

Biomedical Engineering Design

Endoscopic Measurement Device to Monitor Tumor Growth in Vivo

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Abstract

Our clients from the UW Department of Oncology are trying to assess various potential treatments for colorectal cancer. They are doing so by monitoring tumor growth and recession in rats and mice with colorectal cancer by taking images of the tumors with an endoscope. However, the images obtained with the endoscope are distorted and do not have a frame of reference making size comparisons between images difficult. Without accurate measurements of the change in tumor volume, our clients are limited in their research capabilities. We have researched various ways to accurately measure tumor volume and will be moving forward with two of them: an alginate cast to create molds of the tumors, and the program ImageJ to model the tumors in 3D.

Introduction

Background:

Colorectal cancer is the third leading type of cancer in both prevalence and mortality for both men and women. In order to assess the potential treatments for the cancer, our clients are trying to monitor tumor growth and recession over time. In order to increase the sample size they can study, an animal model with rats and mice is being used. The animals have a mutated Adenomatous Polyposis Coli gene in order to induce colorectal cancer [1].

The best way to measure the volume of these tumors would be with computed tomography (CT). However, CT is not an option for our clients. CT scans are expensive, and more importantly, the animals would need to be removed from the cleanroom in order to get a CT scan. Removing the animals from the cleanroom would introduce too many uncontrolled factors into the research. Because of this, our clients have to use an alternate method to image the tumors, colonoscopy. An endoscope is inserted into the colon of the rat or mouse and both images and video can be provided. An example image is shown in Figure 1. This procedure is done with the animal under anesthesia multiple times during the animals' lifespan; the end product being images and/or video of the tumors throughout the cancer's progression [1].

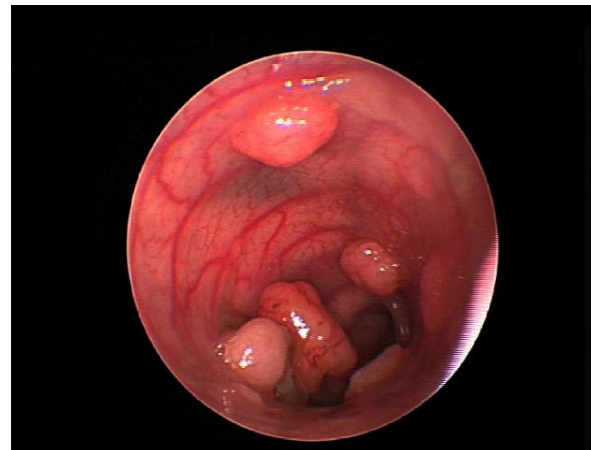


Figure 1. Image obtained from endoscope within a rat colon. Multiple tumors are shown.

Problem statement/Problem Overview:

As stated previously, our clients currently use an optical endoscope, which is capable of capturing video and still images, to monitor the tumor growth. While this device lends itself to provide qualitative observations of a tumor's change over the course of treatment, there is currently no way for our clients to gather any direct quantitative data regarding the changing size of the tumor. In order for our clients to

effectively measure potential treatments for cancer, it is important for them to be able to quantitatively measure a tumor's growth or regression in response to treatments. As such, the main goal of our project is to design a device or a technique that would allow for the researchers to accurately measure the volume of tumors, *in vivo*. Additionally, measured values such as the tumor's diameter, and cross-sectional area are desired in order to aid in the analysis of tumor change with respect to treatment.

The benefit of using the optical endoscope, besides gathering a visual image of the tumor, is that the endoscope has a working channel. This is a channel that runs the length of the endoscope and can essentially allow any tool small enough to fit through the working channel to come into contact with the tumor site, which opens up a wealth of possible approaches to measuring the tumor without any direct change into the basic methodology of the endoscope use.

Problem Motivation:

Beyond the basic need for our clients to be able to monitor tumor growth or recession over the course of treatment, this project has the potential to change a much larger field of research. By developing an effective method to measure tumor volume and dimensions *in vivo*, applications of our design could readily be applied to a clinical environment and be used to assist in the measurement of human colon tumors. The desire for a way to monitor tumor size is not only restricted to studies related to colon cancer, but would also be existent in studies of areas such as the gastrointestinal tract. As such, our motivation for this project is to develop a method of accurately measuring tumor size *in vivo* over the course of an experiment with the goal of not only assisting our clients, but also possibly creating a device that has the potential to assist in other fields of cancer research.

