Snooperscope
Actuation Feasibility Study

Towards a magnetic biopsy probe for early disease detection and diagnosis

November 14, 2007

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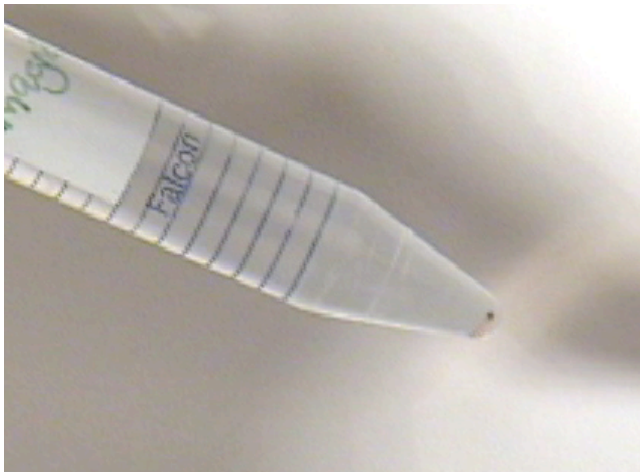

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Fallopian Tube Probe: Actuation Feasibility Study

Investigator: Andrew A. Berlin, Ph.D.
Organizations: Berlin Science and Technology (funded by Canary Foundation) and Stanford University Brown Lab (via volunteer work)

Project Overview and Scope

The ability to detect disease early, and to monitor disease progression, could be greatly enhanced if we had the ability to retrieve fluid and/or tissue samples from extremely difficult-to-access regions of the human body, such as the fallopian tubes. This project investigates the issues associated with applying actuation forces to propel a remotely-driven sample-collection probe within the human body. The specific focus is to determine whether controlled application of magnetic forces can be used to create a robust actuation mechanism suitable for navigation through narrow, fluid-filled channels. Issues such as how to detect the position of the probe within the human body, how to collect the biological sample, and what molecular signatures to scan for in order to detect disease, are beyond the scope of this actuation feasibility study.

Executive Summary

Through simulation and physical experimentation, we have shown that under ideal conditions it is possible to remotely couple energy fields in a way that will propel a magnetic probe through a fluid filled tube, using actuators located a significant (8-inch) distance away. This can be achieved without displacing (pumping) the fluid, using very gentle forces, at modest cost, and with practical control and timing constraints. The next step required to move this technology forward is to gather data regarding the physical properties of the biological tissues of interest, because fundamental properties such as fallopian tube fluid density and viscosity, as well as properties of the tubal wall such as elasticity and yield strength, appear to never have been measured.

Recommendations for next steps

1. Initiate a series of biophysics experiments to characterize fallopian tube mechanical and fluidic properties. Gather critical data for next generation actuator design.
2. Pursue a magnetic sensing feasibility study to complement the actuation feasibility study. Can the location of a magnetic probe in 3-D be detected in a practical manner using remotely located sensors, with sufficient resolution to be useful for navigation? Investigate fusion of magnetic sensing with other imaging techniques (ultrasound).
3. Identify and pursue alternative applications that can serve as ‘low hanging fruit’ entry points for this magnetic probe technology, in settings less demanding than fallopian tube profiling. Create an early success. Consider applications in GI tract and/or lung cancer screening/treatment.
4. Advance the probe technology itself. This would include micromechanical methods for capturing samples, for sensing/limiting force, and for sensing presence of diseased tissue (impedance spectroscopy, etc.).

Additional Acknowledgments

The simulator described in this study was built on the SCMUTILS nonlinear dynamics simulation environment developed by Professor Gerry Sussman, Professor Jack Wisdom, and many of their students and friends, for the MIT graduate course in classical mechanics 6.946. Many thanks to Professor Sussman for making the SCMUTILS system available for this project.

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Introduction

The role of Fallopian tubes in Serous Pelvic Cancer

Serous carcinoma is responsible for the majority of mortality due to ovarian cancer. There is increasing evidence that the fallopian tubes play a key role in the spread of serous carcinoma, serving either as a site of origin of the cancer itself or as an early metastatic site.[15, 16, 17]. Analysis of fallopian tubes that have been prophylatically removed from women genetically predisposed to ovarian cancer, but who have no known disease, yields an interesting window into the status of pre-cancerous fallopian tube lesions. Reported studies of the fallopian tubes include biomarker staining as well as categorization of morphological changes such as absence of cilia, stratified epithelium, and presence of highly disorganized/depolarized/malignant cells. [18] reports that "...the Fallopian tubes of women predisposed to developing ovarian cancer frequently harbour dysplatic changes, accompanied by changes in cell-cycle and apoptosis-related proteins, indicating an increased risk of developing tubal cancer."[1] Very high correlation was found between metastasized peritoneal spread and the presence of serous cancer within the tubal lumen, reinforcing the hypothesis that the fallopian tubes play an important role in the development of pelvic serous cancers. [17]

There is not currently a reliable diagnostic method available for distinguishing a precancerous fallopian tube cell cluster from a normal cell cluster. Although cancerous cells are positive for the p53 biomarker, several non-cancerous controls were found to be p53 positive as well, making cancer diagnosis by p53 biomarker measurement alone problematic. From the perspective of designing a biopsy probe that can detect cellular dysplasia at a pre-cancerous stage, some combination of morphological markers with biochemical indicators will likely be required. Thus the capability to examine cellular structure in situ, as well as the capability to collect cells for later molecular analysis, are desirable. Abnormalities of interest for early detection of cancer in the fallopian tubes were found to occur in the fimbriated end of the tube, the end closest to the ovaries, which is the most challenging region to access via the cervix.

Diagnostic approaches

The lesions of interest in fallopian tubes are smaller than can be imaged using existing radiological techniques. Advances which utilize biochemically targeted contrast agents have the potential to improve this situation in the future. The ability to locally scan for these contrast agents, rather than utilizing blood-based assays or remote body-scans, has the potential to further enhance sensitivity of this new class of contrast agents.

As a step towards gaining access to fallopian tube cell samples, [12] reports on a study of 150 fallopian tube and peritoneal washings (lavage), finding that positive peritoneal washings and cervical involvement were independently predictive of positive tubal washings. The concordance rate of 72% is not sufficient to justify tubal lavage as an independent diagnostic assay. Further improvement of this diagnostic capability with respect to the fallopian tubes could prove to be quite valuable.

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[1] [18], page 195

For other types of cancer, properties of sloughed-off cells have been found to be valuable indicators of cancer. [13] reports on the use of DNA integrity as a potential marker for stool-based detection of colorectal cancer, while [14] reports on epigenetic changes in fecal DNA. [15] moves from fecal analysis to the use of whole-gut lavage fluid, reporting on DNA mutation analysis in colonic effluent samples.

For future work, an interesting direction to pursue would be a combination of lavage, along the lines of the tubal washing approach described in [12] with the magnetic probe technique introduced in this feasibility study. In this scenario, a biopsy brush would be attached to the magnetic probe so as to encourage sloughing-off of cells into the lavage fluid.

