Graduate Research Statement

Introduction

My research aims to design a control system that will allow a new highly accurate and reliable method potentially suitable for early detection of cervical cancer viable for use in research and general medical use. This method, developed in Dr. Igor Sokolov’s lab, is based on measuring an adhesion map of the cell collected from the cervix by means of an atomic force microscope (AFM). Fractal dimensional analysis is conducted on the adhesion map to identify malignancy of the cell of study. Despite remarkable accuracy surpassing all existing methods, there is serious deficiency of this method. The time of collecting one adhesion map is too long to be practical. The goal of my proposed research is to investigate control methods to significantly decrease the time of recording the adhesion map. The immediate goals of my research are to study AFM probe tip to cell surface interactions, study non-linear control methods, and to research the effectiveness of this technique on a wide variety of biological tissues. Some potential broader impacts of this work, to name a few, are a substantial acceleration in the general AFM method, and development of a specialized AFM method for highly accurate screening of cervical cancer, and probably other cancers.

Background

Fractal analysis of cell images to identify cell properties is not a new technique, but it is not well studied as a cancer detection technique. In 2000, Dr. James Baish and Dr. Rakesh Jain suggested in their article Fractals and Cancer[1] that fractal behavior might be connected to cancer. In 2002, a University of Newcastle, UK group was able to differentiate healthy colon cells from cancerous colon cells with a high degree of certainty[2]. However, the analysis was applied to already known morphological features, and had a goal to make the method operator-independent. The results did not show statistically significant improvement compared to just expert judgment. Both cancer and normal cells demonstrated good fractal behavior, although with different fractal dimensionality.

The method developed in Dr. Sokolov’s group showed that fractal behavior emerges on the cell surface when cell becomes malignant[3]. They used AFM adhesion maps of cell surfaces and fractal analysis to differentiate between healthy and cancerous cervix cells. The results showed a very high degree of certainty. They found that the healthy cells displayed multifractal scaling behavior, whereas the cancer cells’ structure displayed true simple fractal geometry. The degree of malignancy was quantified as the fractal dimensionality of the AFM adhesion map. Approximately 300 cells collected
from 12 humans were analyzed. When plotted as histograms, the healthy cells and cancerous cells formed individual and distinct normal distributions with virtually no overlap.

These results have strong implications that cervical cancer can easily and reliably detected by obtaining adhesion maps of a few cervical cells and calculating the fractal dimensionality. At this time, this technique has not been used on many types of cancers, but the potential is there and should be explored in the near future. Using an AFM for diagnostics has the added advantage that the scan needs very few cells. For cervical cells, only a swab of the cervix needs to be taken, not a biopsy. In the same fashion, a scraping of the colon wall is all that is necessary to collect the necessary cells instead of a painful biopsy that risks infection. Mouth and skin cells can similarly be taken by swab in a relatively noninvasive manner, though it is not yet known if fractal analysis is an indicator of cancer in these tissues.

However, this technique is too slow to be viable for medical applications or research. The scan time for a single cell takes about an hour. To be viable, scans of several cells must be taken in a fraction of the time. The issue is that by increasing scan speed, the AFM also produces artifacts in the map due to interaction between the AFM probe and cell surface. To address these issues, the control process of the AFM probe must be improved.

As a student of mechatronics, I propose to research AFM probe interaction with cell surfaces and the control systems capable of increasing the scan speed of AFM. As an extension of this work, I would like to continue on to study the fractal dimensionality of other cancers, as well as develop an AFM mode that is specialized for scanning cells.

**Approach**

Since the slow speed of AFM scans comes from the imperfections of force feedback in the AFM setup, the first step is to develop a new control process. A literature search reveals that certain aspects of this project are already well studied such as AFM probe-cell surface interactions[4, 5]. Thus, modeling the van der Waals forces between the cell surface and AFM probe will not require any original work. Another well studied area is AFM probe dynamics[6] which has resulted in dozens of scanning modes since the invention of atomic force microscopy. The scanning mode that I am focusing on is Bruker’s PeakForce QNM® (Quantitative Nanomechanical Property Mapping).

To create a preliminary simulation in Matlab/Simulink, I have chosen to model the AFM probe as a point mass system with a simple spring-damper relationship to the probe holder. Future simulations may be in the form of a distributed beam model instead to account for additional harmonics if any are
observed beyond the first. These models can then be used to design an optimized PID controller for the probe holder position.

At this point, the AFM hardware will be examined for sampling time and input/output limits (voltage and baud rate). Given the control technology readily available on the market, hardware should not be the limiting factor.

Another technique I propose to develop is a targeted error rescan technique. The current method to smooth error is to pass the probe twice over one line (forward and back), increase the sampling rate, and average the signal over the region. This provides a more accurate feature map at the cost of resolution. The proposed improvement is to identify areas of high error of the feedback on the first scan through, then on adjacent scans, move quickly over areas of low error then slowly over areas of high error to obtain the necessary resolution and correct artifacts. This technique will be reviewed as a secondary improvement because it is estimated that the technique would not show any improvement in scan speed due to the highly irregular nature of a cell’s surface; targeted error rescan technique would be an ideal solution for smooth surfaces with the occasional bump. It should also be mentioned that the scan size can be reduced in some cases, but this may come at the cost of increased error in calculating the fractal dimensionality.

The final area to be researched in this project is the effectiveness of fractal dimensionality analysis to differentiate cancerous cell in a variety of cancers. This technique is all but proven for cervical cells. A literature review must be conducted to see if the efficacy of fractal dimensional analysis to detect cancer in other cell types has been studied, the relative effectiveness of the technique in those cases, and identifying the cell properties that make the technique possible for some tissues but not others (assuming the technique does not work in all cases). Then a number of tissues should be studied. The best early candidates are oral, skin, uterine, and rectal tissues. This is because all of these samples can be obtained with a scraping in a relatively painless procedure.

**Commercial Application and Broader Impact**

To bring the method of early cancer detection to the commercial level, we anticipate that a standard test may be done in a half hour or less. An appropriate AFM method and relevant disposable accessories should be developed for the use in hospitals, and maybe, eventually in private doctor’s offices. The doctor or nurse would simply put the cells from the scraping on a slide and run the test which is already more than 90% percent autonomous on some specialized AFMs.

I also envision a few other easily realized features that would significantly reduce operator error and increase user friendliness. In current operation, the operator has to manually align the probe with the
sample, the laser with the probe tip, and the photosensor with the reflected laser, and then manually lower the probe to the sample surface. All of these alignment procedures can easily be handled by an auto-calibration procedure when the same type of sample is being scanned repeatedly, which is the case in some specialized AFMs. Sample identification and probe alignment can be handled with a simple object recognition protocol. Using this type of protocol, several samples on the same slide can even be scanned in the same test because the operator would simply select the order of scanning using the streamed image displayed in a simple user interface and the computer would take over all of the alignment and data logging tasks. The laser and sensor alignment can easily be automated using stepper motors and a peak-seeking protocol. Then the lowering procedure can be done using a combination of depth of focus comparison and detecting a force on the cantilever.
References