almost −273 degrees Celsius to facilitate sensor superconductivity. MEG requires effective shielding from electromagnetic interferences. The electronic equipment must be installed inside a magnetically shielded room, which attenuates the effects of magnetic fields from external sources. MEG provides signals with higher spatiotemporal resolution than EEG, which reduces the training time needed to control a BCI and speeds up reliable communications [56]. MEG has also been successfully used to localize active regions inside the brain [57]. In spite of these advantageous features, MEG is not often used in BCI design because MEG technology is too bulky and expensive to become an acquisition modality suitable for everyday use. In 2005, Lal et al. [58] presented the first online MEG-based BCI. Although further studies have followed [59–62], MEG-based BCIs, as compared to EEG-based BCIs, are still at an early stage.

Electrocorticography (ECoG) is a technique that measures electrical activity in the cerebral cortex by means of electrodes placed directly on the surface of the brain. Compared to EEG, ECoG provides higher temporal and spatial resolution as well as higher amplitudes and a lower vulnerability to artifacts such as blinks and eye movement [63]. However, ECoG is an invasive recording modality, which requires a craniotomy to implant an electrode grid, entailing significant health hazards. For that reason, the first studies on ECoG were with animals. Early studies involving animals evaluated the long-term stability of the signals from the brain that ECoG could acquire [64-67]. Results showed that subdural electrodes could provide stable signals over several months. Nevertheless, the long-term stability of the signals acquired by ECoG is currently unclear. More recent experiments with monkeys have shown that ECoG can perform at a high level for months without any drift in accuracy or recalibration [68]. The hand positions
and arm joint angles could be successfully decoded during asynchronous movements. These studies have also developed minimally invasive protocols to implant the ECoG probes [69]. In humans, ECoG has been used for the analysis of alpha and beta waves [70] or gamma waves [71, 72] produced during voluntary motor action. With regard to the use of ECoG in BCIs systems, Levine et al. [73] designed a BCI, which classified motor actions based on the identification of the event-related potentials (ERP) using ECoG. Leuthardt et al. [74] showed for the first time that an ECoG-based BCI could provide information to control a one-dimensional cursor, as this information is more precise and more quickly acquired than by EEG-based BCIs. Some years later, Schalk et al. [75] presented a more advanced ECoG-based BCI, which allowed the user to control a two-dimensional cursor. The results of all these studies suggest that it might be more feasible for people with severe motor disabilities to use ECoG-based BCIs for their communication and control needs.

Intracortical neuron recording is a neuroimaging technique that measures electrical activity inside the gray matter of the brain. It is an invasive recording modality in which microelectrode arrays are implanted inside the cortex to capture spike signals and local field potentials from neurons. The first attempts in the intracortical neuron recording field were made in animals. Multi-electrode arrays were used to record neural activity from the motor cortex in monkeys or rats during learned movements [76-78]. These initial studies have shown that intracortical neuron recordings can indicate the nature of a movement and its direction. These studies do not reveal whether the same patterns are present when the real movements are not made. Taylor and Schwartz [79] experimented with rhesus macaques, which made real and virtual arm movements in a computer. Results suggested
that the same patterns persisted. The most recent studies with monkeys investigated the control of prosthetic devices for direct real-time interaction with the physical environment [80–83]. With regard to the application of intracortical neuron recording in BCI systems, microelectrode arrays such as the Utah Intracortical Electrode Array (UIEA) have been reported as a suitable means of providing simultaneous and proportional control of a large number of external devices [84]. In addition, Kennedy et al. [85] employed cortical controls signals to design a BCI that allowed users to control cursor movement and flexion of a cyber-digit finger on a virtual hand.

Functional Magnetic resonance imaging (fMRI) is a non-invasive neuroimaging technique, which detects changes in local cerebral blood volume, cerebral blood flow, and oxygenation levels during neural activation by means of electromagnetic fields. FMRI is generally performed using MRI scanners, which apply electromagnetic fields of strength in the order of 3T to 7T. The main advantage of fMRI is high spatial resolution. For that reason, fMRI has been applied for localizing active regions inside the brain [86]. However, fMRI has a low temporal resolution of about 1 or 2 seconds. Additionally, the hemodynamic response introduces a physiological delay from 3 to 6 seconds [87]. The fMRI appears unsuitable for rapid communication in BCI systems and is highly susceptible to head motion artifacts. In BCI systems, fMRI is typically used to measure the Blood Oxygen Level Dependent (BOLD) during neuronal activation [88]. Although the BOLD signal is not directly related to neuronal activity, a correspondence between both does exist [89]. The use of fMRI in BCI technology is relatively recent. Before the emergence of real-time fMRI, brain activity recording by fMRI has traditionally taken a long time. The data acquired by fMRI techniques were processed offline and the results
only became available after several hours or even days [90]. FMRI-based BCIs are now possible, thanks to the development of real-time fMRI [87, 91, and 92]. The information transfer rate in fMRI-based BCIs is between 0.60 and 1.20 bits/min [93]. Non-clinical fMRI applications are not expected because fMRI requires overly bulky and expensive hardware.

Near Infrared Spectroscopy (NIRS) is an optical spectroscopy method that employs infrared light to characterize noninvasively acquired fluctuations in cerebral metabolism during neural activity. Infrared light penetrates the skull to a depth of approximately 1–3 cm below its surface, where the intensity of the attenuated light allows alterations in oxyhemoglobin and deoxyhemoglobin concentrations to be measured. Due to shallow light penetration in the brain, this optical neuroimaging technique is limited to the outer cortical layer.

In a similar way to fMRI, one of the major limitations of NIRS is the nature of the hemodynamic response, because vascular changes occur a certain number of seconds after its associated neural activity [94]. The spatial resolution of NIRS is quite low, in the order of 1 cm [95]. Nevertheless, NIRS offers low cost, high portability, and an acceptable temporal resolution in the order of 100 milliseconds [96]. A NIRS system consists of a light source, a driving electronic device, a light detector, signal processing devices, and a recording device. The light source is an infrared emitting diode (IRED) placed in direct contact with the scalp. The driving electronic device is an electronic circuit that controls the IRED in order to modulate the light. The light detector is a photodiode placed right next to the light source. Signal processing devices include amplifiers and filters that process the electrical signal and reduce the noise due to ambient
light. The recording device is often a personal computer or any other device that digitalizes, stores, and displays the electrical signal. Although NIRS is relatively new measurement modality, NIRS promises to be a potent neuroimaging modality for future applicability to BCIs [94, 97]. NIRS provides now a low information transfer rate of about 4 bits/min but this might be increased in the future [98]. This neuroimaging modality might be a good alternative to EEG, as neither conductive gel nor corrosive electrodes are required. Nevertheless, communication speeds in NIRS-based BCIs are limited due to the inherent delays of the hemodynamic response. Some studies have already demonstrated the feasibility of mental task detection through NIRS-derived optical responses [99-101].

1.3.3 Microforce Sensors

In micromanipulation, the magnitude of forces may range from 1 $\mu$N down to 1 $n$N and below. Such small forces pose challenge on the design and construction of sensors that can provide measurements with high resolution and high accuracy. To meet these requirements, semiconductor and micro-fabrication techniques have been applied to build sensitive and stable sensing elements. Currently, the types of widely used as micro force sensors are strain gauge, piezoelectric, capacitive, and optical sensor. An understanding of the performance of these sensors (such as their fabrication procedure and resolution, etc.) is necessary for their utilization in various application environments. [102]

A strain gauge has the property that its resistance changes under physical pressure or mechanical work. When a strain gauge is strained or deflected, its internal resistance changes (and remains changed) until its original shape is restored. The change in
resistance is measured by an electric circuit (e.g., Wheatstone bridge). Strain gauges are usually made of a metal foil or of a semiconductor material. The resolution of a conventional strain gauge is usually above 1 \( \mu N \). Semiconductor strain gauges are characterized by a much larger gauge factor than that of the metal type, which translates into a higher sensitivity (usually in the order of more than 100 times). Tanikawa \textit{et al.} \cite{103} designed a force sensor, which has two strain gauges made from semiconductor resistor. It has a designed resolution of 0.5 \( nN \). Menciassi \textit{et al.} \cite{104} developed a symmetrical method to place strain gauges on a microgripper structure. Four strain gauges are mounted in two pairs on the microgripper, with each pair located at a flexure joint: one strain gauge of the pair measures compression while the other one measures tension.

Another way of placing a strain gauge is to attach it to the fixed jaw of a gripper. This configuration is usually seen in the use of piezoresistive force sensor, e.g., in \cite{105} and \cite{106}. (Piezoresistive force sensors belong to the category of semiconductor strain gauge; they exhibits good sensitivity due to the piezoresistive effect of silicon.) A piezoresistive cantilever is bonded to one side of the gripper. When the gripper is in contact with an object, the gripping force is detected from the deformation of the cantilever. The advantage of this approach is that the sensor so placed directly measures the force on the jaw of the gripper. It is also possible to vary the measurement range and the resolution of the force sensor by selecting a cantilever with appropriate mechanical properties. The more stiff the cantilever, the higher the precision in the measurement. With proper arrangement of strain gauges, multi-axis micro force sensing can be achieved. Arai \textit{et al.} \cite{107} designed a triaxial micro-force sensor, and fabricated it by silicon micromachining.
There are other types of multi-axis micro force sensor built with strain gauges, such as a sensor for measuring contact forces at the tip of a microsurgical instrument in three dimensions [108] (resolution: 0.5 mN, range: 1 N), a three-axis sensor mounted on a micro manipulator system in a micro-teleoperated system [109] (resolution: 0.3 mN), a three-axis tactile sensor for micro-material characterization [110], a six-axis sensor for measuring force and moment acting on boundary particles in a turbulent liquid flow [111], and a multi-axis sensor for measuring the instantaneous ground reaction force produced by insects [112] (resolution: 0.5 mN). Currently, there exist several commercial strain gauges for micro-scale force measurement. A miniaturized S-beam force sensor (model number SJR025), made by Mark-10r, can measure tensile and compressive load, with a range of 1 N and a resolution of 0.5 mN. SensorOne manufactures a cantilever-type piezoresistive force sensor (model: AE-801) with a range of 120 mN. The resolution of its analog output strongly depends on the noise level of amplifier and the bridge configuration of the sensor. Since force sensing based on strain gauge requires measurement of deformation in the gauge, there must be enough compliance in the strain gauge to provide sufficiently large deformation. These large deformations are undesirable because they limit the frequency response of the measuring system and introduce geometric changes into the force-measuring path, which inevitably leads to measurement errors (e.g., nonlinearity and hysteresis). This problem, however, does not exist in another type of sensor, namely, the piezoelectric force sensors.