Endoscopy / Falloscopy

Today, short of major surgery, the only way to obtain access to fallopian tubes is via endoscopy. Endoscopic probing of the fallopian tubes via the cervix as a diagnostic technique, a procedure known as falloscopy, received significant attention in the 1990's. While falloscopy has found significant utility in fertility-related procedures, for cancer diagnostics its use is virtually non-existent. The complication rate is unacceptably high for use as a diagnostic screening procedure. One major hospital reported that pinpoint perforations occur in 5.1% of procedures, with the potential for infections and rare serious side effects such as sepsis as a consequence.[11]

The state of the art in endoscopic evaluation of the Fallopian tube is summarized extensively in an article by Surrey [1] and in an article by Gordon et al. [2]. Initially practiced using a guide-wire based catheter, more recently the 'linear eversion catheter' has become the preferred method, as the balloon in the everting catheter exerts no shear stress on the tube wall. Rosch et al. [7] provide an overview of transcervical fallopian tube catheterization techniques.

As we commenced the present study, we believed that this high perforation rate was due largely to the inability of the state of the art in catheters to flex sufficiently to follow the tortuous contours of the fallopian tubes. Hence the desire to develop a small, untethered or very thinly-tethered device.

Next generation technologies

Recently, a group at Massachusetts General Hospital developed a 3-dimensional fiber-optic camera system intended for use in difficult-to-reach areas such as the fallopian tube and salivary ducts.[3] This probe consists of a single optical fiber coupled with an optical system that permits scanning of tissue to produce visual images. The system described is primarily a sensing technique, and would need to be coupled with a navigation system (such as a magnetic guidance system or a linear everting catheter) in order to be used as a fallopian probe.

For the GI tract, numerous companies are working on wireless capsules that collect imaging data, and in some cases capture biological samples. For instance, the ESO-Pill for bolus transit monitoring in the esophagus contains a MEMS accelerometer, an RF

transmitter, and an on-board battery power supply.[4] Similarly, Given Imaging (Yoqneam, Israel) has developed a PillCam that scans the small intestine. Olympus and other medical device companies have significant activity in this area, one of which is exploring magnetically self-propelled capsules at the early research stage.[5]

Related work in magnetic navigation of endoscopes

Magnetic navigation has become well accepted in certain types of cardiac surgery, as well as brain surgery. The leader in this area is Stereotaxis corporation. For the most part these systems consist of small magnetic guidewires fastened to the tip of a catheter, as a means of providing steering of the catheter. Forward propulsion of the catheter (as opposed to steering) is provided by external mechanical forces, not by magnets. Two magnets mounted on either side of the patient are rotated relative to one another to induce bending of the lead-wire, and consequently steering of the catheter. The article by Miller [6] summarizes the benefits.

In the area of untethered probes, the closest related work is that of Mathieu et al. [19] which showed that an MRI system can be used to propel a 3.175mm diameter steel sphere through a fluid filled 6.35mm tube, even in the presence of significant opposing fluid flow. Gonzalez et al. showed that an ingestible capsule may be held in place magnetically to enable it to loiter in areas of interest. [20]

The rotary ‘walking’ propulsion scheme utilized in the demonstration portion of this feasibility study was motivated in part by the work of Chirikjian [21] on the design of spherical stepper motors.

Fallopian tube structure

Kellogg et al. [9] present a structural and morphological map of the human fallopian tube, clearly showing a cannulated region of the fallopian tube surrounded by mucosal folds. Beyond this level of detail, it appears that little is known about the mechanical properties and fluid dynamics of human fallopian tubes.

Actuation System Design

Introduction / key challenges
Remotely actuating a magnetic probe within the body poses several challenges:

- The single most important design requirement is the need to limit the magnitude of the applied forces to ensure that delicate tissues are not harmed. This is challenging because (in the simplified case with magnetic axes of probe and actuator aligned) the forces of attraction between magnet and probe increase very rapidly, inversely proportional to the *4th power* of the distance between actuator magnet and probe magnet. In other words, once the probe starts to move towards the actuator, it will experience very rapidly-increasing forces. Whether actuation is achieved via permanent magnets that are physically moved or reoriented to achieve control over the probe, or via electromagnets that are electrically pulsed, this 4th power of distance imposes constraints on the control system bandwidth, as well as on the direction, magnitude, and distance at which forces that may be applied.
- A secondary challenge is that the actuator and probe magnets are rarely aligned perfectly along their magnetic axis relative to one another, so when applying an actuating force intended to propel a probe forward through a tube, significant translational and/or rotational forces will often be applied to the probe as well.
- A third challenge is that the internal organs of the human body are not rigidly fixed in place, but are free to move to some degree. Hence forces intended to propel a probe through a tube may in part result in motion of the tube itself, rather than motion of the probe relative to the tube. Thus the control system must be robust to translation of the probe relative to its anticipated position.

For the purposes of this feasibility study, permanent magnets are used to illustrate the design tradeoffs involved. Extremely powerful, compact neodymium magnets are now available commercially, in sizes as small as a cylinder of 1mm diameter x 3mm length. Larger neodymium magnets, on the scale of a cylinder 37mm diameter x 37mm length are also available, and are quite suitable for use as actuating magnets. The goal is to use an actuator magnet (or array of actuator magnets) to initiate motion of the probe, with the forces constrained in such a way that the probe is free to move over a substantial distance (at least several centimeters) without generating forces large enough to damage tissue. This design constraint of having a several-centimeter ‘operating region’ also provides a buffer that can minimize the impact of errors in sensing the position of the probe.

Design metrics
A set of parameterized design metrics was developed to characterize the tradeoffs involved in magnetic actuation, using transit through the human fallopian tubes as an illustrative example. This parameterization is designed to capture two forms of uncertainty. First, many of the physical properties of perfused fallopian tubes are not yet known, making it difficult to predict how much force may safely be applied to a perfused

fallopian tube wall. Second, due to position sensing error and motion of the tubes themselves within the body (as opposed to motion of the probe within the tube), the probe may actually be closer or farther from the actuators than the control system expects, and the tube trajectory may differ from the anticipated trajectory as well. To ensure safe operation, the control system must apply forces that are well-controlled under a wide range of positioning and system parameter uncertainties.

As illustrated in Figure 1, for the purposes of developing a design tradeoff parameterization, the following design metrics are defined:

1. **Maximum Propulsive Acceleration** is the maximum force that may be applied to the probe in the direction that is *parallel* to the canal of the fallopian tube at the probe's present location. For the tradeoff curves developed as part of this study, the maximum propulsive force limit is set to a level that would accelerate the probe at **5g**. This level was selected to minimize damage to the fallopian tubes caused by large forces, as well as for practical considerations of control system bandwidth (how quickly the controller can react to probe motion). This limit will need to be revisited once physiological data about Fallopian tube force limitations becomes available.

2. **Minimum Propulsive Acceleration** is the minimum force that the actuators must be able to exert on the probe, in the direction of motion through the tube. This is defined as **1g** acceleration due to the design requirement that the system be able to overcome gravity, driving the probe vertically upwards within the body. In practice, additional force may be required to overcome stiction or obstacles within the tube itself, so this limit may need to be increased once physiological data becomes available.

3. **Maximum working distance** is defined for a single-actuator, single-probe configuration as the largest linear distance from the center of the probe to the center of the actuator, at which the *minimum propulsive acceleration* is achieved. In other words, the absolute limit on how far actuator and probe can get from one another.

4. **Minimum working distance** is defined as the linear distance from the center of the probe to the center of the actuator at which the *maximum propulsive acceleration* limit is achieved. In other words, the absolute limit on how closely actuator and probe can approach one another.

5. **Operating Region Size** is defined as the difference between the minimum working distance and the maximum working distance. For a fixed actuator location, this distance defines the region in which the probe can move relative to the actuator without exceeding the actuation force limits.

