DEPARTMENT OF
Biomedical Engineering
UNIVERSITY OF WISCONSIN–MADISON

Microscope Slide Scanner

BME 200/300 - Preliminary Report

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Abstract

Many cytology labs require the use of microscope slide scanners to have digital images of their microscope slides. There are many current slide scanners on the market that are able to provide fast, high resolution images of slides. However, these slide scanners are extremely expensive, and out of reach for those working in low budget cytology labs. Thus, there is a need for a new method of slide scanning that is cost effective and accessible to more labs. The team has been tasked with creating this new method of slide scanning for the client that will improve on either the speed of the scanning, the image quality and resolution, or the storage of the images themselves. The slide scanner should take 10-15 minutes a scan, provide clear images with proper image stitching, and should not damage any of the microscope slides. Additionally, the scanner should not interfere with any other equipment in the lab, and should work until a new slide scanner is able to be purchased. In order to solve this problem, the team designed an automatic slide glider. This slide glider will automatically move the stage of a microscope with a high resolution camera in small increments to get images of the slide. Then, the team will use software to stitch all the images together and provide the client with high resolution images of the slides. In order to ensure that the slide glider is meeting the criteria provided by the client the team will perform tests and evaluate the glider based on various criteria. If any design specifications or requirements are not met, the team will discuss future modifications.

Table of Contents

I. Introduction

Motivation

Cytology labs require the use of microscope slide scanners in order to have digital copies of the slides they scan. Digital microscopy has introduced novel ways to improve tissue-based research and imaging. They do this by allowing for faster and easier sharing of images via computers, improving storage methods, and allowing for annotations of features on the slides. Additionally, they provide many benefits when it comes to education. [1] However, many slide scanners are expensive, and hard to acquire for cytology labs, especially those at public universities. Therefore, there is a need for a method to create a low cost slide scanner to expand accessibility and availability of high quality slide scanners to a broader audience.

Existing Devices and Current Methods

The client's lab currently uses a Leica Aperio CS2 Slide Scanner. This slide scanner creates digital images of microscope slides from your desktop [2]. However, the client has found many issues with this scanner. Because this is an older version scanner, the device does not scan slides quickly, and the clients are unable to scan as many slides as they would like in a day. Additionally, this slide scanner is unable to capture the high resolution images the client needs, especially of the nucleus of cells. This is in part due to the old camera on the scanner, but also due to the z-axis limitations that the scanner has.

There are currently several commercial microscope slide scanners on the market that meet all of the needs of our client. The Hologic Genius Digital Imager uses Volumetric imaging to capture high resolution, in-focus digital images of microscope slides. It also utilizes AI capabilities and images of multiple z-axes of the slide to address the issue of multiple z-axis. Additionally, this scanner has a 400 slide capacity, and can scan slides at a much higher rate [3]. Morphle Labs Inc also creates microscope slide scanners that offer live z-stacking, volume scanner, and whole slide imaging. These scanners offer high resolution images, can image around 120 slides a day, and have a short scanning time [4]. The Hamamatsu NanoZoomer S20 Digital Slide Scanner is also highly rated for pathology, and can scan approximately 20 slides in 15 minutes. They also offer desktop digital slide scanners such as the NanoZoomer-SQ, which allow for fast slide scanning, though they do not provide as high resolution of images [6]. Though these commercial slide scanners address the needs of our client, they are extremely high in cost, and thus not feasible for our clients to purchase and utilize.

Problem Statement

The team has been tasked with finding a more efficient way to scan microscope slides using digital scanning. The client's department already has a scanner, but it is time consuming and provides low quality images. Therefore, the team must find a way to enhance the user quality of their digital scanner, as well as the images themselves. The department has also asked our team to create software capable of housing the images. This project will benefit multiple labs who utilize slide scanning on campus, including the primate lab and SMPH.

II. Background

Relevant Biology and Physiology

The clients are currently utilizing the microscope slide scanner in a cytology lab. Thus, there are certain aspects of these scans that are more important to focus on than others. For the specific needs of our clients, it is imperative that the nucleus of all the cells on the slide are visible. Additionally, our clients utilize whole slide imaging, and thus it is important that the device is able to capture an image of the entire slide.

Client Information

The clients, Terri Stewart and Joshua Faulkes, are employees of a cytology lab at the University of Wisconsin-Madison. They require a microscope slide scanner that provides high quality images of microscope slides, especially the nucleus of cells, for their work needs.