A piezoelectric force sensor generates a voltage when a force stresses it. The material for making this type of sensor exhibits high stiffness comparable to steel. Therefore, the deformation of the sensing element in a piezoelectric force sensor is much smaller than in
other measuring systems (e.g., in a strain gauge). This property greatly reduces the geometric changes caused by the measurement. For example, in the measurement of mechanical force response of a living cell, the force applied to the membrane results in large deformation of the cell, which may lead to greater error in force measurement. In order to resolve this problem, not only does the cell need to be more stiff (by chemical fixation, for example), but a rigid sensing device (including the manipulator and the sensor) is necessary. The high rigidity of piezoelectric force sensors also provides an inherently high natural frequency and short rise time. This permits the measurement of extremely fast events. The most widely used piezoelectric force sensor is fabricated with the polyvinylidene fluoride (PVDF) film. PVDF is an idea-sensing device because of its responsiveness to a wide range of frequencies, high mechanical strength, and high sensitivity. Kim et al. [113] designed and fabricated a PVDF force sensor, which can be integrated into a tweezers type microgripper. This PVDF sensor enables the microgripper to sense gripping forces with magnitudes under 100 $\mu N$. A PVDF sensor can be directly installed on the grasping surface of a gripper (as in [113] and [114]). It can also be integrated into a probe-tip to detect the contact force exerted at the tip. This configuration is useful for measuring contact force or injection force in micromanipulation. For example, Kim et al. [115] bonded a microinjection pipette on the tip of a PVDF force sensor, and used it as a one-axis force sensor (with a resolution in the order of $\mu N$) to characterize the mechanical properties of the membrane of zebrafish eggs. Shen et al. [116] designed a two-axis PVDF force sensor with sub-micron resolution based on the same approach. In each direction, a beam of PVDF is used to detect the force. This two-
axis micro-force sensor has been used to detect impact forces during lifting of micro mirrors.

A key characteristic of piezoelectric sensors is that the electrical signal generated by the piezo element decays rapidly after the application of force. This renders piezoelectric sensors unsuitable for detecting static force (as demonstrated in [117]). To measure static forces, strain gauges are suitable, while another type of sensor, namely, the capacitive force sensor, offers an alternative [102].

Capacitive force sensors make use of change in capacitance between two metal plates due to application of force. When a force is applied, the distance between the plates or the effective surface area of the capacitor changes. Since the capacitance $C$ between two parallel plates is proportional to $1/d$ (where $d$ is the distance between the plates), a change in $A$ (area of the plate) or $d$ will cause a change in capacitance. The applied force can then be calculated based on measurement of such change in capacitance by a bridge circuit.

Compared to strain gauges and piezoelectric force sensors, capacitive force sensors are more stable and sensitive, and exhibit no hysteresis [118]. Capacitative force sensors have been successfully used for investigation of properties of biological materials through force measurement. In the work reported by Sun et al. [2], a two-axis capacitive force sensor was used to study the mechanical properties of mouse zona pellucida during fertilization. The device is capable of sensing forces applied to the cell, as well as tangential forces resulted from the miss-aligned probe.

For cell manipulation with capacitive sensing, a pipette (such as injection pipette [119] or holding pipette [2]) is usually attached to the probe tip of the sensor. However, pipette displacement reveals one disadvantage of capacitive force sensor. The signals in
capacitive displacement sensing are proportional to the surface area of the elements. Surface area decreases very drastically with miniaturization [120]. This leads to limited measurement range for capacitive force sensors. To solve this problem, electrostatic micro actuators are integrated to enable the sensor to operate in an active servo mode, in which system stiffness is modulated using force compensation [121]. When the micro force is actively served, the electrostatic forces generated by the electrostatic micro actuators within the sensor balance and externally applied force. The movable parts of the sensor are maintained in the equilibrium position, making the system a regulator system. Force measurement is obtained by interpreting the actuation voltages. This method effectively increases the dynamic range of a force sensor. For example, the dynamic range of a capacitive force sensor with three μm springs can be increased from five μN (normal mode) to 35 μN (active servo mode) [121]. In capacitive force sensors, piezoelectric force sensors, and strain gauges, the sensing elements measure through contact the strain of the micromanipulator (such as a gripper or probe). However, there may be cases where the manipulator is too small (compared to the miniaturized force sensor) for the force sensor to be integrated into the manipulator. For such cases, non-contact sensing is needed. Optical sensor is an effective method for non-contact force measurement [100].

For micro force sensing, the technique of optical beam deflection shows great potential, due to its electromagnetic immunity and high resolution (down to nN) [122]. A primary advantage of this technique is that it can be used in a non-contact mode if certain structural members within a micro-device can be designed with appropriate stiffness so that they deflect a measurable amount without compromising the structural integrity of
the overall device. One of the applications of this technique is the atomic force microscope (AFM). An AFM mainly consists of a manipulator integrated with nano-scale force sensing to characterize features on various kinds of surfaces (from the micrometer scale to the nanometer scale). Besides its capabilities as a nano-scale characterizer, AFM can also be used as a nano-scale robot, i.e., for modifying surfaces or manipulation structures such as nano-particles and nano-rods [123-129]. As the cantilever (with a sharp tip at its end) in an AFM scans over a sample at distances on the order of a few nanometers, inter-atomic forces (in the order of nN) occur between the tip and the sample. This small force is reflected in the deflection of the cantilever, and is measured by a laser diode and a photodiode.

There are a couple of major sources of error associated with this technique. Due to the reflection of the substrate surface, the output of quad-photodiode detector is changing when the tip approaches the substrate surface. The reflection of the substrate surface changes the original tuning position and creates a false force signal. Moreover, there may exist mounting error of photodiode detector in practice. This can cause crosstalk between normal and lateral signals of the photodiode. Li et al. [130] developed a force compensation method to resolve these problems. The effect of compensation permits the measurement of 3D interaction forces between cantilever tip and the manipulated objects.

In certain applications, force-sensing using an AFM has limitations in terms of accuracy and range. When an AFM is used in aqueous mediums where biological cells survive, the reflection and refraction of the transmitted light may reduce the accuracy the measurement. Another limitation is that the photodiode can only detect deflections within a small range. As a result, force measurement range of AFM sensor is restricted. Each of
the four types of force sensing techniques discussed above has its advantages and disadvantages. Certain techniques are often more suitable in a particular application compared to others. Strain gauges are easy to use, but their proper placement is crucial to obtaining good results. Piezoelectric force sensors are best at detecting forces that very quickly, but are not useful for static force measurement. Capacitive force sensors are more sensitive than the above two types, but their measurement range is usually limited. Finally, AFM has the highest sensitivity and may be used in non-contact force detection, but it has rather limited measurement range and requires additional force signal compensation.

1.4 Summary

In this thesis, we address developing a cost-effective, high efficient, multi-degree-of-freedom, and multi-modal micro-biomanipulation research platform that is in a symbiotic relationship with human operators to improve processes of micro/nano biomechanical characterization and its automation level. As a first step, several important sensors and interfaces for our multi-modal and interactive micro-biomanipulation system are developed, custom designed, and tested, including a position sensitive detector (PSD) based micro/nano position sensing system, a non-invasive Electroencephalography (EEG) interactive interface, and hybrid piezoresistive based highly sensitive 1-D and 3-D microforce sensors with self-decoupling functions. Beyond that, relying on these developed sensors and interface, a network-enabled system architecture is established and three system applications are successfully conducted and demonstrated.
The reminder of this thesis is organized as follows. Chapter 2 describes the developed PSD based micro/nano position sensor. Chapter 3 presents the EEG based BCI interface. Chapter 4 states the designed microforce sensors. Chapter 5 presents the system integration, network communication and the applications. Chapter 6 concludes our work.
CHAPTER 2
HIGH PRECISION MICRO/NANO POSITION SENSITIVE DETECTOR SYSTEM

2.1 Introduction

The position sensitive detector (PSD) based position sensing interface unit is one of the important features of our system. The unit can monitor and display the motion control commands in real time. The sensing results can greatly help to evaluate the system performance and to understand manipulation behavior of operators.

A position sensitive device (PSD) is a sensor capable of tracking the location of a light beam on its surface. It consists of either one or two resistive layers (One-dimensional or two-dimensional PSD) placed on the surface of a high-resistive substrate (see Figure 2.1 for basic PSD schematics)

![Figure 2.1: Schematics of a one dimensional PSD chip. The device consists of three semiconductor layers of which only the top one is used to determine the position. In two-dimensional devices, the bottom layer is used in an analog manner to gather positional information.](image)

The principle of operation of a PSD is quite simple: If the top P-layer is stimulated with a beam emitted from a light source, an electric charge is generated that is proportional to
the light intensity. This potential in the resistive layer causes photocurrents to flow between the spot of stimulation and the two electrodes on either end of the layer. Due to the uniformity of the resistive layer $I_1$ and $I_2$ are inverse proportional to the distance between the location of the potential (i.e. spot of light) and the respective electrode:

$$ U = R \cdot I \quad (2.1) $$

$$ I = \frac{U}{R} \quad (2.2) $$

Since the resistive layer is as mentioned uniform, the following equation holds true

$$ R = \delta \cdot \frac{l}{A} \quad (2.3) $$

$$ R \propto l \quad (2.4) $$

using equations 2.1 to 2.4 we can conclude:

$$ I \propto l \quad (2.5) $$

$I$ : occurring current [A]

$U$ : generated potential [V]

$R$ : resistance of the photo-active area [Ω]

$l$ : distance between light spot and respective electrode [mm]

$A$ : cross-sectional area of the resistive layer [mm²]

$\delta$: specific electrical resistance of resistive layer material [Ω·m]

Output currents of resistive layer can then be derived by:

$$ I_1 = \frac{L_x - \Delta x}{L_x} \cdot (I_1 + I_2) = \frac{L_x - \Delta x}{L_x} \cdot (I_0) \quad (2.6) $$

$$ I_2 = \frac{L_x + \Delta x}{L_x} \cdot (I_1 + I_2) = \frac{L_x + \Delta x}{L_x} \cdot (I_0) \quad (2.7) $$
\[
\frac{I_1-I_2}{I_1+I_2} = 2 \frac{\Delta x}{L_x}
\]  
(2.8)

\[
\frac{I_1}{I_2} = \frac{L_x-2\Delta x}{L_x+2\Delta x}
\]  
(2.9)

$I_1, I_2$ : Output currents of resistive layer [A]

$I_0$ : Total photo-current ($I_1 + I_2$) [A]

$L_x$ : Total length of active area (resistive layer) in between electrodes [mm]

$\Delta x$ : Distance of light stimulated spot from center of the PSD [mm]

There are two basic types of PSD which are Lateral PSD and segmented PSD. Both types are produced in one- and two-dimensional versions. They have some characteristics in common but others that are unique and superior compared to other optical tracking devices: They offer outstanding positional resolution for a wide spectral range of light used to stimulate the PSD. They also respond to changes almost without delay even without any additional biasing efforts that can be performed to reduce the delay.