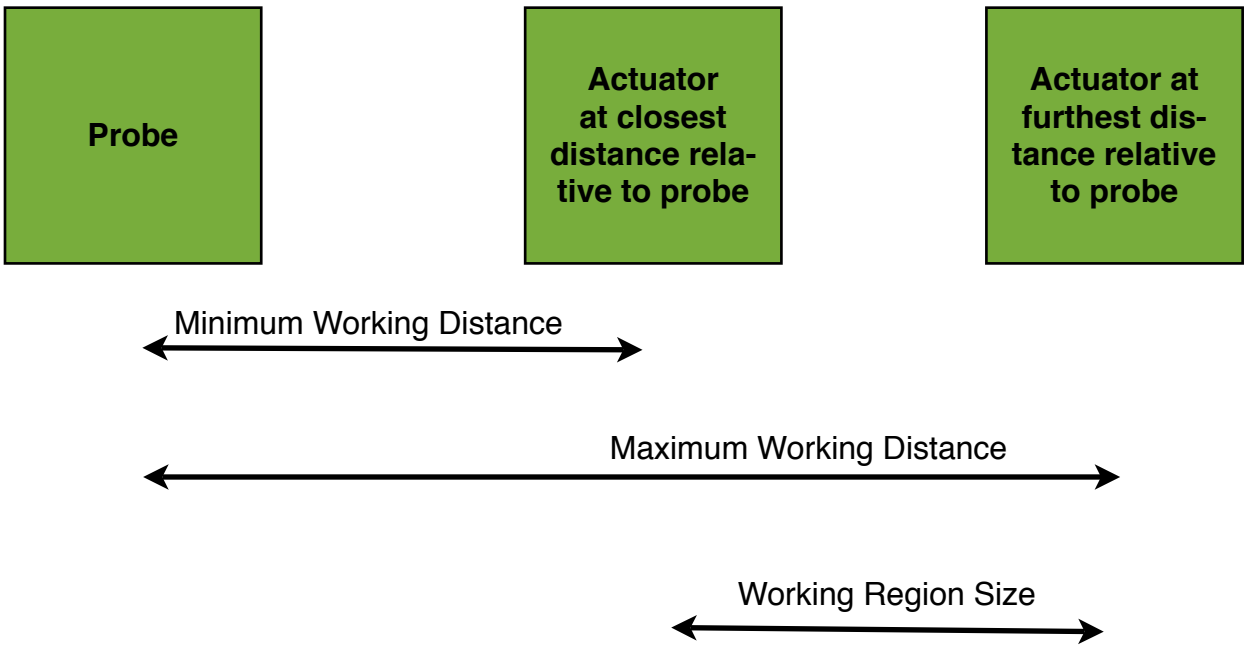


Figure 1: Design constraints for attractive actuation in a single actuator, single probe configuration. In this scenario, the actuator and probe are aligned with parallel magnetic axes, with the magnetic axis parallel to the direction of forward motion through the fallopian tube.

6. **Maximum Sidewall Force**. In addition to the on-axis constraints defined above, a limitation is imposed on how much force may be applied to the sidewall of the fallopian tube. The *maximum sidewall force* design constraint limits how close the probe and actuator may be to one another, as a function of actuator and probe orientation, thereby decreasing the *operating region size* below that of the on-axis scenario illustrated in Figure 1. For the purposes of the experiments conducted in this study, the *maximum sidewall force* limit is chosen to be the amount of force that would lead to a **10g** acceleration of the probe tip in the direction of the probe wall.

   As illustrated in Figure 2, there are two sources of sidewall force:

   A. Translational forces applied to the probe by the actuator, typically resulting from off-axis actuation.

   B. Rotational forces applied to the probe by the actuator, in which the torque exerted on the actuator causes the ends of the actuator to press against the sides of the tube. This arises in configurations in which the probe is sufficiently long that it is not able to rotate freely within the confines of the tube.

   Sidewall force may be distributed along the length of the probe, or may be concentrated in one or two points, depending on the orientation of the probe relative to the sidewall. In the simulation results presented in this study, a conservative estimate of maximum sidewall force is used that combines translational force with an estimate of rotational force exerted by the ends of the probe.

To evaluate these design metrics, a series of single-actuator to single-probe interaction experiments were defined, examining both on-axis, off-axis, and rotational actuation design constraints.