Design Specifications

This design is being built for our client's lab to scan and take high quality images of slides until our client can receive the grant needed to purchase a new one. Due to the client's 20 year old scanner, many issues have been made clear. The images are blurry, dark, take extremely long, and do not have good z axis resolution. We have decided that it is vital to get a 10 - 15 minute scan time to help tackle the thousands of slides the lab has. The final images must be clear with proper stitching. The slides must retain zero damage and be left completely intact during and after the scan. Our design must last the lab until they get a grant for a newer/better professional scanner. They have scanners in mind that are very good and expensive so we are providing them with a lasting solution until then. Another important factor of our design is it must not interfere with other equipment in the lab. Our design must be small, built in,

and compact to prevent interference with equipment. Lastly we cannot exceed a capital purchase of greater than 5000 dollars. We do not see this as being an issue and should not be a serious cause for concern on this project.

III. Preliminary Designs

The Slide Glider

The Slide Glider design consists of a 3d printed stage for a microscope with 2 motors for moving a slide along an x and y axis coordinate system. The stage will be bolted into the place of the old stage and the motors will be placed onto each side of the stage. The slide will be held on by a clamp that lays on a thin piece of plastic resting on tracks that lay in the x and y directions. There will be an algorithm that will tell the camera to take a photo after moving the slide the preferred distances. The algorithm will crop the image to 75 percent field of few and the motors will move the slide the exact distance from where the last crop was and take another photo. After doing this, the images will be stitched together making a high quality, clear image that is able to be looked at in high detail clearly by lab techs or students. This is highlighted by the three step process : crop, stitch, save. This design has similar implications to that of Zaber products [5], however ares differs in two motor system and 3d printed replaceable stage.

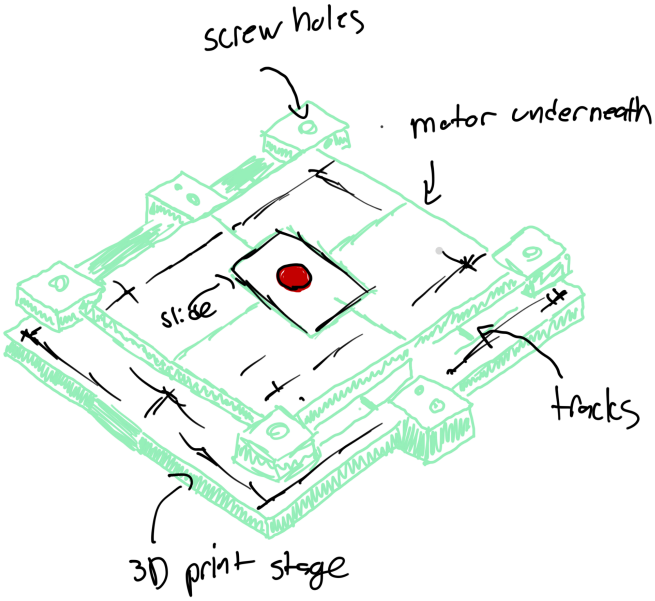

Figure 1: The Slide Glider

Deconvolution Software

The deconvolution software uses multiple different algorithms to remove the blurriness seen in the slides scanned by the current microscope slide scanner. The software will get the already scanned image of the slide from the microscope slide scanner and break it down to its initial components before they are stitched together by the software of the slide scanner. The main algorithm that is used is the multi-neighbor deblurring algorithm that will use the other layers of the image (Z-stacks) to predict the structure hidden behind the blurriness[10]. This is just a prediction and can have an inconsistent accuracy especially with complex images such as the cell cultures scanned by the microscope slide scanner. Therefore, we included the unsharp masking and fourier space algorithms working together with the multi-neighbor deblurring to improve accuracy and make sure the pictures don't miss anything[11]. The unsharp masking will reconstruct the image by making the improved and original the same resolution and then comparing and reconstructing the improved image based on the comparison[11]. The fourier space algorithm will achieve the same goal of increasing accuracy but by determining the traces of the images, original and improved, and fixing the image produced by the unsharp masking algorithm[9]. Once the improved images are produced they will be stitched back together and easily viewed by our client.