Segmented PSDs are common substrate photo-diodes that are divided in segments and separated by a gap (see Figure 2.2). This gap also referred to as “dead region” is a section of the chip that is not affected by any form of light stimulating it. The gaps are necessary to electrically isolate the PSD segments. Segmentated PSDs are produced with either two (one-dimensional) or four (two-dimensional) segments.
Figure 2.2: Schematic illustration of a two-dimensional segmented PSD. When light hits the active surface photo-currents occur in each segment. Those currents can be measured at the respective electrodes attached to each segment to determine the position.

The principle of operation again is rather simple. When a beam of light hits the surface of the chip photo-currents are generated as explained previously. Currents are proportional to the intensity of the light the segment is exposed.

Therefore, the relative position of the beam can be expressed as:

\[ X = \frac{(I_B + I_D) - (I_A + I_C)}{I_A + I_B + I_C + I_D} \]  
\[ Y = \frac{(I_A + I_B) - (I_C + I_D)}{I_A + I_B + I_C + I_D} \]

X: relative beam position on X-axis [mm]

Y: relative beam position on Y-axis [mm]

\( I_A, I_B, I_C, I_D \): photo-currents measured in PSD segment noted in the indices (see Figure 2.2).

The positions in X and Y directions can easily be calculated based on the photocurrents measured in each segment. The achievable resolution (i.e. minimal detectable change in beam position) with this type of PSD is approximately 0.1μm. However, several
restrictions need to be fulfilled in order to get correct results:

- the beam has to overlap all segments at all times
- the diameter of the focused beam has to be larger than the gap in order to reach the active area and generate an output
- the beam’s intensity distribution must the uniform since photo-currents in the respective segments are proportional to intensity

The second type of PSD tested for this project is usually referred to as lateral PSD. This type is also available in one- and two-dimensional realizations. The one-dimensional version is shown in the previous section (Figure 2.1). The chip used for 2D position detection is manufactured in a similar way. The only difference is that the bottom-layer is also equipped with two electrodes. This second layer works exactly the same way as the top layer. The only difference is that the electrodes mounted on the bottom layer are aligned in a 90° angle relative to the top layer to represent the Y-axis (see figure).

We have chosen a high-resolution lateral effect PSD chip (OSI Optoelectronics DL-4S) for building up the position sensing interface unit. The PSD sensor has many advantages for example high resolution (0.5µm), fast response (Rise Time: 80ns), direct coordinate output, high sensitivity and precision, wide dynamic range, wide spectral response, radial distortion and noises. As shown in Figures 2.3-2.5, the chosen lateral effect PSD is with 4mm×4mm active area with a widely band width. The lateral effect PSD is a 2-D sensor capable of tracking the location of a laser beam shot on its surface [190]. In a lateral effect PSD, the relative two-dimensional position of e.g. a laser beam on the active surface of the chip can be expressed as:
\[ X = \frac{(I_{x1} - I_{x2})}{I_{x1} + I_{x2}} \]  

(2.12)

\[ Y = \frac{(I_{y1} - I_{y2})}{I_{y1} + I_{y2}} \]  

(2.13)

Where \( x \) is the relative position of laser spot on \( X \)-axis and \( y \) the relative position on \( Y \)-axis. \( I_{x1}, I_{x2}, I_{y1}, I_{y2} \) are photocurrents measured in the direction indicated by their subscript. The major advantage of the lateral type is the fact that the accuracy of the output is not affected by the laser spot profile or its intensity distribution. The positional resolution of about 0.5\( \mu \)m is sufficient for monitoring our biomanipulation processes in micro scale. Another outstanding property of this type is the position linearity over relatively large areas of the active surface of the chip. This is important for our task since it allows us to keep the error at a low level during the mapping and compensation process. The related signal conditioning circuit of the PSD can be employed and found in [190].

Figure 2.3: Photograph of lateral effect PSD chip.
2.2 PSD Interface Circuit Design and Tests

Before an actual calibration task could be implemented, a signal processing circuit (Figure 2.6) was designed and set up in order to test the properties of the chosen PSD chips (i.e. position linearity over active chip area, positioning sensitivity etc.). Since the active chip area of the PSD is comparatively small (i.e. 4mm × 4mm) measurements had to be performed by applying high precision tools to position the laser beam over the surface. Therefore, a Sutter high precision probe was used to produce sufficient accuracy to calibrate the chip. The purpose of this board is simply to process the PSD sensor’s raw output to be able to determine the relative 2D position of the beam on the chip’s surface.
The design can be structured into three functional stages. In the first stage, the output signal of the four PSD electrodes is amplified using operational amplifiers. The second and third stages are used to perform the computations needed to be able to determine the spot position. In the second stage, summing amplifiers and differential amplifiers are occupied to generate the input signals for the divider ICs (third stage).
Figure 2.6: (a) Schematics of the test board circuit used to experiment with lateral PSD. The design can be structured into three functional stages: amplification, subtraction/adding, and divider. (b) Prototype of the circuit board.

Figure 2.7: Calibration set-up of PSD sensor
2.3 PSD Distortion Rectifying, Mapping and Verification

To map the PSD position sensing system (PSD and the interface circuit), as seen in the Figure 2.7, a 670 nm laser diode was fixed on the 3-D micromanipulator moving stage perpendicular to the PSD surface. The moving stage allows it to position the laser beam in 2 Degree of freedom (DOF) \((x; y)\) over the PSD surface with high precision (moving resolution: 1µm/steps) The PSD chip was fixed on a floating, shock absorbing Newport workbench together with a 3-D micromanipulator moving stage to eliminate influence of e.g. operator movement and vibrations. Based on this setup, the mapping experiments on the middle active area (3×3 mm²) of the PSD chip were conducted. The results of the complete 2-D area scanned by the laser beam along \(X\) and \(Y\) directions are shown in Figure2.8. In Figure 2.8, to cover the whole chip area, 22 lines were scanned (11 lines for \(X\) and 11 lines for \(Y\)). Note that, in order to match two Cartesian coordinates (one on the PSD chip surface and one is on the position sensing software interface) a rotation matrix \[
\begin{bmatrix}
cos \theta & -sin \theta \\
sin \theta & cos \theta
\end{bmatrix}
\] has been used to correct mismatch between two coordinates, where \(\theta = 0.008\) is the calibrated mismatch angle between two coordinates. As shown in the figure, the PSD output clearly shows a pincushion-type radial distortion caused by the integration process of PSD chip and its interface circuit. To improve accuracy of the PSD mapping, we found a modified polynomial mapping method to effectively rectify such distortion. After rectifying the rotated \(x\) and \(y\) values, the rectified values \(x_{rect}\) and \(y_{rect}\) is the final mapping values of the PSD position sensing interface unit. As the radial distortion in the location of a PSD output point is proportional to the distance from the output point to the geometrical center of PSD, our modified polynomial mapping method
rectifies the distortion in each PSD output point by considering the distance-dependent coefficients into the following equations:

\[ x_{\text{rect}} = x - \beta xy^2 \]  \hspace{1cm} (2.14)

\[ y_{\text{rect}} = y - \gamma yx_{\text{rect}}^2 \]  \hspace{1cm} (2.15)

where \( \beta \) and \( \gamma \) are constants. The best values \( \beta = \gamma = 0.0731 \) for two constants were found empirically. To evaluate the mapping performance after the coordinate rotation and distortion rectifying, the laser diode mounted at the 3-D precision moving stage was used to generate various laser traces onto the selected middle active area (3mm×3mm) of the PSD. In Figure 2.9, the rectangular loops show the position mapping result. In the area around the center of the PSD, a good result could be achieved. On the outer regions, only small deviation can be found that originates from the mapping method. Note that the dust on PSD causes some small bumps on the traces.

Figure 2.8: PSD 2-D raw output with Pincushion-type radial distortion.
Figure 2.9: PSD mapping traces following a laser rectangular loops (after distortion rectifying).

Figure 2.10 demonstrates three circular traces with different radii (0.25mm, 0.5mm, and 1mm) output by the mapped PSD interface unit. In the figure, the blue traces represent real laser traces controlled by the moving stage. The red paths are the mapping results output by the PSD interface unit. The results demonstrate good mapping performance. All calibration paths are displayed using a PSD software interface shown in Figure 2.11.
Figure 2.10: PSD mapping traces following three laser circles (after distortion rectifying).

Figure 2.11: PSD software interface
CHAPTER 3

EMOTIV EEG BASED BRAIN COMPUTER INTERFACE

3.1 Introduction

This chapter describes the development of a 16-channel Emotiv Electroencephalographic (EEG) interfaced with a PSD sensor and a micromanipulator and EEG data analysis using BCI2000.

Studies to date show that humans and animals can learn to use electroencephalographic activity (EEG) recorded from the scalp, electrocorticographic activity (ECoG) recorded from the cortical surface, or signals recorded within the cortex (neuronal action potentials or local field potentials (LFPs)) to control the movements of a cursor or other device in one or two dimensions[131,132,39,133,134,79,135-142,81]. Three-dimensional (3D) control has been reported only for intracortical signals (i.e. neuronal action potentials) in monkeys [133,141]. Both actual movement and movement imagery are accompanied by changes in the amplitudes of certain EEG rhythms, specifically 8–12 Hz mu rhythms and 18–30 Hz beta rhythms. These changes are focused over a sensorimotor cortex Pfurtscheller et al [143] in a manner consistent with the homuncular organization of this cortical region [144]. Thus, people could learn to use EEG for two-dimensional (2D) movement control. Wolpaw and McFarland [137,138] began a training process by using for control the mu- and/or beta-rhythms changes normally associated with left-hand or right-hand movement imagery and extended this strategy to 3D control by beginning the training process from the mu- and/or beta-rhythm changes normally associated with left-hand, right-hand or foot movement imagery [142,145]. These results show that EEG can support 2D and even 3D movement control.
3.2 Emotiv EEG Interfacing, Programming, and Data analysis

3.2.1 Emotiv EEG system

The EEG device used in this project is made by Emotiv. It is a high resolution, multi-channel, wireless neuroheadset. The Emotiv headset shown in Figure 3.1 uses a set of 14 sensors plus 2 references to tune into electric signals produced by the brain to detect the user’s thoughts, feelings and expressions in real time. The Emotiv headset allows accessing to raw EEG data [146].