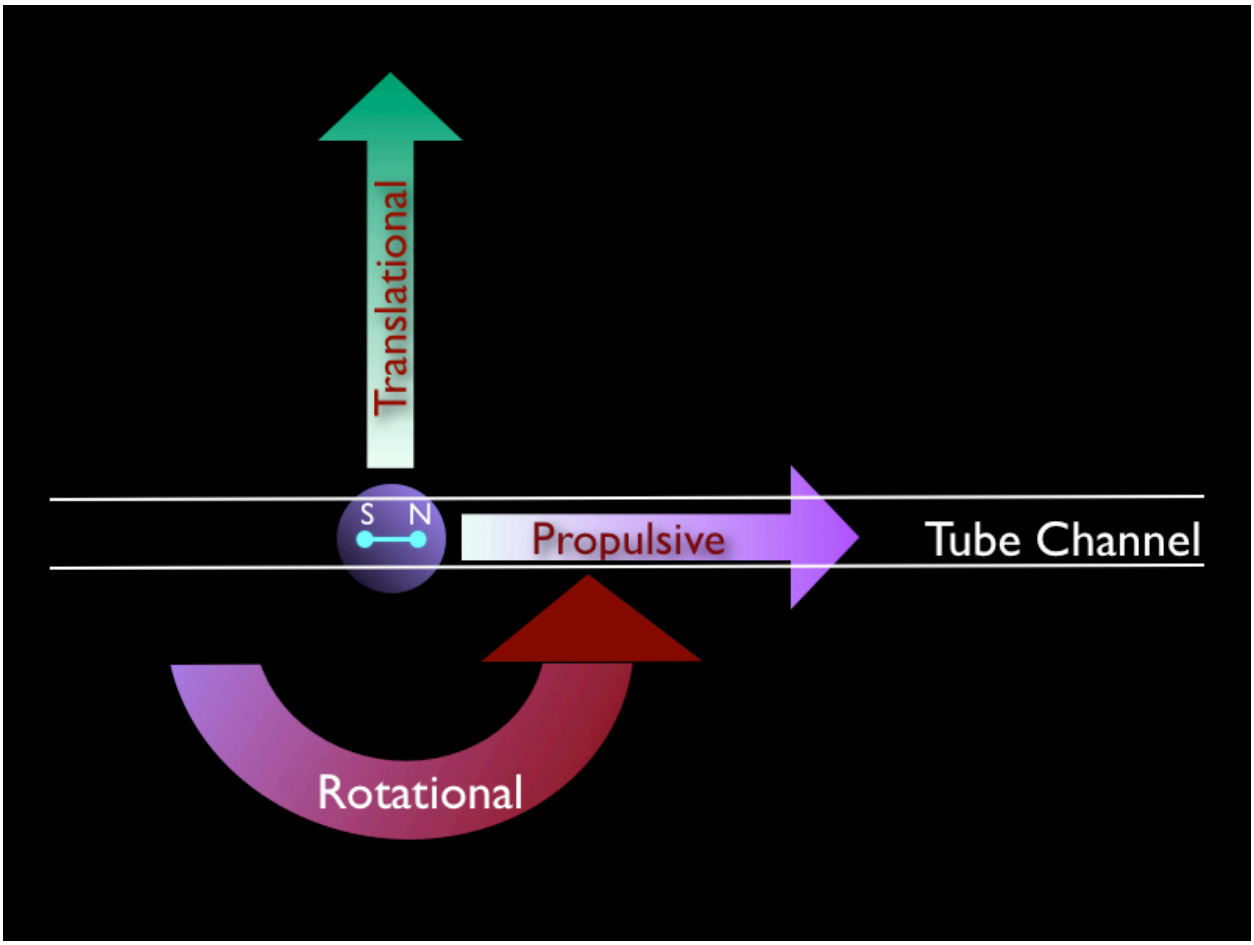
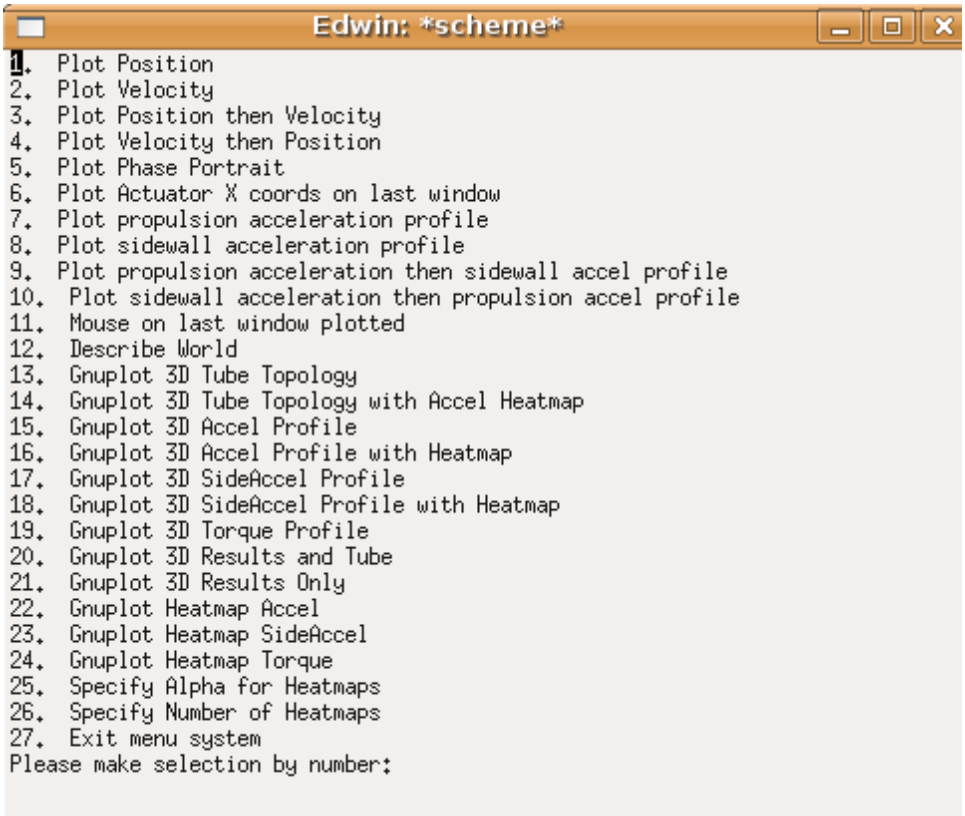


Figure 2: Forces acting on a rod-shaped magnetic probe (shown within the purple circle) due to a single actuator (not pictured). Sidewall force acting on the tube channel wall is a composite of translational force plus rotational force.

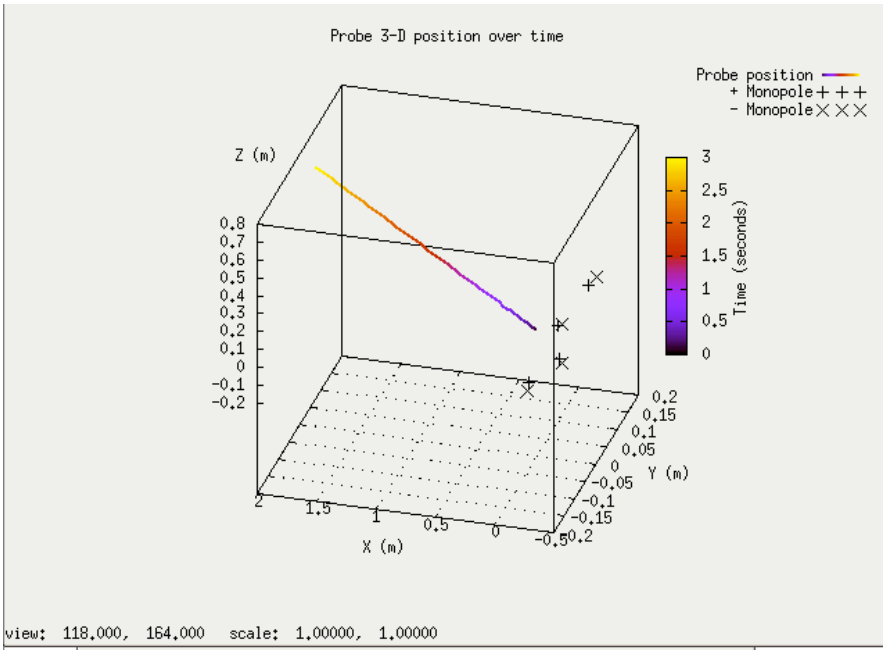
Simulator Development

To characterize design tradeoffs, a simulator was constructed that models the motion of a probe through a tube under magnetic actuation. The simulator computes values for the various design metrics, and also includes a graphical routine that plots quantities such as sidewall force as a heatmap in a cylindrical region surrounding the tube. This permits visualization of the impact of translation of the fallopian tube relative to where the control system expects it to be. The simulator handles multiple actuators operating in coordination with one another, and dynamically computes forces as the probe moves through the tube. The simulator also includes an optimization capability that permits actuator location and orientation to be dynamically varied as the probe moves through the tube, in a manner that maximizes/minimizes a user-specified design criteria.

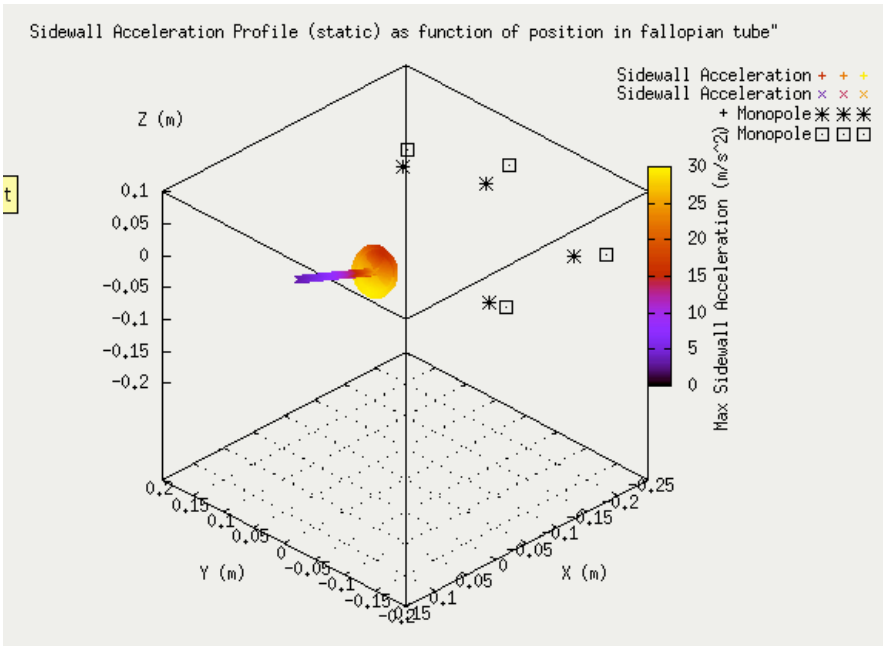
The simulator, which is available for download under the Gnu Public License from http://www.berlinscienceandtechnology/downloads/magsim, implements a wide range of functionality, as illustrated in the screen captures included below:



Main menu of simulator. Functionality includes the ability to handle multiple actuators in both attractive and repulsive configurations.