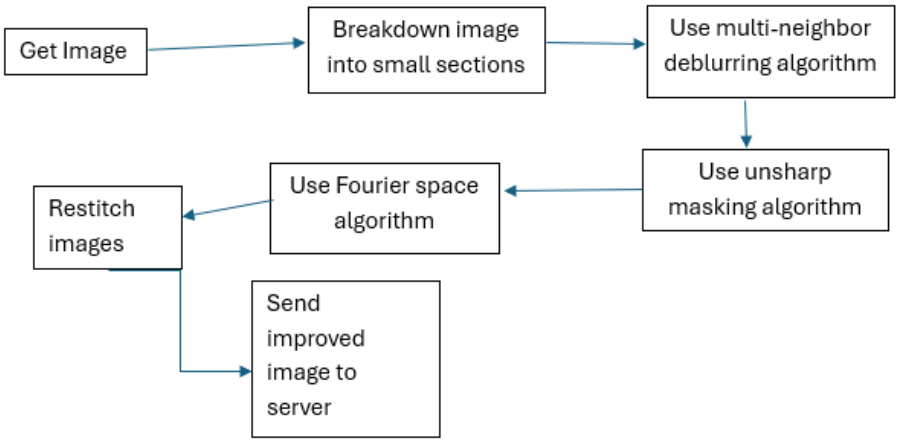

Figure 2: Deconvolution Software Flowchart

AI Image improvement

The use of AI Image improvement to consistently improve the image quality is very beneficial as it will remove all issues the client is facing with the image clarity. The main component of the AI design is the Super resolution convolutional neural network (SRCNN) that will look at all parts of the image and determine the parts that need improvement. SRCNN will then run the part of the image through different improvements and determine the best one and will repeat until the improvement is negligible[8]. Then we will grade the image based on our needs and determine if the image needs further improvements or if it's

satisfactory. If it fails the grading we will run the image through the Deep Image Prior algorithm which will calculate the different depths of the image based on color and complexity and determine the best improvement needed for the image[10]. To make sure that the image isn't changed from the Deep Image Prior the image will run through the Fourier transformation algorithm, which will make sure the image is unchanged by comparing the traces of the image and fixing them if needed[11]. Then the Image will be sent to a server where it will be accessed by our client and others.

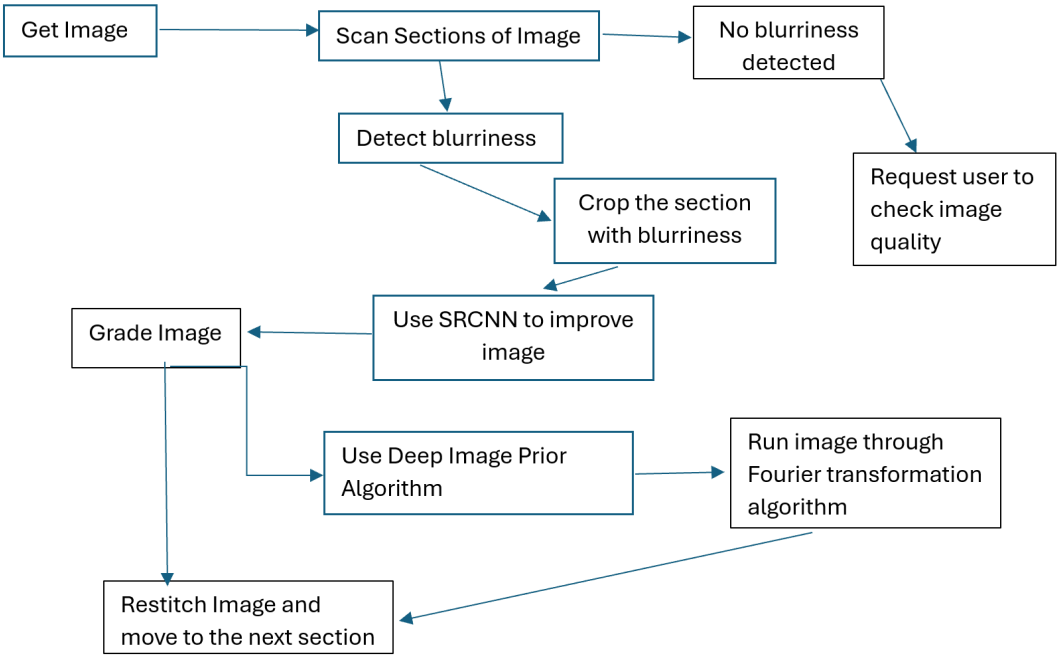

Figure 3: AI Imaging Software Flowchart

IV. Preliminary Design Evaluation

Design Matrix

Design Criteria	Design #1: Automatic Slide Glider		Design #2: Deconvolution		Design #3: AI Image Improvement	
Accuracy (30)	4/5	24	3/5	18	4/5	24
Feasibility (25)	3/5	15	3/5	15	2/5	10
Useability (20)	4/5	16	4/5	16	3/5	12
Speed (15)	4/5	12	2/5	6	3/5	9
Cost (5)	3/5	3	5/5	5	5/5	5
Manufacturability (5)	4/5	4	5/5	10	4/5	8
Total (100)	74		70		68	