Emotiv EEG system offers a Direct API that has access to all Emotiv detection suite inputs and controls, as shown in Figure3.2, including training, profile management and gyro outputs. A user also has access to EEG data in real time and can be programmed in C++ and other compatible languages (.e.g. .NET (VB.NET, C#), Java. The system includes “Testbench” software that can record, play back, analyses EEG data and spectra in real time, produce EDF, and CSV data formats compatible with most analysis packages. The EEG has real-time compatibility with OpenViBE, BCI2000, and BioExplorer.

Figure 3.1: Photograph of Emotiv EEG headset EPOC.
Emotiv EEG has 14 EEG channel names based on the International 10-20 locations are: AF3, F7, F3, FC5, T7, P7, O1, O2, P8, T8, FC6, F4, F8, and AF4. Their locations are shown in Figure 3.3

Figure 3.2: Emotiv Control Panel SDK interface.

Figure 3.3: EEG headmap for the Emotiv EEG
This experiment makes use of a program called “Cognitiv Control” in the Software Development Kit (SDK). The software interface is shown in Figure 3.4, for the original program, a user moves a cube up to four motions by imagining movement of the cube in the screen after training. The cube moves to the direction based on an operator’s wish. Speed of the cube movement is dependent on the intensity of signal generated form operator’s brain waves. Based on programming using the SDK, the direction and intensity are extracted and processed, and then sent to a server PC for driving the micromanipulator. The sampling rate of the EEG system is 128 times per second where the wave frequency generated from the human brain is usually less than 60 Hz.

3.2.2 Practical Strategy for Realizing a Full 2-D Mind Control

Due to limitations on the resolution of EEG equipment, it is hard for a user to control motion in 3-D and even full 2-D motion accurately after a short training time. Since the
EEG has gyro sensors for detecting head motion, we found a practical solution that the Gyro sensor output can be used as a trigger for realizing a full 2D motion control without long training times. The idea is that a user can switch the manipulation direction by just changing head movement direction. In this manner, a user only need to think about moving in one direction and then switch directions using gyro signals that correspond to head motions in four directions. That is, head moving forward changes the mind control direction to moving up in a 2-D plane, head moving backward represents the moving down, head turning left switches to moving left, and head turning right corresponds to mind motion to right. The interface window of the gyro sensor outputs is shown in Figure 3.5.

Figure 3.5: Software Interface of the gyro sensor outputs.
3.2.3 Mind Motion Control Analysis Using BCI2000

In order to understand the relationship between the motion and brain wave to improve manipulation efficiency, we use a software program called BCI2000 as an analysis tool. BCI2000 is a general-purpose system for brain-computer interface (BCI) research. It can also be used for data acquisition, stimulus presentation, and brain monitoring applications. The BCI2000 system is available free for non-profit research and educational purposes. It has been provided to about 600 laboratories around the world [147].

BCI 2000 can be used to analyze the raw data from EEG to study the relationship between brain waves and motion. For example, the results in Figure 3.6 can be easily used to compare the power of brain signals in the all channels and frequencies. BCI 2000 can also focus on processing the intensity of the brain signal and location of specific frequencies, as shown in Figure 3.7, and allows the user to focus and study a specific channel with different frequencies as shown in Figure 3.8.

Figure 3.6: BCI2000: Signal interface
The mind controlled (or volitionally controlled) motion commands (i.e. up, down, left, and right movements) are usually generated by using a weighted combination function. The function includes the brain activity amplitudes over sensorimotor cortex [137]. It is
widely known that these movements are controlled by a mu rhythm around 12Hz or/and a beta rhythm around 22Hz over sensorimotor cortex. Amplitudes of two rhythms change (decrease from the amplitude in the absence of movement) when the volitional movement is produced (produces event-related desynchronizations (ERDs) [148]. To use the EEG system for volitional 2-D motion control in our work, we have investigated an operator’s brain EEG activity map when the volitional movements are generated. Figure 3.9 shows scalp topographical color maps of $R^2$ values for 12 Hz and 22 Hz. The $R^2$ values are between up movement control and rest (a), down movement control and rest (b), left movement control and rest (c), and right movement control and rest (d). Note that the results are achieved by interfacing the EEG system with the BCI2000 [149] and using “P3signalProcessing” for signal processing, “StimulusPresentation” for application. Then load parameter is “InitialMuSession.prm”. The operator completed 20 sessions for each movement. A session consisted of five 5-second “seeing directional arrow” separated by 2-second or 4-second breaks (rest). As shown, the different volitional movement has the different map (that may include eye movement activity). The preliminary results will motivate us to correlate brain activities with the manipulation behaviors in the future work.
Figure 3.9: Topographical color maps of $R^2$ values for requested 12Hz and 22Hz: (a) between up movement control and rest; (b) between down movement control and rest; (c) between left movement control and rest; and (d) between right movement control and rest.
CHAPTER 4
DURABLE AND HIGHLY SENSITIVE MICROFORCE SENSORS

4.1 Introduction

A highly sensitive, robust, and low-cost microforce sensor is developed for the bio-
manipulation system. The sensing material is a hybrid carbon/polymer-based 
piezoresistive film with thickness of 0.127\text{mm}, width of 3\text{mm}, and length of 12\text{mm} in the 
Figure 4.1. It has the advantages compare with other sensors that include high sensitivity 
($\mu\text{N}$), thin (0.005\text{inch}), light, low cost, wide temperature range: -35 °C to +85 °C , low 
thermal drift, low hysteresis (7%), robust and reliable. This chapter presents sensors 
performance test and validation.

![Image 1: Photograph of Hybrid carbon/polymer-based piezoresistive films](image1)

Figure 4.1: Photograph of Hybrid carbon/polymer-based piezoresistive films

4.2 Tests on Hybrid Carbon/Polymer Based Piezoresistive Film

This section made many experiments to test the sensor film to understanding of the sensor 
performance.

![Image 2: Hybrid Carbon/Polymer Based Piezoresistive Film](image2)
The first test shown in the Figure 4.2 is a thermal drift test. The thermal drift test uses three components: a laser temperature sensor, a soldering iron and a multimeter. The soldering iron is used as a heater to change the temperature around the sensor film, the laser temperature sensor measures the temperature on the sensor film, and the resistance change of the sensor film is measured by a multimeter. Figure 4.2 contains three experiment runs, the blue line shows result after linear fitting and the red line shows the mean curve of the three runs.

![Thermal drift test of sensor film](image)

**Figure 4.2: Thermal drift test of sensor film**

The following is a performance-robustness test of the sensor shown in Figure 4.3 and Figure 4.4. Figure 4.3 shows the voltage and deflection curve after three weeks of environmental exposure on the sensor. The sensor film was left outside and exposed to large temperature changes caused by sudden changes in the weather. During the three weeks, the sensor experienced high winds, a sunny environment and snow. The sensor
was bent to an extreme range (180 degrees) and left at that position for three weeks. The sensor was then tested and results, after the three weeks, are shown in Figure 4.4. The curve shows that after three-week of bending, the film is still sensitive without greatly changing linearity. This indicates that the sensor film and its properties are very robust and durable.

Figure 4.3: Environmental exposure test of sensor film

Figure 4.4: Maximal deflection test of sensor film
Figures 4.5 and 4.6 show the dynamic behavior of the sensor film. The free vibration test shows a natural frequency around 20Hz. The natural frequency could be increased when the sensor is microfabricated or the support film of the sensor is enhanced.

![Figure 4.5: Free vibration test](image1)

![Figure 4.6: FFT for the free vibration test.](image2)
Figure 4.7 shows results obtained with INA 101, INA 103 and AD620 (three different amplifiers) The figure shows the experimental results obtained when the gain is varied over the range 50x, 100x, 200x, 500x. The green curve is the movement of the manipulator, the blue line is the sensor raw data obtained with the DAQ and the red line is the data that was processed to obtain a 100-point average curve fitting. Note that, the re-set up of experiments or slightly varied engaging status of the sensor tip with the calibration sensor may cause the different voltage output from the same sensor even when the same gain was set to OpAmps.
Figure 4.7: Different OpAmp Circuit tests for the circuit selection: (a) INA101; (b) INA103, and (c) AD620.
After conducting these tests, it can be seen that this sensor film is a good candidate for developing microforce sensors and the chip AD620 is the best for development of its processing circuit.

4.3 1-D Microforce Sensors Design, Modeling, and Testing

4.3.1 Design and Dynamic Modeling

The structure of the high-sensitivity microforce sensor has a large degree of flexibility due to the use of piezoresistive film. It contributes to making the integrated sensor and micromanipulator system a flexible robot system. As shown in Figure 4.8, and 4.9, during manipulation, we consider the sensor as a one-link flexible arm with a rigid contact tip. A linear micromanipulator motor along the Z-axis and X-axis in the horizontal and vertical direction respectively drives it. $EI$, the uniform flexural rigidity of composite beam ($EI = E_1I_1 + E_2I_2$); $\rho$, the uniform mass per unit length of the composite beam; $Mm$, the mass of the translational motor base; $\rho t$, the uniform mass per unit length of the tip; $Fx(t)$; $Fz(t)$, the control input forces applied to the linear motor base along X and Z axes; $x(t)$; $z(t)$, the positions of the motor base along X and Z axes; $\omega(L, t)$, the elastic deflection at the free end of the flexible link; and $p(r, t) := z(t) - \omega(r, t)$, the displacement variable along Z axis. Since we consider regulating the microforce along Z axis, an assumption of small deflection of the beam is made, then we can ignore the effects of centripetal acceleration and axial compression of the beam.
Figure 4.8: Illustration of 1-D microforce sensor

Figure 4.9: 1-D microforce sensor with a rigid tip driven by the micromanipulator.
The position vector of contact point of the rigid tip is given

\[
p_t = \begin{bmatrix} p_{ty} \\ p_{tz} \end{bmatrix} = \begin{bmatrix} (L + L_0) \cos \theta \\ Z(t) - \omega(L, t) - L_0 \sin \theta(t) \end{bmatrix}
\]  
(4.1)

Where \( \theta(t) = \omega'(L, t) \approx \sin \theta(t) \approx \frac{\omega(L, t)}{L} \)

Then, a constraint surface \( \phi(z(t), \omega(L, t), \omega'(L, t)) = 0 \) for the system is found by

\[
p_{tz} = \phi(z(t), \omega(L, t), \omega'(L, t)) \\
\approx z(t) - \omega(L, t) - L_0 \omega'(L, t) \\
\approx z(t) - \omega(L, t) \left( \frac{L + L_0}{L} \right)
\]  
(4.2)

Based on the system motion (i.e. planar motion), the total kinetic energy \( E_K \) is given by

\[
E_K = \frac{1}{2} M_m \dot{z}^2(t) + \frac{\rho}{2} \int_0^L \dot{p}^2(r, t) dr + \frac{1}{2} I_b \omega_b^2 + \frac{1}{2} I_t \dot{\theta}^2(t)
\]  
(4.3)