Simulation of probe motion over time through a linear tube under repulsive influence of an array of four actuators, whose North (+) and South (X) monopole locations are shown to the right of the tube.



Example of 'heatmap' showing force on the tube sidewall in a region surrounding the simulated fallopian tube. This feature is quite useful for visualizing the impact of sensor/actuator misalignment as would typically be caused by sensor measurement error or unanticipated motion of the fallopian tube itself (as opposed to motion of the probe through the tube).

Design Tradeoff Experiments

To illustrate the design tradeoff space, a series of single-actuator, single-probe interaction experiments were conducted, based on a cylindrical 1mm diameter x 4mm length probe magnet and a cylindrical 37mm diameter x 37mm length actuator magnet.

Experiment 1: On-axis Actuation

In the simplest configuration, a single magnetic probe and a single magnetic actuator are oriented on-axis with one another in an attractive configuration, as illustrated in Figure 4a. For this on-axis configuration, the fallopian tube is aligned along the vertical axis, and the force required to achieve 1g acceleration (the point at which the object first becomes levitated) is calculated.

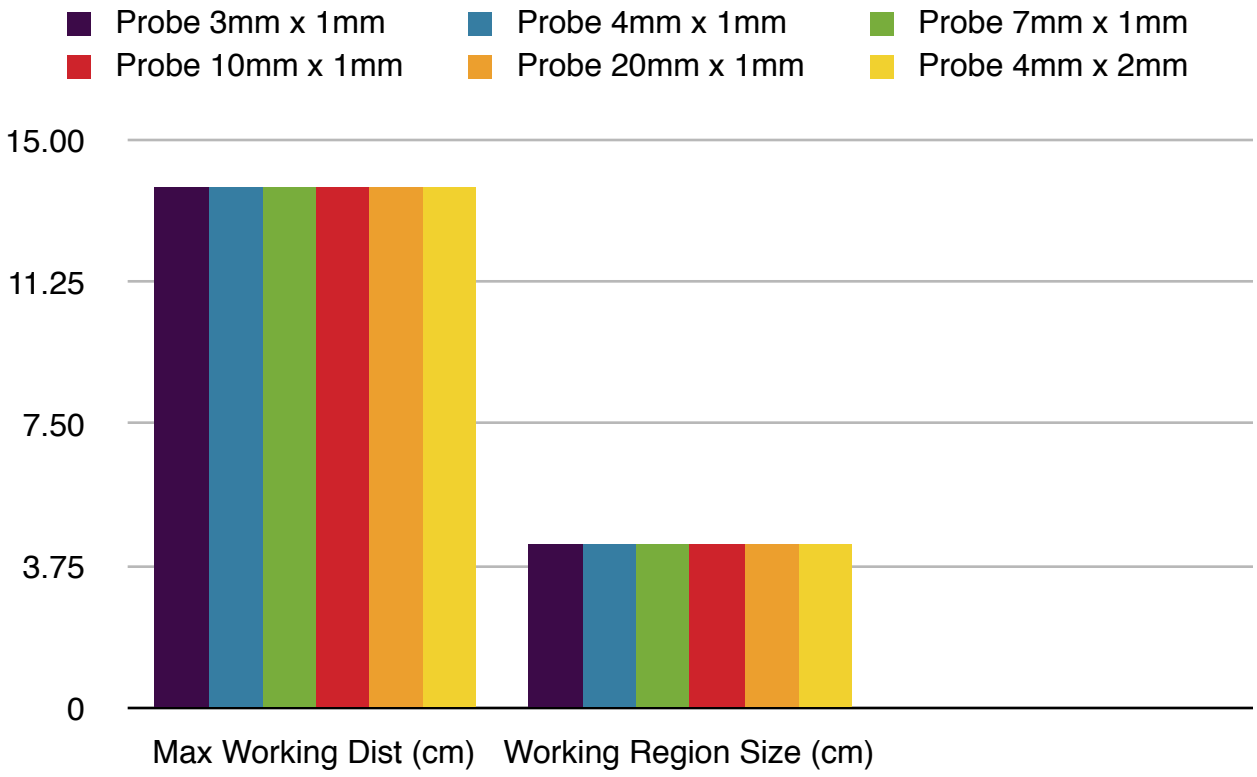
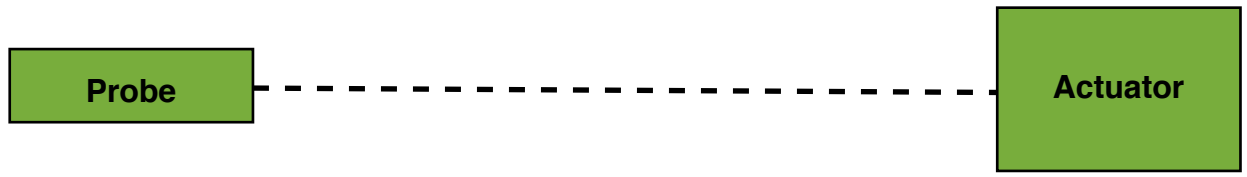
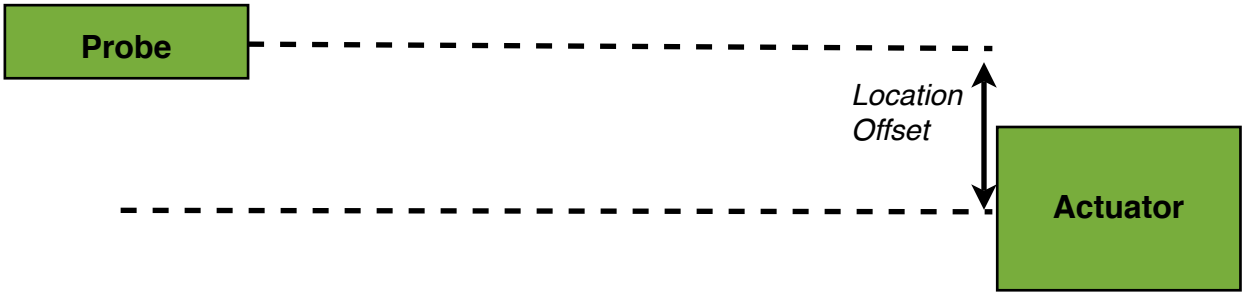