Client requirements:

The main stipulation of our project is that our measurement technique or device must not harm the tumor or the surrounding tissue of the animal. It would be undesirable if the measurement technique interfered with the experiment. From these measurements it would be ideal to get an absolute volume of the tumor during each measurement. However, our clients would be satisfied with a technique that could measure relative changes in tumor volume; this comes with the thought that the absolute volume can be measured at the end point, and then from the relative volumes, absolute volumes at the different stages can be measured. Our measurements must not allow more than 10 to 15 % error. Measurements of specific tumors might be monitored upward of six times throughout an experiment, so our device must be able to be used often. In addition, our technique would need to minimize experimenter error by placing the burden of acquiring accurate results on the device and not the experimenter. Our design must also be able to fit within our clients' specific protocol for their lab. Finally, our project was provided with a budget of \$1000 to complete this project.

Current Devices:

Endoscopes are currently used to visually assess the size of tumors throughout their development. The Storz 7219BA endoscope is used for rat test subjects and the Storz 1232AA endoscope is used for mouse test subjects. The endoscope used for rat testing has a 30 degree tilt angle while the endoscope used for mouse testing has a 0 degree tilt angle. Figure 2 shows the effect lens tilt angles have on the field of view of an endoscope.

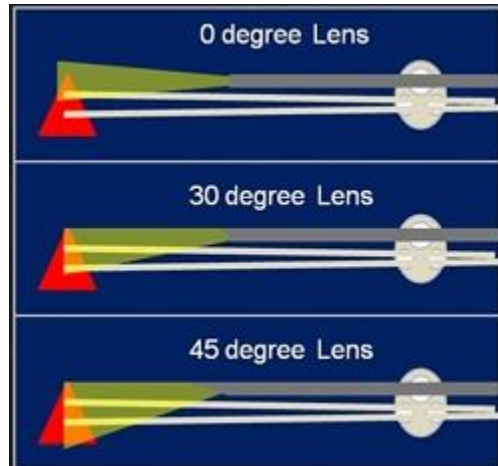


Figure 2: Different lens angles for endoscopes
Source: <http://www.karlstorz.com/cps/rde/xchg/karlstorz-en/hs.xsl/146.htm>

The lens for each endoscope creates a fish-eye distortion. The effect of fish-eye distortion can be seen in figure 3. Notice how the fish-eye lens distorts in image, causing straight lines to become curved and the relative size of objects to be altered. The distortion of size and shape created by a fish-eye lens makes it impossible for the client to determine the true size of any tumors viewed with the endoscope.



Figure 3: Top-image taken using a fisheye lens;
Bottom-Image taken using a non-distorting lens
Source:
<http://en.wikipedia.org/wiki/File:Panotools5618.jpg>

Competing Methods:

In a paper titled *Three dimensional measurement endoscope system with rulers*, Nakatani, et al. describe a method of fish-eye distortion correction and 3D visualization of tumors. Such a method could provide researchers with the ability to create 3D representations of tumors and use software to determine the volume of these 3D shapes. Nakatani, et al. attached four lasers to the end of an endoscope (Figure 4)