Where \( I_b = \frac{\rho L^3}{12} \) is the moment of inertia of the flexible beam. \( \omega_b = \frac{\theta(t) L_0}{L} \) is the angular velocity of the flexible beam. \( I_t = \frac{\rho L_0^3}{3} \) is the moment of inertia of the rigid tip. In addition, the total potential energy \( E_P \) is

\[
E_p = \frac{EL}{2} \int_0^L (\omega''(r, t))^2 dr
\]  
(4.4)

In the system, the virtual work \( \delta W \) is given by

\[
\delta W = \delta z(t) F_z(t)
\]  
(4.5)

Substituting the above equations into the Ex-tended Hamilton’s Principle (Meirovitch, 1975):
\[
\int_{t_1}^{t_2} (\delta E_K - \delta E_P + \delta W + \delta \delta \phi) dt = 0
\] (4.6)

Where let $\delta$ is a Lagrange multiplier associated with the above constraint (4.2). The contact force between the constraint surface and the rigid tip can be represented in the term of the Lagrange multipliers. Then we obtain the following dynamic equations of the constrained one-link flexible arm along Z-axis.

\[
M_m \ddot{z}(t) + \rho \int_0^L (\dddot{z}(t) - \dot{\omega}(r, t)) dr = F_z(t) + \delta \frac{\delta \phi}{\delta z(t)}
\] (4.7)

\[
\dot{\omega}(r, t) + \frac{E I}{\rho} \omega'''(r, t) = \ddot{z}(t)
\] (4.8)

In addition, the corresponding boundary conditions as follows

\[
\left(\frac{\rho L_0^2}{12L} + \frac{\rho_0 L_0^3}{3L^2}\right) \omega(L, t) - E I \omega'''(L, t) = \epsilon \frac{\delta \phi}{\delta \omega'(L, t)}
\] (4.9)

\[
E I \omega''(L, t) = \epsilon \frac{\delta \phi}{\delta \omega'(L, t)}
\] (4.10)

\[
\omega(0, t) = \omega'(0, t) = 0
\] (4.11)

Moreover, the relationship between the contact force $f_c$ and the Lagrange multiplier $\epsilon$ can be given by

\[
J_c^T f_c \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix} = \epsilon \begin{bmatrix} \delta \phi \\ \delta z(t) \\ \delta \phi \\ \delta \omega(L, t) \\ \delta \phi \\ \delta \omega'(L, t) \end{bmatrix}
\] (4.12)

Where $J_c$ is Jacobian matrix between the Cartesian coordinate and the generalized coordinate$[z(t) \omega(L, t) \omega'(L, t)]^T$. From equation (4.12), we obtain
To realize the micro contact force control, we consider the relation of $f_c(t)$, $\omega(r,t)$, and $z(t)$.

Let $f^d_c$ be the desired contact force, $\omega_d(r)$ the related static deformation of the flexible beam, and $z_d$, the related static position of the motor base at the equilibrium state. At the equilibrium state $(f^d_c, \omega_d(r), z_d)$, the relation is found as

\[ z(t) = \dot{z}(t) = 0, \]
\[ \omega(r,t) = \dot{\omega}(r,t) = 0 \quad (4.14) \]

And based on the above equation and equation (4.8), we have

\[ \omega''''_d(r,t) = 0 \quad (4.15) \]

By considering the kinematics of the sensor structure, the relation of the quasi-static deformation $\omega_d(r)$ (assumed the bending of the beam mostly appears in the first shape mode in this micro assembly.) and the desired contact force $f^d_c$ is given as

\[ \omega_d(r) = \frac{1}{6EI} (3Lr^2 - r^3 + 3L_0 r^2) f^d_c \quad (4.16) \]

From the constrained condition of system motion in eqn. (4.2), then the relationship between the $z_d$ of the motor base and the desired contact force $f^d_c$ is given

\[ z_d = \omega_d(L) \frac{L + L_0}{L} = \frac{2L^3 + 5L^2 L_0}{6EI} = \frac{2L^3 + 5L^2 L_0 + 3L_0^2 L}{6EI} f^d_c \quad (4.17) \]

This relationship can be used to set a $z_d$ corresponding to a desired contact force $f^d_c$. In addition, considering the linear motor moves along X axis, we assume that the motion along X axis (vertical motion) doesn't affect the bending of flexible link, so we have the dynamics of system along X axis as follows,

\[ M_m \ddot{x}(t) + (m_b + m_e)x(t) = F_x(t) - G \quad (4.18) \]
Where \( m_b \) is the mass of the beam, \( m_t \) the mass of the tip. \( G \) is gravity of the system.

4.3.2 Static Testing

We firstly constructed a 1-D microforce sensor for static tests. A Wheatstone bridge was chosen and designed to convert the resistance change to a voltage change through connecting the sensor to an amplifier (AD620) as shown in Figure 4.10. From the testing results shown in Figure 4.7, the AD620 amplifier produces the best results with the lowest noise level. Moreover, the AD620 can amplify signals up to 10,000 times.

![Interface circuit schematic for 1-D microforce sensor](image)

**Figure 4.10:** Interface circuit schematic for 1-D microforce sensor

Our 1-D sensor was calibrated and tested using both Femto FT-S540 microforce sensor (range: 180 µN, Resolution: 0.05 µN at 30 Hz, 0.3 µN at 1000 Hz) and Femto FT-S270 microforce sensor (range: 2000 µN, Resolution: 0.4 µN at 30 Hz, 2 µN at 1000 Hz). The calibration sensors were placed perpendicular to our sensor under a microscope and the calibration setup is shown in Figure 4.11 (a). Figure 4.11 (b) shows a visual...
representation of the experiment using a microscope. Results are compared in Figure 4.11 (c). In addition, the resultant force-deflection curve and the average value of force-deflection are shown in Figure 4.13(d). The constant of force/deflection, was calculated and shown in Figure 4.11 (e). Calibration results show that our sensor has a resolution of hundreds of nano Newtons.
Figure 4.11: Calibration with Femto microforce sensors: (a) Calibration set-up; (b) sensor calibration under microscope (c) Force measurement comparison between our sensor and FT-S540; (d) Force-deflection curves; (e) Average force/deflection (27.16 N/m with standard deviation 0.329 under testing 9 times).

We have conducted the second calibration on the structure-modified 1-D sensor using high-accuracy Shimpo FGV-1XY digital force gauge. In the process, the sensor was attached to a manipulator, so that the amount of displacement can be accurately moved with one micro-meter step, and the calibration force sensor, Shimpo FGV-1XY digital force gauge (Capacity: 5N, Resolution: 0.001N), was also attached perpendicular to the sensor for comparison. The experimental setup is shown in Figure 4.12 (a). Figure 4.12 (b) contains the output of the FGV-1XY digital force gauge compared with our sensor. The structure-modified 1-D sensor is shown in Figure 4.12(c). The sensor with two adapters on both the sensor tip and the sensor beam can save the manipulation space, stabilize the structure, improve the force measure efficiency, and make the sensor tip replaceable. We have used FGV-1XY to calibrate nine times on this new sensor and experimental results
are shown in Figure 4.12(d).
Figure 4.12: Calibration result of the 1D micro force sensor

Figure 4.12: Calibration with FGV-1XY digital force gauge (a) Test set-up; (b) long range Voltage-Force test in 40X gain; (c) Modified 1-D microforce sensor prototype; (d) Calibration result of the 1D micro force sensor.
In addition, to measure the dynamic properties of the 1-D sensor, a laser sensor (Baumer, OADM 2016x41/S14F, measuring range: 30-70 mm, Maximum resolution: 4µm) was set up parallel with the manipulator to measure the displacement of the sensor. The experimental set-up is shown in Figure 4.13. The bode plot (deflection input and voltage output) of the 1-D microforce sensor is shown in Figure 4.14.

Figure 4.13 Experimental set-up for dynamic property measurement.

Figure 4.14: Bode plot of the 1-D microforce sensor
4.4 Design and Testing of 2-D and 3-D Microforce Sensors

We developed the 3-D microforce sensors after we validated the 1-D sensor with high sensitivity, low thermal drift, and low hysteresis effects. The 3-D microforce sensors are designed with self-decoupling mechanisms. Note that, 2-D force sensing can be implemented using the designed 3-D sensors.

4.4.1 3-D Microforce Sensor Design and Simulation

Both parallel and serial structured 3-D sensors were designed and simulated with the similar sensing film characteristics stated earlier. These designs are shown in Figures 4.15 and Figure 4.17. We used AnSYS to simulate both sensors design and results are shown in Figure 4.16 and Figure 4.18. Simulation results in Figure 4.16 show the naturally decoupling effect of three axes, (i.e. each axis output is independent) based on our design. In the simulation of the 3-D microforce sensor with a serial structure, the material of the sensor film is polyethylene with a density of 950 kgm$^3$. The size of the sensor film is 16 mm x 6 mm x 0.14 mm. The adapter material has a density of 7750 kgm$^3$ and the size of the adapter is 0.5 mm x0.5 mm x6 mm. The sensor tip has same density with the adapter and radius of the tip is 0.25 mm, the height of the tip is 10 mm, and the color bar shows the Von Mises’s stress intensity. Force applied on each axis is increased from zero to 50 N during the simulation.
Figure 4.15: Design of a 3-D microforce sensor with the serial structure.
Figure 4.16: Structural simulation of the serial 3-D microforce sensor using AnSYS, (a) Force applied in the X-axis, (b) Force applied in the Y-axis, (c) Force applied in the Z-axis.
Figure 4.17: Design of a 3-D microforce sensor with the parallel structure
Figure 4.18: Structural simulation of the parallel 3-D microforce sensor using AnSYS, (a) Force applied in the Y direction, (b) large force applied in the Y direction, (c) force applied in the Z direction.
In the simulation of the 3-D microforce sensor with the parallel structure, shown in Figure 4.18, the material of sensor film is polyethylene with a density of 950 \( \text{kg/m}^3 \). Both the adapter and tip materials are stainless with a density of 7750 \( \text{kg/m}^3 \) and the size of the adapter is 0.5 mm \( \times \) 0.5 mm \( \times \) 6 mm. The radius of the tip is 0.5 mm, the height of the tip is 25 mm. The color bar shows the Von Mises’s stress intensity. Force applied on each direction (axis) is increased from zero to 50 N during the simulation. Note that, the parallel structured sensor owns the symmetrically allocated beams. This symmetrical structure will be one of the important features that help to reach the self-decoupling function of the 3-D sensor.