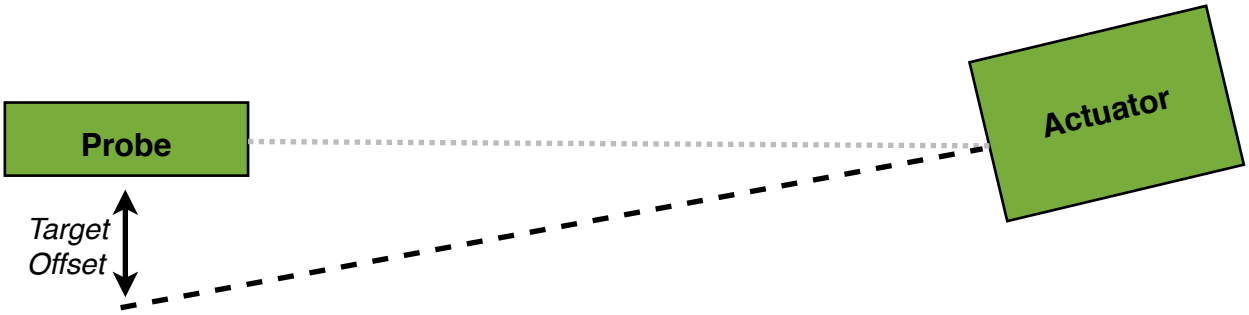
Figure 3: *In the on-axis configuration, both the maximum working distance and the operating region size are* ***independent of probe size.*** *This is because the force of gravity acting on the probe, and the magnetic force, are both proportional to the volume of the probe. A physical experiment was conducted to calibrate the simulator. Results indicated that the maximum working distance for a cylindrical 1mmx4mm probe actuated by a cylindrical 37mmx37mm magnet matched the simulation results to within the 0.5cm measurement error of the experimental setup.*



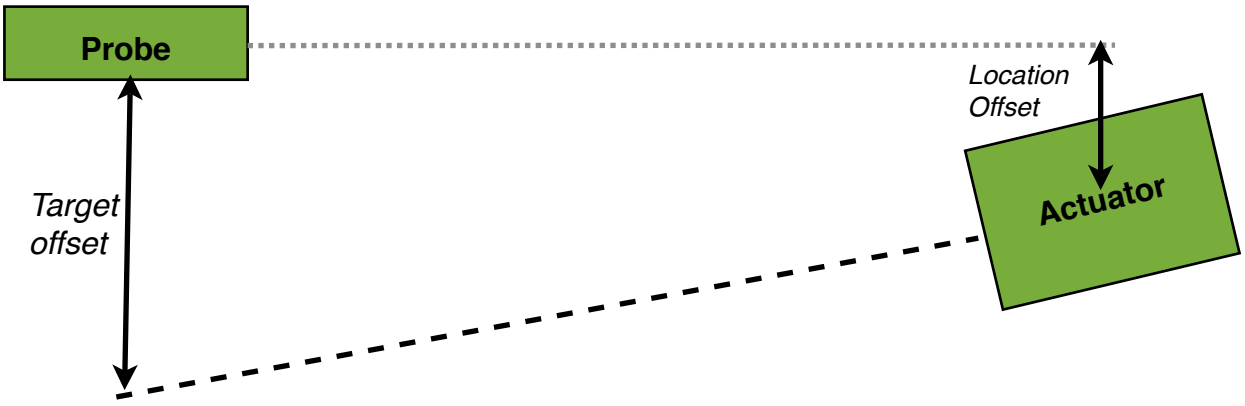
a. Actuator and Probe aligned on-axis



b. Simple translation of actuator relative to probe: Magnetic axes remain parallel



c. Rotation of actuator relative to probe: Definition of *target offset* as measure of rotation.



d. Simultaneous translation and rotation of actuator relative to probe. Note definition of *location offset* and *target offset*.

Figure 4: *Translation and Rotation configurations*

Experiment 2: Lateral misalignment of actuator and probe
This experiment explores the configuration in which the probe and actuator are momentarily laterally offset from one another, but continue to have parallel magnetic axes. This is a realistic situation which could occur due to probe location measurement error (leading to actuator placement error), as well as due to motion (lateral offset) of the fallopian tube within the body relative to where the actuation system expects it to be.

As the actuator translates laterally it leaves the magnetic axis of the probe, as illustrated in Figure 4b. In this scenario, the actuator remains aligned parallel to the axis of the probe (i.e. the actuator is not angled towards the probe, but is merely offset laterally). The impact of this translation on maximum working distance and operating region size is shown in the following graphs, for a representative cylindrical probe Neodymium magnet of length 4mm and diameter 1mm, actuated by a cylindrical Neodymium magnet of length 37mm and diameter 37mm. The trends shown in these graphs reflect several compounded effects. As the offset of the actuator increases:

1. The probe needs to be kept closer to the actuating magnet in order to achieve the minimum 1g of propulsive acceleration. This reduces the *maximum working distance*, and also tends to reduce the *operating region size*.

2. The probe is able to come closer to the actuator prior to reaching the 5g *maximum propulsive acceleration* limit. This tends to increase the *operating region size*.

3. The misalignment of actuator and probe leads to lateral translational forces, as well as torques, being applied to the probe. The *sidewall force limit* design constraint then limits how close the probe and actuator may be to one another, thereby reducing the *operating region size*.

Finally, in the case of lateral misalignment of actuator and probe, the distance between the actuator and the probe comprises an on-axis component plus a lateral ‘offset’ component. In the design tradeoff graphs below, the ‘on-axis’ component is reported as the ***working-distance-on-axis*** and the full distance is reported as the ***working-distance-absolute***. In computing the *operating region size*, the on-axis distances are utilized.

Variation of *working distance* with *lateral offset of actuator*

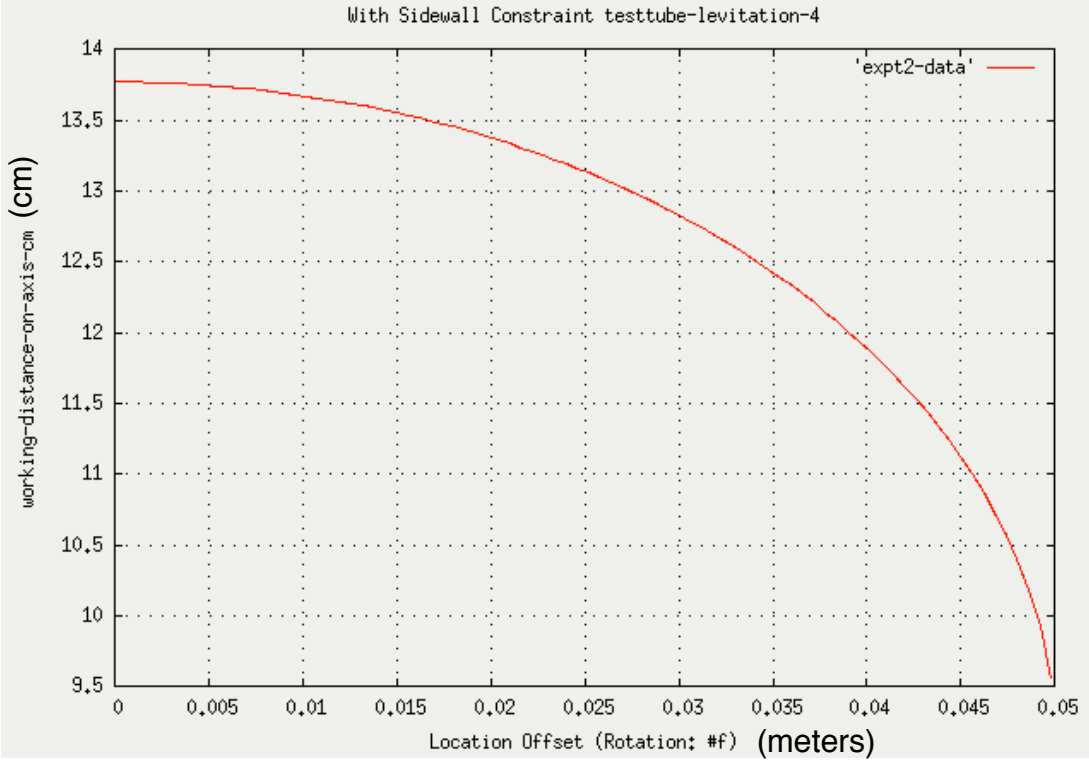
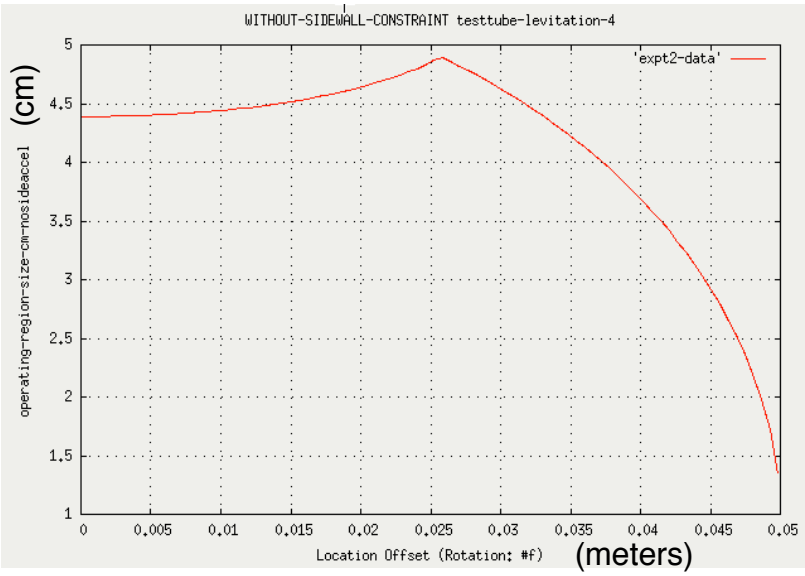