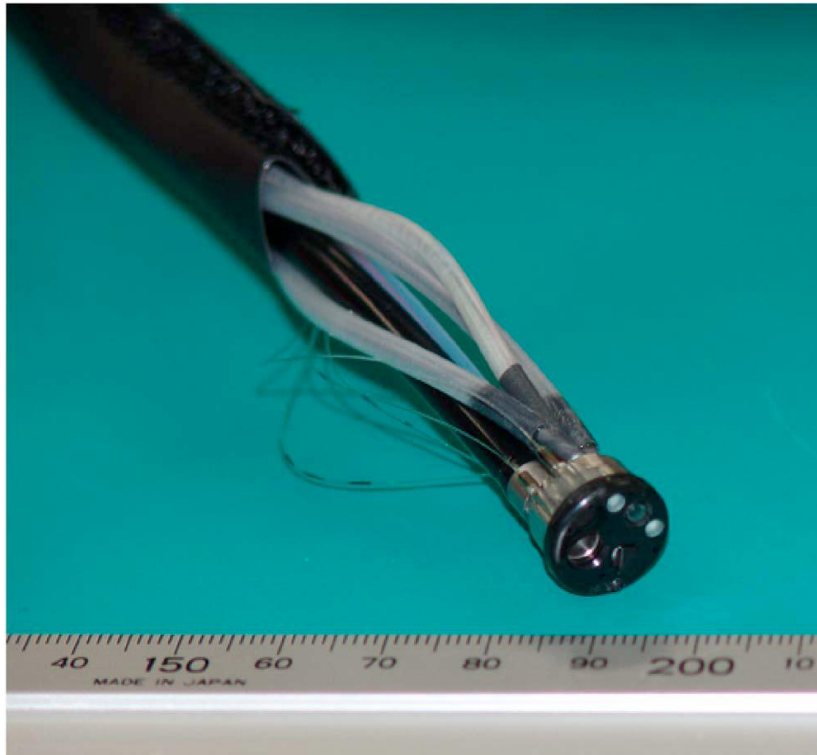


Figure :4 Distal end of an endoscope altered by the addition of four lasers (Nakatani, et al.)

Using contrast detection software, Nakatani et al. were able to locate each of the four laser points in the endoscope's field of view. The location of the four laser points relative to one another was used to determine the curvature of the surface onto which the four lasers projected. By determining the curvature of tumors, Nakatani et al. were able to create 3D representations of these tumors. We decided not to attempt to recreate this approach due to the cost constraint of \$1000 on the project and the time constraint of one semester. Due to the extensive testing needed to configure such a system we determined it would take far too long to implement this approach.

Potential Designs

3D Image Creation:

One design uses a series of pictures taken by the endoscope to stitch together a 3D image of the tumor. This approach requires first that the endoscope fish-eye distortion be corrected. We have contacted Storz, the company that manufactures our client's endoscopes, and found that they do not currently have any software available to correct fish-eye distortion. If our team were to use this approach we would need to develop fisheye correction software on our own. *Videoendoscopic Distortion Correction and Its Application to Virtual Guidance of Endoscopy* by Helferty et al. outlines a set

of algorithms that can be used to create this type of software for an endoscope. This process would require testing to ensure that the correction variables for the client's endoscopes are correct. To create a 3D representation of the tumors using 2D images, the exact positioning of the endoscope would need to be known for each of the 2D images taken. This could be achieved using a moving stage with a micrometer on each dial (figure 5).

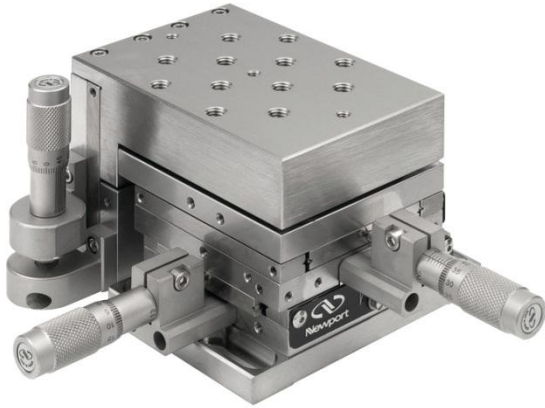


Figure 5: A moving stage with micrometers on each dial.

Source:

<http://www.newport.com/store/product.aspx?id=140089&lang=1033>

The path taken by the endoscope in this method is shown in figure 6. The endoscope would first take images moving down the depth of the tumor (Y direction), then along the length of the tumor (X direction). Each time an image is taken the position of the moving stage would be recorded.