4.4.2 3-D Parallel Structured Microforce Sensor with Self-decoupling Mechanism

Based on simulation results, the parallel structured design has an increased resonant frequency and the size of the parallel structured is generally smaller than the serial structured sensor. The self-decoupling method for the parallel structured sensor is dependent on (1) symmetrically allocated sensing beams and (2) voltage output cancelling mechanism within the designed Wheatstone Bridge group. A similar sensing structure and decoupling mechanism can be found in [150,151]. However, those cited sensors with decoupling mechanism need to be microfabricated and most of them rely on a complicated Jacobian matrix for multi-axis force decoupling. In addition, the materials used for those sensors are usually rigid silicon, so the deformation of the element is less, thus affecting sensitivity of sensors and the resolution is generally around mN to N. To depict the decoupling mechanism of our 3-D sensor, Figure 4.19 shows the allocation of
our piezoresistive films in the symmetrical sensor structure. Figure 4.20 illustrates deformation and resistance changes of allocated piezoresistive films in the sensor structure when force is applied to sensor tips. Table 4.1 lists all possible resistance changes of allocated piezoresistive films under various applied forces. This table well illustrates our self-decoupling mechanism.

Figure 4.19: Sensor films allocation
Figure 4.20: (a) Resistance change when the force is applied along the Z-axis, (b) Resistance change when the force is applied along the X or Y axis.

We also recorded the absolute value of voltage change in both top and bottom films when one double-side sensing film was bent. Results are shown in Figure 4.21. From the results, we found that the voltage-changing rate has large differences between top and bottom films beyond a small bending range even when they are expanded and compressed respectively under the same bending condition. To deal with this problem, we designed a self-decoupling circuit using the Wheatstone half-bridge principle shown in Figure 4.22. The three-axis voltage output relationships are shown in Equations 4.19-4.21. Equations 4.22-4.26 present the voltage output when the force is in the Z-direction. Equations 4.27-4.33 derive the voltage outputs when the force is applied along the X-direction. Equations 4.34-4.40 present the voltage output when the force is applied along the Y-direction. Through the above derivative, the effectiveness of our proposed self-decoupling mechanism based on the half-bridge circuit and sensor symmetrical structure is theoretically proved.
Table 4.1: Self-decoupling Strategy of a 3-D microforce Sensor with Parallel Structure

<table>
<thead>
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Figure 4.21: Voltage outputs of double-side sensor films (top and bottom)
Figure 4.22: Wheatstone half-bridge based self-decoupling circuit

\[ V_X = V_S \left( \frac{R_{T3}}{R_{T3} + R_C} - \frac{R_{T1}}{R_{T1} + R_C} \right) \]  \hspace{1cm} (4.19)

\[ V_Y = V_S \left( \frac{R_{B2}}{R_{B2} + R_C} - \frac{R_{B4}}{R_{B4} + R_C} \right) \]  \hspace{1cm} (4.20)

\[ V_Z = V_S \left( \frac{R_{B1}}{R_{B1} + R_C} - \frac{R_{T3}}{R_{T3} + R_C} \right) \]  \hspace{1cm} (4.21)

1) Normal Force \( F_Z \):

\[ \Delta R_{T1} = \Delta R_{T2} = \Delta R_{T3} = \Delta R_{T4} \]  \hspace{1cm} (4.22)
\[ \Delta R_{B1} = \Delta R_{B2} = \Delta R_{B3} = \Delta R_{B4} \quad (4.23) \]

\[ \Delta V_x = \Delta V_S \left( \frac{\Delta R_{T3}}{\Delta R_{T3} + R_C} - \frac{\Delta R_{T1}}{\Delta R_{T1} + R_C} \right) = 0 \quad (4.24) \]

\[ \Delta V_y = \Delta V_S \left( \frac{\Delta R_{B2}}{\Delta R_{B2} + R_C} - \frac{\Delta R_{B4}}{\Delta R_{B4} + R_C} \right) = 0 \quad (4.25) \]

\[ \Delta V_z = \Delta V_S \left( \frac{\Delta R_{B1}}{\Delta R_{B1} + R_C} - \frac{\Delta R_{T3}}{\Delta R_{T3} + R_C} \right) = \Delta V_S \left( \frac{\Delta R_{B1}(\Delta R_{T1} + R_C) - \Delta R_{B1}(\Delta R_{B1} + R_C)}{(\Delta R_{B1} + R_C)(\Delta R_{T3} + R_C)} \right) = \]

\[ \Delta V_S \left( \frac{(R_C)(\Delta R_{B1} - \Delta R_{T3})}{(\Delta R_{B1} + R_C)(\Delta R_{T3} + R_C)} \right) = \Delta V_S \left( \frac{(\Delta R_{B1} - \Delta R_{T3})}{(\Delta R_{B1} + R_C + 1)(\Delta R_{T3} + R_C + 1)} \right) \quad (4.26) \]

2) Normal Force \( F_x \):

\[ \Delta R_{T1} = \Delta R_{B3} \quad (4.27) \]

\[ \Delta R_{T2} = \Delta R_{B4} = 0 \quad (4.28) \]

\[ \Delta R_{T3} = \Delta R_{B1} \quad (4.29) \]

\[ \Delta R_{T4} = \Delta R_{B2} = 0 \quad (4.30) \]
\[ \Delta V_X = \Delta V_S \left( \frac{\Delta R_{T3}}{\Delta R_{T3} + R_C} - \frac{\Delta R_{T1}}{\Delta R_{T1} + R_C} \right) = \Delta V_S \left( \frac{\Delta R_{T3} (\Delta R_{T1} + R_C) - \Delta R_{T1} (\Delta R_{T3} + R_C)}{(\Delta R_{T3} + R_C)(\Delta R_{T1} + R_C)} \right) = \] \\
\[ \Delta V_S \left( \frac{(R_C)(\Delta R_{T3} - \Delta R_{T1})}{(\Delta R_{T1} + R_C)(\Delta R_{T3} + R_C)} \right) = \Delta V_S \left( \frac{(\Delta R_{T3} - \Delta R_{T1})}{(R_C + 1)(\Delta R_{T3} + 1)} \right) \] (4.31) \\
\[ \Delta V_Y = \Delta V_S \left( \frac{\Delta R_{B2}}{\Delta R_{B2} + R_C} - \frac{\Delta R_{B4}}{\Delta R_{B4} + R_C} \right) = 0 \] (4.32) \\
\[ \Delta V_Z = \Delta V_S \left( \frac{\Delta R_{B1}}{\Delta R_{B1} + R_C} - \frac{\Delta R_{T3}}{\Delta R_{T3} + R_C} \right) = 0 \] (4.33) \\

3) Normal Force \( F_Y \):

\[ \Delta R_{T1} = \Delta R_{B3} = 0 \] (4.34) \\
\[ \Delta R_{T2} = \Delta R_{B4} \] (4.35) \\
\[ \Delta R_{T3} = \Delta R_{B1} = 0 \] (4.36) \\
\[ \Delta R_{T4} = \Delta R_{B2} \] (4.37) \\
\[ \Delta V_X = \Delta V_S \left( \frac{\Delta R_{T3}}{\Delta R_{T3} + R_C} - \frac{\Delta R_{T1}}{\Delta R_{T1} + R_C} \right) = 0 \] (4.38)
\[ \Delta V_Y = \Delta V_S \left( \frac{\Delta R_{B2}}{\Delta R_{B2}+R_C} - \frac{\Delta R_{B4}}{\Delta R_{B4}+R_C} \right) = \Delta V_S \left( \frac{\Delta R_{B2}(\Delta R_{B4}+R_C)-\Delta R_{B4}(\Delta R_{B2}+R_C)}{(\Delta R_{B2}+R_C)(\Delta R_{B4}+R_C)} \right) = \]

\[ \Delta V_S \left( \frac{(R_C)(\Delta R_{B2}-\Delta R_{B4})}{(\Delta R_{B2}+R_C)(\Delta R_{B4}+R_C)} \right) = \Delta V_S \left( \frac{(\Delta R_{B2}-\Delta R_{B4})}{(\Delta R_{B2}+R_C)(\Delta R_{B4}+R_C)} \right) \]  \hspace{1cm} (4.39)

\[ \Delta V_Z = \Delta V_S \left( \frac{\Delta R_{B1}}{\Delta R_{B1}+R_C} - \frac{\Delta R_{T3}}{\Delta R_{T3}+R_C} \right) = 0 \]  \hspace{1cm} (4.40)

In practice, it is difficult to assemble the sensor films perpendicular to each other to ensure the symmetry when we build our 3D parallel structure sensor. We designed an assembly adapter shown in the Figure 4.23 to help assembling the sensor films, as well to ensure the symmetry of the sensor structure. Follow this adapter, a new design and its assembled prototype of our parallel structured 3-D microforce sensor are shown in Figure 4.24.
Figure 4.23: Two views of an assembly adapter for the parallel structured 3-D microforce sensor.
A FGV-1XY digital force gauge was used to test the parallel structured 3-D microforce sensor. Figure 4.25 shows the experimental set-up for testing the parallel structured 3-D microforce sensor on X & Y direction. The parallel structured 3-D microforce sensor was fixed on a stage. The FGV-1XY sensor was attached on the manipulator and the movements were given by computer commands. For the Z direction test, the set-up of the FGV-1XY sensor needed to be aligned vertically to touch and push the sensor tip of the fixed parallel structured 3D micro-force at the stage.
Figure 4.25: Calibration set-up (FGV and parallel structured 3-D microforce sensor).

Figure 4.26 shows the self-decoupling and sensitivity results when force is applied along the X-axis and Figure 4.27 presents the self-decoupling and sensitivity results when force is applied along the Y-axis. The gain for these two tests is set to 10x. Self-decoupling and sensitivity results when force is applied along the Z-axis are shown in Figure 4.28. The gain on the Z-axis is 50x. Note that, a large electronic gain for the Z-axis is necessary as it is used to compensate for structural insensitivity along Z-axis.
Figure 4.26 Self-decoupling and sensitivity results when force is applied along the X-axis (a) measured voltage and force, (b) converted forces, (c) force (input $F_x$) vs. voltage (output $V_x$). Linear fit: $V_x = 12.467F_x + 0.010249$
Fig. 4.27 Self-decoupling and sensitivity results when force is applied along the Y-axis (a) measured voltage and force, (b) converted forces, (c) force (input $F_y$) vs. voltage (output $V_y$). Linear fit: $V_y = 50.837F_y + 0.0050404$
Figure 4.28 Self-decoupling and sensitivity results when force is applied along the Z-axis (a) measured voltage and force, (b) converted forces, (c) force (input $F_z$) vs. voltage (output $V_z$). Cubic fit: $V_z = -4776.9F_z^3 + 428.61F_z^2 + 2.2615F_z + 0.061942$, and Linear fit: $V_z = 11.416F_z + 0.0050404$

The above experiment results show that forces in X and Y axes are decoupled very well and force measurements in all axes are very close to the measurements from the calibration sensor. Force vs. voltage plot for the x axis demonstrates a big hysteresis effect, the effect may be caused by assembly quality and inconsistent sensing film properties. In addition, the decoupling effect in force along Z-axis can be improved. As mentioned above, the main reason for downgrade of Z-axis decoupling is structural insensitivity. Ongoing work will focus on solving the coupling and insensitivity issues along Z-axis.
4.5 Summary

This chapter shows how we tested and developed micro-force sensors. A highly sensitive, low thermal drift, low hysteresis and very robust 1-D micro force sensor is presented. Two 3-D sensors are designed and simulated by AnSYS. The parallel structured 3-D sensor was chosen and tested. The parallel structured 3-D sensor has good results in the X-axis and Y-axis, but Z-axis performance can be improved through structure sensitivity compensation and assembly improvement.
CHAPTER 5
MULTI-MODAL SYSTEM INTEGRATION AND APPLICATIONS

This chapter presents our system integration and three integrated system applications based on the developed micro position sensor, EEG BCI interface and microforce sensors.