Figure 5: *Variation in the **maximum working-distance-on-axis** (how far apart magnet and probe can be from one another) relative to the **lateral offset** of the actuator from the axis of the probe magnet. At offset=0, the maximum working distance corresponds to the on-axis levitation distance of 13.77 cm reported in Figure 3. As offset of the actuator from the axis increases, the maximum working-distance-on-axis decreases. Data shown is for a 4mmx1mm cylindrical probe with a 37mm (length) x 37mm (diameter) actuator.*

Variation of operating region size with lateral offset of actuator



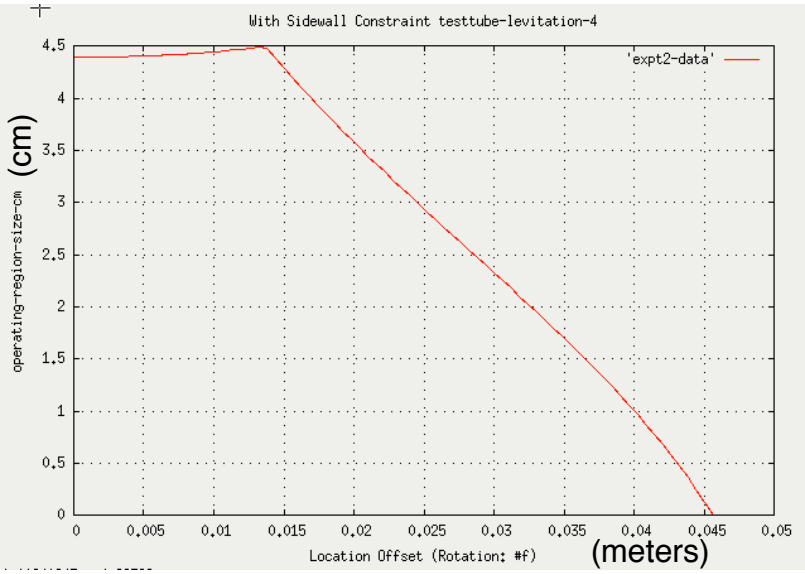


***Figure 6**: **Operating region size vs. location offset**, without (upper) and with (lower) side-wall force limitation of **10g**. As actuator offset increases, the operating region size initially increases due to the ability of the probe to get closer to the actuator magnet before reaching the **5g** maximum propulsive acceleration limit. The operating region size then decreases dramatically with further offset of the actuator due to the limitation on sidewall force (lower). When sidewall force is not constrained (above), operating region size eventually begins to decrease with increasing lateral offset due to the need for the actuator to be close enough to the probe to maintain the 1g minimum propulsive acceleration.*

Experiment 3: Rotational Misalignment of Actuator

Another important scenario, illustrated in Figure 4c, is one in which the actuator and probe centers are aligned, but in which the actuator's magnetic orientation is rotated relative to that of the probe. In this scenario, the *maximum working distance* is decreased due to the magnetic axis misalignment. Additionally, the *sidewall force* is dramatically increased due to the magnetic forces acting to align the probe's magnetic orientation with the magnetic orientation of the actuator.

In the plots below, the axis 'target offset' reflects amount of rotation of the actuator's magnetic field axis relative to the probe's magnetic field axis, as measured by the length of one side of the right triangle formed by the magnetic axis of the actuator, the line from actuator center to probe center, and the line perpendicular to the axis of the probe (along which 'offset' is measured), as illustrated in Figure 4c. In other words, the actuator's magnetic axis is directed at a point that is 'target offset' distance away from where the probe's center actually lies.

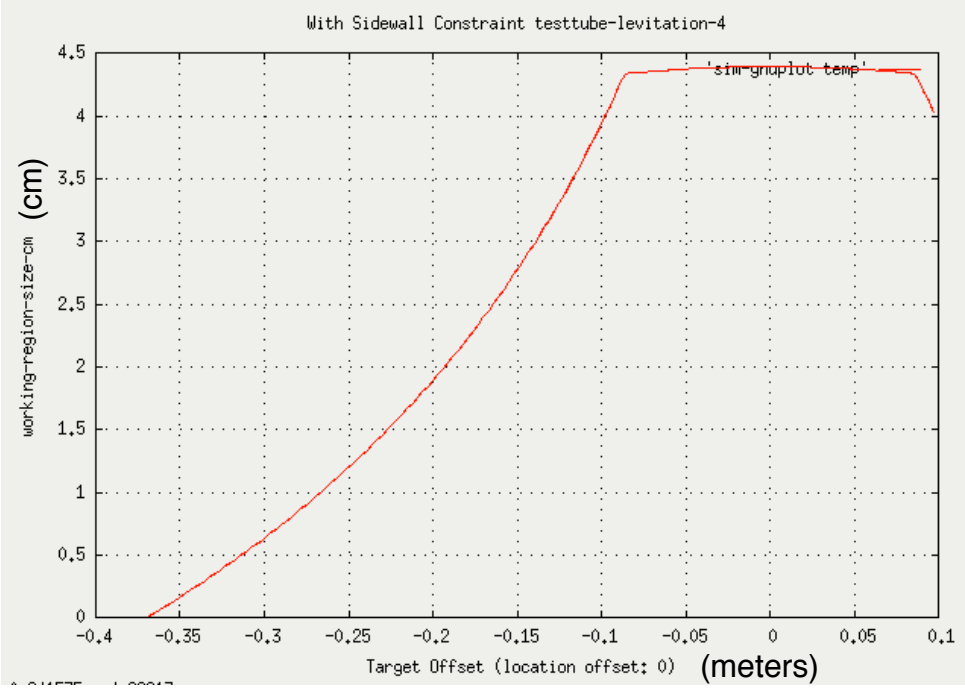


***Figure 7**: Rotation (measured by target offset in meters) vs. operating region size (cm). As the amount of rotation (represented by 'Target Offset') increases, the operating region size decreases due to the need to restrict the probe to remain closer to the actuator in order to maintain the minimum 1g of propulsive acceleration, and due to the need to limit the rotational force (torque) applied to the probe to remain below the maximum sidewall force limitation.*