Figure 4: Design matrix evaluating three preliminary designs

As shown above the team decided to evaluate the three preliminary designs on a basis of 6 criteria. All categories were given a weight based on client requirements with all 6 adding up to 100 . The highest weighted criteria, accuracy, refers to how well the design is able to improve the image quality of the scans. This is the most important criteria as the client wants the slide image to be improved as much as possible. The next criteria makes sure the design is feasible to make during the semester, so that the client is able to start preparing scans for teaching purposes. The team also saw useability as an important factor as the finished design needs to be easy for the client to use and understand. The client also mentioned that they would like the speed of the scans to be improved if possible, however it was not the most important improvement that needs to be made so this category was only given a weight of 15. Since there is a budget for this project cost given consideration for the designs, however it was not as important due to the low cost of the designs. The last category describes the ability for the design to be replicated, however, this is not a huge concern for this semester so it was rated as one of the lowest categories.

The first design, the Automatic Slide Glider, scored the highest in most categories. This design has already shown to be accurate due to the fact that the client's current microscope already achieves the kind of clarity she is looking for. It's also relatively feasible to fabricate due to the team's previous and existing knowledge of the skills and techniques required to build the required mechanism. The entire process from scanning the slides to stitching the photos together will be fully automated making this

design very easy for the client to use. Also, the mechanism will be able to take photos quicker than the client's current scanner allowing the design to also score high in speed. Cost and manufacturability received a middle range rating due to the materials/motor required and relatively reproducible design. This design was therefore rated highest overall since it scored higher in the categories deemed most important.

The second design, deconvolution, scored relatively low in accuracy since the team is not sure if this method would fix the current problem with blurriness seen in the scans. However, it did score high in feasibility and useability since our task will be utilizing pre-existing programs in an easier to use interface for our client. This design did score low on speed, however, since it requires the use of different z axis images which takes a while to collect and for the algorithm to process. This would also be a very low cost option earning it the highest score in that category since the only materials needed would be storage. It is also a very easy to reproduce product since it is all software based.

This design only scored highest in accuracy and cost. This is due to the fact that more advanced scanners use AI and have attained better image quality. It is also all software based so cost will be very minimal. Despite its strong accuracy to our clients needs, it has the negative aspect of slow processing and continuous use that could hinder our overall clients experience with the finished product. Additionally it was not feasible for the group to make since the level of knowledge regarding programming AI is missing.

Proposed Final Design

The final design was decided to be the Automatic Slide Glider. A huge consideration for this decision was the already proven accuracy of the design. Since it would utilize the camera on the client's microscope, the team rated its accuracy by comparing images from the microscope with those from the client's current scanner and the microscope showed a level of clarity that the client thought very acceptable. The skills needed to fabricate this design are also already established within the team making it feasible to build within a semester so that the client can start preparing scans for teaching purposes. The process of scanning will be almost fully automated and much easier for the client to use. Lastly, since the other two designs still utilized the current scanner, this design was the only one shown to be able to improve the speed of the current process. The only difficulties compared to the other two designs are in terms of cost and manufacturability. However, since the cost will still be under budget and manufacturability is not a huge concern for this semester, it was chosen to be the final design.

V. Fabrication/Development Process

Materials

At this point in the design process the material list has not been finalized. However, the team plans to incorporate the use of arduino compatible stepper motors. The design will also require the use of gears and bands. The gears will be attached to stepper motors so that bands connected to a small stage in both the x and y axes can run through the gears allowing the motors to move the stage in small x and y axis increments. Therefore the use of screws and bolts will be necessary to attach the bands to the stage as well as a clamp to secure the stage to the microscope itself. The stage itself will be prototyped out of PLA filament due to its relatively low cost [13]. However, the final design will possibly utilize a material of higher quality to ensure the longevity of the product.

Methods

The stage will be modeled using SolidWorks so changes can be made over time to ensure the stage can be fitted to the client's current microscope. It will then be exported to the UW Makerspace to be 3D printed using PLA filament. There will be indents designed into the stage to house the slides so that securing them to the platform does not alter the slides in any way. There will also be notches designed into the platform so that bands can be attached using screws and bolts. The bands will then run through gears the team will attach to the stepper motors. Once the stage is fabricated, the stepper motors will be coded to move the stage in xy increments that ensure all parts of the slide are being captured by the microscope. Software will then be developed that will crop each image taken of the slide to a consistent size. The images will then be stitched together using the same program so that a final scanned photo can be outputted and stored for the client to use.