5.1 System Integration and Components

Figure 5.1 displays the system flow chart of current integrated multi-modal micro-biomanipulation platform.

Figure 5.1 Flow chart of the integrated multi-modal manipulation system.
5.2 Network-enabled Communication and Programming

Figure 5.2 shows the programming flow chart of the EEG based mind control system.

Figure 5.2: Flow chart of mind-controlled micro-biomanipulation system.
Figure 5.3 shows the programming flow chart for musical tuning enhanced micro palpation system.

After describing our micro-biomanipulation system and its integration, we focused on implementing several applications to validate our integrated system.
5.3 Application 1: Musical Tuning Enhanced Micro Palpation System

The motivation for mechanically characterizing micro or nano biological entities, like cells, embryos, tissues, and organs is to better understand their biomechanical properties or mechanical bio-markers as well as to mathematically model the physical character or growth, morphology, interaction functions that might relate to development, diseases, pathological and physiological studies [9]. Bao et al. in their studies have confirmed that mechanical properties can affect cell growth, differentiation, locomotion, adhesion, signal transduction, and gene expression [152]. The key to addressing all these issues is to study the motion and force-induced conformational changes of biological entities. Lim et al. [11] investigated the structure-mechanical property–function relationship of cells and biomolecules to understand their important physiological implications as well as establish possible connections to human diseases. Additionally, Addae-Mensah and Wikswo [8] surveyed the mechanical properties of cells and their disorders, and concluded that they are implicated in many aspects of human physiology and pathophysiology. Recently, in-vitro micro-/nano-mechanical studies have shown that cultured cancer cells are elastically softer than normal (i.e. healthy) cells, and new measurements on cells from cancer patients suggest that this mechanical signature or mechanical bio-marker can be a powerful means to detect cancer in the clinic [153]. Currently, the most popular way to conduct micro/nano mechanical characterization of biological entities is to use atomic force microscopy (AFM) to quantify the measurements and process them offline without assisting by humans’ multi-modal perception capabilities. Interestingly, Pelling and Gimzewski [154] first amplified the measured nanoscale yeast cells oscillation results in
a sound that lies within the human audible range and suggested "Sonocytology" as the term for this cutting edge field of study.

Inspired by above research, we have created a musical tuning enhanced *in-vitro* micro/nano palpation system illustrated in Figure 5.4, that will help to intuitively and interactively identify (by hearing) the mechanical signature or bio-marker of multi-scale biological entities, including cells, embryos, tissues, and organs. The core of the system is our developed low-cost and highly sensitive microforce sensor. A user in real time converts measurements from the sensor actively touching the bio-entities into 88-key piano musical voices for hearing and identification. This helps the user to listen online to the mechanical properties change of biological entities.

For this application, musical tuning is based on 88-key piano system, shown in Figure 5.5. The 88 keys on the piano are covered from 27.5Hz up to 4186.01Hz in frequencies. The measured microforce is converted into these frequencies associated with 88-key piano following the procedures: (1) the measured microforce is converted into one of numbers of the key, $n$ ($n=1-88$), according to its amplitude; (2) the piano audio frequency $f$ of the $n$th key corresponding to the measured microforce is then achieved by $f(n) = \left(\sqrt[12]{2}\right)^{n-49} \times 440Hz$. 
Figure 5.4: Overview of musical tuning enhanced micro palpation system

Figure 5.5: An 88 key piano Keyboard

We have conducted musical tuning enhanced micro palpation on the membrane surface of the grapefruit vesicles to verify the performance of the system. The experimental setup is shown in Fig. 5.6. Fig. 5.7 shows the software interface. Fig. 5.8 (a) and (b) demonstrate two conducted experiments. In the top plots of Fig. 5.9 (a) and (b), blue curves represent measured micro force signals during the palpation on the vesicles; green curves show the converted piano audio frequency waveforms. The bottom plots of Fig. 5.10 (a) and (b)
demonstrate the captured piano voices using a high performance microphone following the measured micro force. All experimental results verify the effectiveness of the developed system approach that is multi-modal, intuitive, and interactive for biomedical studies.

Figure 5.6: Experimental set-up of the musical tuning enhanced micro palpation.

Figure 5.7: Software interface for musical tuning enhanced micro palpation.
Figure 5.8: Results of musical tuning enhanced micro palpation (a) *In-vitro* musical tuning enhanced micro palpation on the vesicle 1, (b) *In-vitro* musical tuning enhanced micro palpation on the vesicle 2.
In addition, to verify our sensing performance, the force is measured from the vesicle of grapefruit when we are adding 100% Ethanol to the surface. Results are shown in Figure 5.9. The findings show that our sensor can detect small mechanical property change of the sample surface caused by the chemical solution, like Ethanol.

![Graph showing force and frequency profile](image)

**Figure 5.9**: Force and frequency profile when adding Ethanol to the surface of bio-sample.

### 5.4 Application 2: Brain Driven Micro-Biomanipulation

Basic research on brain-computer interfaces (BCIs) and applications has been growing fast since the first experimental demonstration in 1999 that ensembles of cortical neurons could directly control a robotic manipulator [39] [40]. Since then, tremendous research efforts have been made in BCIs or brain-driven applications among the scientific community [40]. Generally, to conduct the BCIs and applications, two methods including
invasive and non-invasive electrophysiological (EEG) recordings are widely used. Invasive methods are based on recordings from ensembles of single brain cells (also known as single units) or on the activity of multiple neurons (also known as multi-units) [40], which feasibility was proved by several research using intracranial electrodes implanted in the motor cortex of monkeys [39]. Non-invasive EEG-based BCIs try to decipher the user’s voluntary intentions and decisions through measurements of the combined electrical activity of massive neuronal populations [40]. This approach has proved effective for helping the users develop ways of communication with the external world or devices. This approach is also preferable for development of human machine interfaces without exposing the human user to the risks of brain surgery. In addition, non-invasive EEG techniques were found that they could detect modulations of brain activity that correlate with visual stimuli, gaze angle, voluntary intentions and cognitive states. These properties have led to offer some practical human-machine interface solutions, such as cursor control [155] [138], computer game operation [156] and wheelchair control [157]. Following these solutions, more research investigations towards the applications of non-invasive EEG-based BCIs on moving robots or prosthetic devices have fascinated. Beyond that, decoding human EEG signals representing the global activity of millions of neurons in these applications are inspiring cognitive and neurobiofeedback research activities. For example, Wu et al: recently presented a novel embedded-internet robot system, called eRobot, based on an internet robot agent and the brain-computer interface (BCI) scheme [158]. In [159], the research work shows that the signals derived from an EEG based brain-computer interface (BCI) are sufficient to continuously control a miniature mobile robot in an indoor environment with several
rooms, corridor, and doorways. Yamanoi et al. investigated the brain activity during human recognition of characters and symbols representing directional meaning using the EEG. The EEG results that are from right frontal area, corresponding to directional meaning of symbols, have been used to control the motion of a micro robot [160]. In this research area, a survey on current successes in brain-driven robotic navigation control methods can be found in [161]. In addition, linked with the non-invasive EEG-based BCIs applications on human-robot interface or prosthetic devices, Hammon et al. explored that EEG signals contain sufficient information to decode target location during a reach and during the planning period before a reach [162].

Despite having the great advantage and the strong potential in related research and applications, non-invasive EEG-based BCIs techniques provide communication channels of limited capacity and have been considered too slow for controlling rapid and complex sequences of movements [40]. This drawback may not be a stumbling-block for creating a new application on micro-biomanipulation that currently is a slow and simple motion/force control process at micro scale. This has motivated us to incorporate the non-invasive EEG (measuring human intelligence) with our micromanipulation system offering machine precision for investigating and realizing a mind-controlled biomanipulation at micro scale. Micro-biomanipulation is a research process involving the manipulation (e.g., mechanosensing, injection, separation, cutting, and alignment) of biological entities such as individual cells and early embryos. Current automation methodologies developed for micro-biomanipulation include the use of magnetic, microelectromechanical systems (MEMS)-based approaches, optical trapping, dielectrophoretic force, and mechanical probe techniques etc… A review of engineering
approaches to biomanipulation can be found in [163].

In this section, we develop a networked noninvasive EEG-based brain-computer interface system to decipher the user’s behaviors/strategies in micro-biomanipulation or micro-assembly tasks through measurements of the combined electrical activity and tracking the motion traces in real time. The networked system incorporates a non-invasive electroencephalogram (EEG) device with a high-precision automated micromanipulator system that has the controllable 3-D moving stage. At the stage, a finely pulled micropipette tip is attached for micromanipulation. The manipulation process can be observed using a microscope. In addition, to evaluate system performance, our custom-built high-precision position sensing detector (PSD) interface is used for recording the record of human mind manipulation during the process, and EEG activity analysis corresponding to 2-D mind movements are presented. An overview of the system can be found in Figure 5.10.