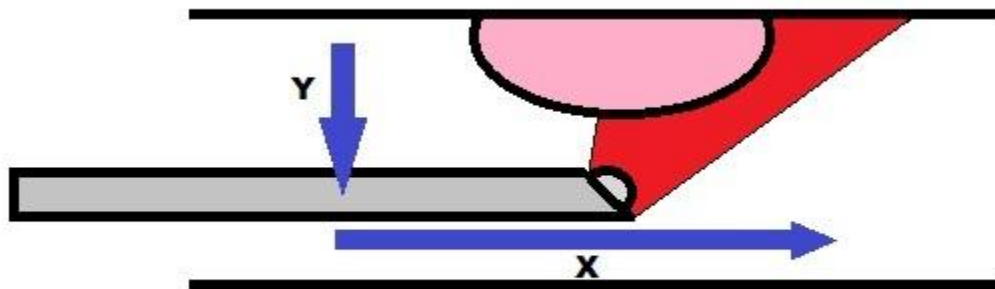


Figure 6: The path taken by an endoscope in the 3D image method

The reconstruction of the 2D images into a 3D image could be accomplished using ImageJ software. ImageJ is an open source imaging software. Independent developers have created plugins to the program that would allow us to stitch together a series of 2D images into a 3D representation. Once a 3D representation of the tumor is created, the volume of the tumor could be determined using ImageJ software.

Alginate Cast:

Our next design idea is to make an alginate cast of the tumors that we can analyze for volume outside of the rats. Alginate (Figure 7) or alginic acid is an anionic polysaccharide found in the cell walls of brown algae. When treated with Ca^{2+} ions and D-glucono-d-lactone (GDL) homogeneous, strong and biocompatible gels can be formulated with controlled gelation rates

proportional to the concentration of Ca^{2+} ions. These gels can gel *in situ* in 30 seconds to a minute [4]. It is these properties that make alginate a good candidate for a gel cast of the tumors.

To see the procedure to form this cast see appendix Alginate Cast. First an angioplasty balloon will be threaded into the colon from the *anus* so that the bulb of the balloon marks the end of the area of interest to the researchers. This balloon, along with the tube leading to it will be inflated to create a temporary blockage in the colon. At this point the alginate will be prepared and injected into the colon from the *anus*. This gel will then fill the colon completely and stop at the blockage. After 30 seconds to a minute the alginate will have gelled. At this point the angioplasty balloon will be deflated along with the tube leading to it. This will free up space down the central axis of the gel cast allowing the gel to press less tightly against the walls of the colon. The gel will then be gripped with a pair of tweezers from the entry way to the colon and removed, with the intention of not harming or removing any of the tumors.

This gel will be a cast of the negative volume of all of the tumors. These tumor voids can be filled with soft clay to exactly match the shape of the tumor molds. Once these pseudo tumors have been formed the gel can be stored or discarded. The clay tumors can then be individually placed in a graduated cylinder filled with water to assess water displacement and therefore tumor volume.

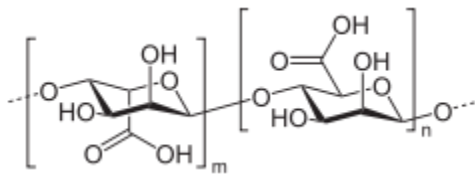


Figure 7: Chemical Structure of Alginate

Physical Estimation:

In this design, direct physical measurements of specific parts of the tumor are utilized in order to estimate the tumor’s dimensions and its overall volume. This is accomplished by modeling the tumor as an ellipsoid. Under this model, the tumor volume would be provided by the following equation:

$$\frac{4}{3}\pi abc.$$

Here, a, b, and c represent the largest radius of the tumor in the x, y, and z directions with respect to the tumor. This is illustrated in Figure 8. In this figure, a radius value of the tumor would be measured coming orthogonal to the colon wall, a denoted by the yellow line. Another radius value would be measured going parallel to the wall, as denoted by the black line. A final radius measurement would be measured going from the anterior to the posterior regions of the tumor, as denoted by the blue line. Ideally, these