Testing

The stage will be fitted to the microscope so that the team can make sure the design does not interfere with the microscope itself while making sure it is securely in place. The design will then be tested without any slides in place so the process can be observed. Once the process has shown to not be damaging to the slides in any way, it will be run with slides that have already been scanned by the client's current scanner. The runtime of the entire process, including stitching the photos together, will be recorded using multiple slides. The scans themselves will then be analyzed next to pictures from the client's current scanner. Regions of blurriness in the images from the scanner will be closely observed in

the scans taken with the final design. This will help the team determine if the quality of the scans is significantly better than that of the client's current method.

VI. Results

No testing has been completed at this time. However, once the scan times have been recorded over multiple trials, a t-test will be performed. This will determine if the runtime of the final design is significantly faster than that of the current scanner. The standard deviation of the runtimes will also be noted to evaluate the consistency of the final process. The average runtimes of the old and new processes will be represented using matlab with standard deviation bars outfitted to the graphs so that the methods can be compared. Sections of the scans themselves will be closely analyzed across multiple slides. These images will be displayed next to each other so that the image quality can be easily compared to determine if the new process achieves a higher clarity in the cells' nuclei and around the edges of cell clusters.

VII. Discussion

The design of the product, the slide glider, is made so that it can be used by any microscope with a camera able to take pictures of the slides. This flexibility will allow not only the client, but many others to scan slides in an efficient manner.

The accumulation of the group's research plus the data and information provided by the client have allowed the team to determine the proper safety regulations that need to be followed. Since this is intended to be used for medical diagnostics as well as research it would need to meet FDA's standards regarding attachable microscopic bases as well as the standard for microscope slide scanners as this design is counted as both. The product should also provide significantly improved results compared to the microscope slide scanner without hindering the current capabilities of the client. The slide glider should be easily attached to the microscope without breaking or affecting the microscope it is being attached to. Additionally it should be able to operate without affecting the functionality of the microscope by either creating an alignment issue or clogging gears used for the Fine Focus or Coarse Focus or any other rotary based function used to adjust the microscope.

Possible sources of error that could lead to these issues are inaccurate measurements of the intervals the product should be moving in the x-axis and the y-axis and the force used to move the slide. The dimensions of the product should also be accurately calculated to prevent interfering with the

microscope functions. Additionally, a default position, (0,0) calculated based on the microscope's center should be easily accessible by the product after it has finished its scanning so that it is easier for the client to use the default functions of the microscope. This will also prevent the issue of misalignment with the microscope.

VIII. Conclusions

Scanners can be very useful for labs in order to digitize slides for online diagnostic and educational purposes. The client's current scanner is not providing her with adequate resolution surrounding the nuclei of cells and the edges of cell clusters and takes a long time to scan slides. The client's lab has budget restraints that have prevented her from obtaining a new, updated scanner. Therefore, the team has been tasked with finding a low cost solution that will speed up her current process and provide her with clearer images.

The final design consists of a movable platform that will replace the current platform on the microscope. It will incorporate the use of arduino compatible stepper motors and tracks/bands to move the stage in x and y directions. The camera attachment already on the client's microscope will then take a picture of each part of the slide. An algorithm will then be implemented to crop the pictures to a consistent size and stitch them together so that the entire slide can be incorporated into one photo. This design was chosen among two others due to the high quality of the microscope's camera showing that this method will achieve a high level of accuracy. It also completely bypasses the client's current scanner, making it possible for this design to speed up the client's current process.

If time permitted, the team would have spoken to the client more frequently to better understand the direction she wanted to go in. That way, the preliminary designs might have been more specifically geared towards a mechanical solution. However, the team did not know which problem the client wanted to focus on, causing the designs to be very different and less detailed.

Next steps for this project include compiling a finalized list of materials. The team then needs to model the platform on SolidWorks and begin prototyping so a correct size can be achieved. The team then needs to fabricate the rest of the platform once materials are obtained. As for the software portion, an algorithm needs to be developed and tested for cropping and stitching the photos together. The team also needs to better finalize a storage method for the scans. The arduino also needs to be coded to move the stepper motors so the slide can automatically move underneath the microscope. The team then needs to test the method for speed and closely observe differences in scans taken with the old scanner and the final design.

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