![Figure 5.10: Overview of brain driven micro-biomanipulation system](image-url)
The developed multimodal micro-biomanipulation platform for the brain-driven application, shown in Figure 5.11, consists of four subsystems: the non-invasive EEG system, the high-precision micromanipulator, the microscope system, the micro-force sensor, the data analysis board and the position sensing interface for tracking the mind control commands from the EEG system. The operator is stimulated by watching live microscope images in the PC1 generated by a Qimaging Camera (Qcam) with a high resolution of 1392 x1040 pixels. A non-invasive Emotiv EPOC EEG wireless headset worn by operator records operator’s EEG activity signals and decodes them into motion control commands according to his/her intent and alertness level. The decoded motion control commands from the EEG are transferred to a control command server PC2 from the client PC (PC1) through the high-speed network with bandwidth of 100 Mbit/s. The motion control commands will drive the micromanipulator (Sutter MPC 385, 65nm/step) connected to the PC2 to perform manipulation on samples through a mounted finely pulled micropipette tip. The Qcam camera interfaced with an image server PC3 captures the whole manipulation process. The live images displayed in the PC3 are then duplicated on the PC1 by tele-conference software through the network. Note that, to speed up computing, there are two separated servers (command and image servers) rather than one server. During manipulation, the motion control commands from the mind of operator can be tracked by a custom-built position sensing interface unit, which includes a laser diode attached to the micromanipulator and a position-sensing detector (PSD). As the sub-systems are incorporated through high-speed network of 100Mbit/s, the developed system can be also expanded to use as an Internet-based mind-controlled micro-biomanipulation platform.
Relying on integrated sub-systems, we have conducted several experiments to demonstrate the performance of the whole developed system. Several position controls and path tracking controls by the operator's mind through the developed platform were performed. Figure 5.12 demonstrates the 2-D position control by the human mind. In the figure, we set both the initial position and the final position on the mapped PSD software display interface. By observing the interface, the operator start to control the movement of the laser diode mounted at the moving stage using his/her mind. The movement of the diode drives the laser beam to move across the PSD and generate the moving traces on the PSD software interface. The displayed trace guides the operator’s mind to move the laser beam from the initial position to the final position.
We have performed mind-based position control five times. All five traces recorded are displayed in Figure 5.12 and the results show the success of the mind position control. Note that, around the final position, the mind control command is not easily terminated. This results in small offsets of the traces shown in the interface. Figure 5.13 shows $x$ and $y$ position errors of five traces during the position control by the mind. The distance between the initial and final positions is 1.2 mm, and both $x$ and $y$ position errors are below 0.18mm.

In addition, we have conducted the mind-controlled path tracking. For this experiment, we set a 4-step-change path as the reference on the PSD software interface. The operator carefully used his mind to follow the step-change one by one. The mind traces were tracked by the PSD position sensing interface unit. We have done the path tracking three times with all mind controlled path tracking results plotted in Figure 5.14. From the plots, the repeatability of path tracking is demonstrated and the performance of the completely brain-driven system is experimentally verified.

All experiments clearly show that the system can effectively perform mind-controlled position approaching and tracking tasks.
Figure 5.12: Mind controlled 2-D motion (5 times).

Figure 5.13: Errors of mind controlled 2-D motion.
The experimental setup for conducting mind-controlled micro-biomanipulation with position sensing feedback is shown in Figure 5.15. The moving stage of the micromanipulator is controlled by the operator mind (the decoded EEG raw signals). The movement of the finely pulled micropipette tip attached to the 3-D moving stage of micromanipulator is sensed by the PSD sensing interface unit including the laser diode, the PSD chip, and the software interface. The micro-biomanipulation images are captured by the microscope camera and observed by the operator via the LCD monitor of PC1. The bio-sample used is a juice vesicle of a grapefruit. The sample with the length of 10 mm and the width of 1.5 mm is soft and its membrane is elastic and suitable to mimic biological samples such as embryos and cells. The aim of the biomanipulation experiment is to control the tip to approach the vesicle and then scratch on its surface. To implement such biomanipulation, an unmovable yellow scratch path is marked on the vesicle in the living images using software. During the experiment, the operator watched...
the living microscope images in which there are the controlled micropipette tip and the partial juice vesicle with the marked scratch path. The path provides a position reference for the operator’s mind to approach and follow. As shown in the bottom right of Figure 5.15, the displayed X and Y coordinates match the coordinates in the PSD sensing interface unit.

Figure 5.15: Experimental set-up for conducting brain-driven micro-biomanipulation with position sensing feedback.

Figure 5.16 illustrates the experimental results. The trace plot in the middle of the figure is the sensed output from the PSD software interface. In Figure 5.16(a), the whole process took about 95 seconds. Four manipulation images (1, 2, 3, and 4) were extracted from the recorded video to show the statuses corresponding to four moving points in the four extracted images are the images at 5, 35, 75, and 95 seconds of the biomanipulation
process, respectively. Results demonstrate a successfully micro-biomanipulation on the vesicle performed by the operator’s mind. Note that, the trace of the mind may be dependent on the initial position of the tip and the distance between the tip and the scratch path maker.

The trace plot of the tip in Figure 5.16(b) presents the manipulation was performed only by one motion along the X and one motion (scratch) along the Y direction. In this experiment, the operator finished the scratch biomanipulation on the vesicle by taking below 70 seconds. During the experiments, it is apparent that after performing the micro-biomanipulation several times, the operator can gradually improve his manipulation skill by accurately finishing the task in short time and in short path.
Figure 5.16: Results of brain-driven micro-biomanipulation with position sensing feedback: (a) a 95-second manipulation; (b) a 70-second manipulation.

Note that, the above manipulations are not a full 2-D mind control process due to operators’ training issue and EEG system limitation. As described in Section 3.2.2, we have developed a practical method to realize a full 2-D motion control without long time training by incorporating the Gyro sensor outputs as a motion direction trigger. Here we implement this method. Figure 5.17 shows the head movement measurement by gyro sensors. Gyro sensor X detects the head movement in left and right directions and Gyro sensor Y can detect head movements in up and down directions. Figure 5.18 shows mind motion traces displayed on the PSD interface. In the figure, the manipulator moves to left
or right after Gyro sensor X detecting a large movement in left or right direction following the mind. When Gyro sensor Y detects a large movement in up or down direction, the manipulator moves forward or backward following the mind.

Figure 5.17: Gyro sensor signals from head movement.

Figure 5.18: Full 2-D mind motion control trigged by Gyro sensor signals.
5.5 Application 3: Portable Radial Artery Pulse Sensing System

From antiquity, the presence of arterial pulse has been understood as a fundamental sign of life. Many cultures and civilizations developed qualitative interpretations of changes in the *texture* and *strength* of the arterial pulse and the associated change in health and disease [163]. The history of diagnosis from the radial pulse dates back several thousand years [164]. Palpation of the radial artery pulsations is one of the four main methods used in traditional Chinese medicine patient evaluation [163]. Despite such a long history, E. J. Marey, who created a device that used a mechanical membrane and lever system to write the radial pulse waveform directly to smoked paper [165], did not make the first actual recordings of the arterial pulse contour until 1863. Marey’s sphygmographs were copied and improved upon by others for several decades [166,167]. The first practical arterial occlusive device was made in 1876 by von Basch [168], but widespread use of cuffs did not occur until around 1900, following the seminal publication by Riva-Rocci [169]. Sphygmographs eventually lost ground to electrocardiograms for cardiac rhythm analysis and occlusive cuffs for blood pressure measurement around 1920 [170,171] and were considered to be a superseded technology for many years. Pressman and Newgard [172] rediscovered the sphygmmogram by using the technique of applanation tonometry to measure arterial pressure wave shapes in 1963. It is the basis of the widely used type of transducers for accurate, non-invasive detection of peripheral arterial pressure wave shape [173,174]. Penaz [175] later introduced the vascular unloading method of measuring continuous blood pressure and its contour non-invasively in the finger using the photoplethysmographic technique.
Currently there are many different ways to detect the pulse such as application tonometry, modified tomometric devices, vascular unloading method, fluid-filled pulse detectors, cuff devices for detection of the arterial pulse and photoplethysmography. In addition, there are many groups who are expanding upon these methods. Details can be found in a topical review [176].

Using the highly sensitive hybrid piezoresistive film described in Chapter 4, a highly sensitive, low power consumption, and low-cost radial pulse detector was designed and built by us. Figure 5.19 shows the design of the device. Figure 5.20 shows the prototype fabricated by a 3-D printer. Figure 5.21 presents measured radial pulse data over 20 seconds and Figure 5.22 shows basic analysis of the rate of the measured pulse. Figure 5.23 shows a referenced pulse signal measured by other researcher and Figure 5.24 shows our pulse signals in detail.
Figure 5.19: Portable radial pulse sensor design: (a) Assembly structure; (b) Three views of the assembled sensor.

Figure 5.20: Portable radial pulse sensor prototype.
Figure 5.21: Radial pulse sensor signals.

Figure 5.22: Radial Pulse signal data analysis.
Figure 5.23: Representative pressure pulses obtained with the transfer functions for a normotensive subject. Real brachial (solid line) and radial artery pulses (dotted line), and simulated radial artery pulse (dashed line) after parameter estimation [177].

Figure 5.24: Radial pulses signal from our sensor.
As seen in Figure 5.23 and 5.24, our measured signal has excellent agreement with the referenced signal. This indicates that our sensor has high performance that allows closely monitoring the detail of radial artery pulses.
CHAPTER 6

CONCLUSIONS AND FUTURE WORK

6.1 Conclusions

In this thesis, we address developing a cost-effective, high efficient, multi-degree-of-freedom, and multi-modal micro-biomanipulation research platform that is in a symbiotic relationship with human operators to improve processes of micro/nano biomechanical characterization and its automation level. In the first step, several important sensors and interfaces for our multi-modal and interactive micro-biomanipulation system were developed, custom designed, and tested, including a position sensitive detector (PSD) based micro/nano position sensing system, a non-invasive Electroencephalography (EEG) interactive interface, and hybrid piezoresistive based highly sensitive 1-D and 3-D microforce sensors with self-decoupling mechanisms. Relying on these developed sensors and interface, a network-enabled system architecture is established and three system applications consisting of (1) musical tuning enhanced micro palpation of biological entities; (2) brain-driven micro-biomanipulation; and (3) portable radial artery pulse sensing system are successfully conducted and demonstrated. Extensive simulation and experimental results validate that our work will be a major step toward a multi-modal and interactive micro-biomanipulation system for varied biomedical research.

6.2 Future work

The thesis presents the first phase of the our research project. In the next phase, we will focus on improving the performance of the developed sensors, interface and systems as well extending their applications. The efforts include calibration of 1-D microforce
sensor using AFM; simulation and experiments on dynamic sensing of 1-D microforce sensor; force controller design with the dynamic model of 1-D microforce sensor; experimental test on 3-D microforce sensor with serial structure; dynamic modeling of 3-D microforce sensor with parallel structure; force controller design with the dynamic model; varied micro biomechanical characterization using the developed microforce and microposition sensors; 3-D tracking and motion control using the EEG; human manipulation behavior study through high performance EEG; and radial pulse related pathology studies etc.
REFERENCES


[175] J. Penaz, “Photoelectric measurement of blood pressure, volume and flow in the finger” *Dig. of the 10th Int. Conf. on Medical and Biological Engineering* ed A Albert, W Vogt and WHellig (Oresden: International Federation for Medical and Biological Engineering) 1973 p 104.