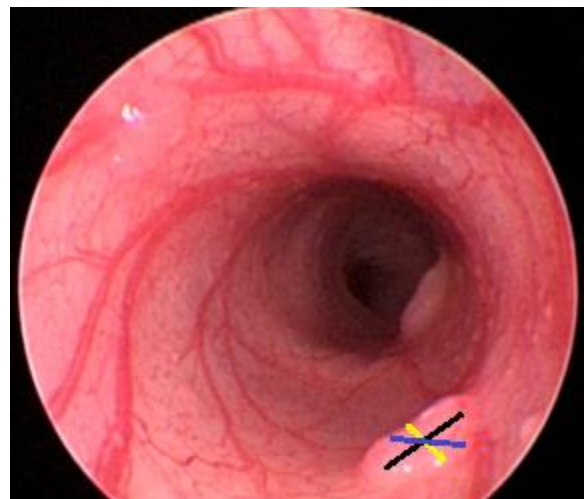


Figure 8: Orientation of the respective tumor radii needed to model the equation.

measurements would be able to be recorded by a small caliper-like device that is fitted through the working channel and is controlled externally by the experimenter.

We were able to locate a paper which used a similar approach to measure tumor volumes. One factor they needed to add in order to get accurate measurements was to multiply the ellipsoid volume equation by a constant, which was determined experimentally in order to account for the irregular shape of tumors [5]. With a calibrated equation the researchers were able to acquire statistically accurate readings within a p-value of .001 for their calculations of the tumor volume and the actual tumor volume [5]. The need for the experimental constant in order to compensate for the size would make this design less than ideal, as we would have to sacrifice many animals in order to obtain a corrected equation. In addition, this method may prove difficult in measuring the radii of small, flat tumors, placing more of an emphasis on the operator’s dexterity in acquiring the needed values than the actual method itself. Additionally, this method assumes that the measured radii of the tumor are in fact the largest values. This assumption may not hold true, as the determination of where to measure would lie with the experimenter, leaving this design open to human error. Even greater possibilities for error would result if more than one individual were to acquire the data as there would be inconsistencies with the points of measurement between the researchers.

Final Design Selection/Design Matrix

Table 1: Design Matrix

	Ease of Procedure	Time Requirements	Cost	Estimated Accuracy	Adherence to Protocol	Repeatability	Potential Damage to Tumor	Applicability to Different Tumor Shapes	Resolution	Total
Maximum Points	10	10	5	15	5	15	15	10	15	100
Alginate Cast	8	8	2	12	1	12	6	8	15	72
3D Image	4	3	5	9	5	8	15	8	10	67
Physical Measurement	5	5	1	7	5	6	12	7	5	53

Our design matrix determined that the alginate cast idea is our best option. The alginate cast benefitted from being simple and easy to perform repeatedly. It also has the potential to be the most accurate. The cast would give an actual representation of the entire tumor unlike the other two ideas. The physical measurement idea would only have actual information for the dimensions measured, and the 3D Image idea would have no information for the back side of the tumor where the endoscope cannot reach. The 3D Image idea suffered from being a tedious procedure that even with precise measurements would be hard to repeat exactly due to peristalsis causing the colon to move. The physical measurement idea’s main flaws were that it would be very difficult for us to fabricate a device both small and precise enough to be used. It also would require a high degree of dexterity by the user.

However, the alginate cast idea still has some potential flaws. The most likely flaw is that removing the cast could also remove tumors, especially for larger tumors which would provide more resistance against the cast. Removing a tumor would be very bad for our client’s research, as they would be unable to monitor the further progression of that tumor. Because

of this, we have decided not to eliminate the 3D image idea yet. 3D image analysis was determined to be our second best choice, and it also complements the alginate cast very well. The alginate cast may be unusable for larger tumors, but modeling larger tumors in 3D is actually easier since more spatial information could be inferred from the endoscope images. The alginate cast could also provide the information on the back side of the tumors which would otherwise be lacking in the 3D image idea, increasing the accuracy of the approximation. Even if the alginate cast accurately gives volume change, 3D imaging could still be useful since the 3D models could be easily stored, which may be useful for our clients.

Future Work/Conclusions

Our team must acquire alginate, CaCl_2 , and GDL to perform the “slow-gel” method described by Kuo et al. Properties of this gel that must be assessed are gel time, preparation time, consistency and elasticity. The gel must be strong enough to keep its form throughout the entire procedure, but be elastic enough to not harm the tumors or the rats when being removed. We will first attempt our procedure on a mock colon made out of a plastic straw and clay tumors before we attempt to test the model *in vivo*. If the mock tests work, we will need to acquire an angioplasty balloon from our clients and perform *in vivo* testing.

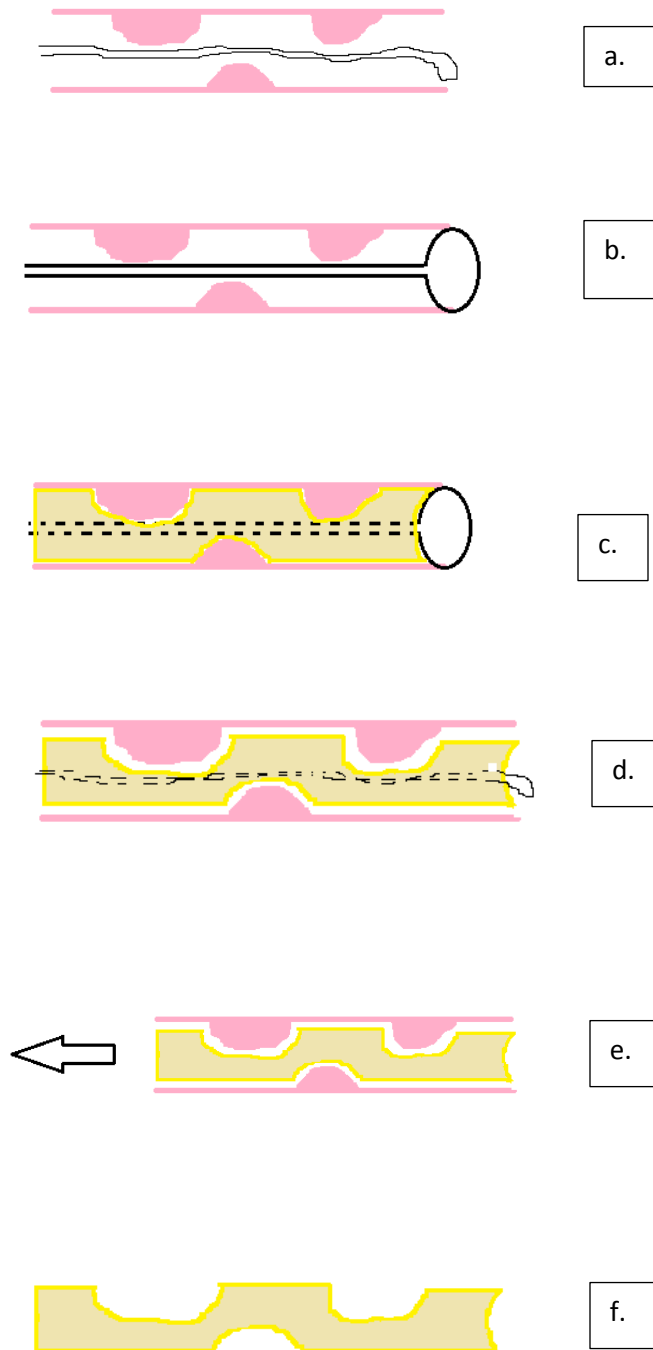
If the alginate tests fail, we will pursue our second design option of modifying the current endoscope with image analysis software. We will need to find a program to fix the inherent “fish-eye” quality of the lenses. We will also need to test the image J software stitching and analysis. This will be done first on an object of known volume in ideal conditions to see if we can find its volume. If these tests work, we will need to construct the “breadboard” structure consisting of a stage, animal restraints, and endoscope restraints. This procedure will then be tested *in vivo*.

References

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- [2] Nakatani, H., Keiichi, A., Miyakawa, A., Terakawa, S. Three-dimensional measurement endoscope system with virtual rulers. (2007) *J. Biomed. Optics*. 12(5)
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- [4] Kuo, C., and P. Ma. "Ionically crosslinked alginate hydrogels as scaffolds for tissue." *Biomaterials*. 22. (2001): 511-521. Print.
- [5] Mai, K. et al. 2003. A Simple Technique for Calculation of Volume of Prostatic Adenocarcinomas in Radical Prostatectomy Specimens. In Pathology. 599 – 604

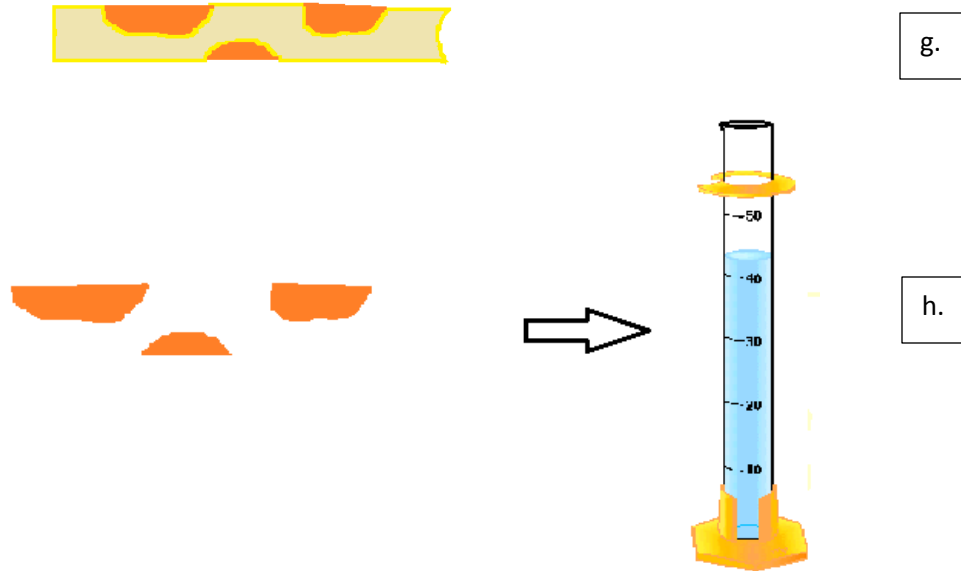
Appendix

Alginate Cast:



Alginate Cast Procedure:

- a) Balloon threaded into colon
- b) Balloon inflated
- c) Colon filled with gel
- d) Balloon deflated
- e) Alginate cast removed
- f) Alginate cast alone
- g) Clay tumors made from alginate cast
- h) Alginate cast discarded; clay tumors analyzed for volume in graduated cylinder.



Product Design Specifications:

Function:

Our goal is to devise a method for measuring the size (ideally volume) of tumors by looking at pictures of tumors within a rat's colon taken with an endoscope. This must be done without harming the animal or destroying the tumor. This will allow our clients to better research colon cancer with an animal model.

Client Requirements:

- Find volume of tumor
- Can't harm the animal
- Can't harm the tumor
- Budget of \$1000 to build
- Less than \$100 per measurement
- Animals can remain in clean room
- Clients have to be able to use any software necessary in our design

Design Requirements:

1, Physical and Operational Characteristics

a. Performance Requirements:

- Usable up to ten times per day
- b. Safety:
 - Biologically compatible materials
 - No danger of parts breaking off
 - No sharp edges ideally
- c. Accuracy and Reliability:
 - Measure volume consistently with under 5% error
- d. Life in Service
 - Must be operational for daily use for 5 years
- e. Shelf Life:
 - The shelf life would be the same as the shelf life of the endoscope and the computer
- f. Operating Environment:
 - Within a rat or mouse colon in an oncology lab
- g. Ergonomics:
 - No more challenging or uncomfortable than using an endoscope
- h. Size:
 - Any device would have to fit in a 2.2-2.5 mm (5 french) working channel
 - Programming should be limited to be a reasonable file size for a personal laptop
- i. Weight
 - Light weight enough for one person to hold and maneuver comfortably
- j. Materials
 - Aluminum shaft used as a cover for the scope probe
- k. Aesthetics, Appearance, and Finish:
 - Programming would need a simple enough GUI for our clients to be able to use without much programming background

2. Production Characteristics

- a. Quantity: 1 deliverable
- b. Target Product Cost: Less than \$1000

3. Miscellaneous

- a. Standards and Specifications: Adhere to any standards for animal testing
- b. Customer/Patient related concerns: Cannot harm rat or user either by shock or physical damage
- c. Competition: Nothing currently available that deals exactly with this problem. Some things deal with facets of the problem but nothing covers it all.