Experiment 4: Simultaneous Lateral Offset and Rotation of Actuator

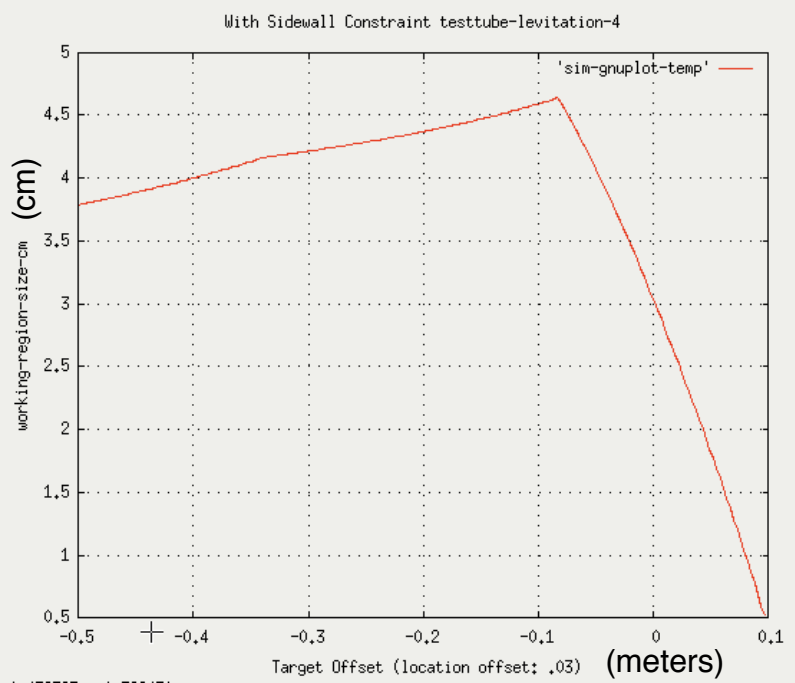
In the case of simultaneous rotation and lateral offset, careful control of actuator rotation can lead to improved results. As lateral offset increases, the *maximum working distance* begins to decrease due to the need to maintain the 1g *minimum propulsive acceleration*. Rotating the actuator so that its magnetic field is maximally coupled to the magnetic field of the probe can partially restore (increase) the propulsive force and help to maintain the *minimum propulsive acceleration*. This additional rotation also creates added *sidewall force*, which depending on the angle may be reduced to some degree by the lateral offset. Finally, rotation can help decrease the *minimum working distance* (the 5g max acceleration limit) by misaligning the fields at points along the tube where the probe is closer to the actuator.

These effects interact with one another and are fairly complex, but performance can still be represented quite compactly by the focusing on the *maximum working distance* and *operating region size* metrics. Figure 8 illustrates a situation in which actuator and probe are initially located on-axis at a distance of 19.6-cm (about 7.7 inches). The actuator is then translated by 3cm orthogonal to the actuator-probe magnetic axis. The actuator is then rotated such that instead of being parallel to the probe ('aimed' at a point 3cm offset from the probe), it is aimed at the probe's location + an additional *target offset* amount, as shown in Figure 4d.

Figure 8 plots the impact of this additional *target offset* rotation amount on the *maximum operating region size* and the *maximum working distance*. The data shows that for a 3cm lateral offset, the **best values for the both *maximum working distance* and *operating region size* occur when the actuator is rotated towards the probe.** In fact, due to the shape of the magnetic field lines, it is advantageous to rotate the actuator to aim at a point well beyond where the probe lies. In the scenario shown, the optimal value for *maximum working distance* occurs when the target offset is -6cm (as measured at a probe-actuator distance of 19.6cm, corresponding to the start of the simulated fallopian tube). This corresponds to rotation of the probe at an angle of 25 degrees relative to its initial orientation. However, at an actuator-probe separation corresponding to this maximum working distance of 13.3cm, the rotation of the probe required for it to be 'aimed' directly at the actuator is 12 degrees. Thus in the optimal configuration, **the actuator is rotated significantly more than would be the case if it's axis was directly 'tracking' that of the probe.** Rotating an additional amount helps align the magnetic field lines of the probe in the propulsive direction with those of the actuator in the propulsive direction, to achieve maximum propulsive force. The optimal rotation to maximize *operating region size* can similarly be determined, as shown in Figure 8, and for this configuration (3cm lateral offset) is quite compatible with the rotation to maximize the *maximum working distance*.

Design optimization

An optimization procedure was created that automatically maximizes the *operating region size* by selecting the optimal degree of rotation of the actuator based on the topology of the fallopian tube and the degree of lateral offset of the actuator. For a linear tube, Figure 9 shows the optimal relationship between lateral offset and rotation.



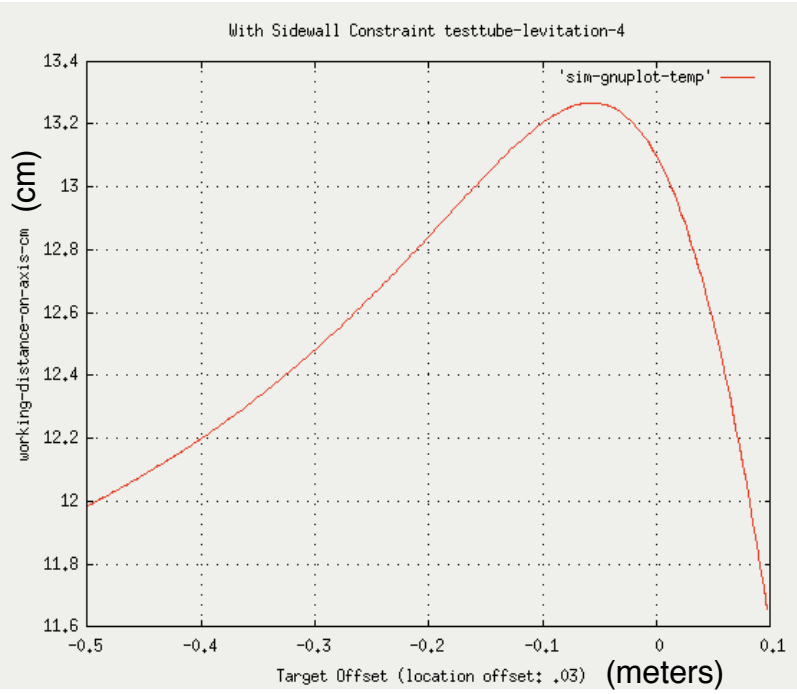


Figure 8: *Maximum working distance on-axis (below) and operating region size (above) for an actuator offset from probe by 3cm laterally, with a probe rotation measured by 'Target offset'. Target offset is a measure of angle, represented by intercept of the actuator's magnetic axis with the lateral axis at origin of the fallopian tube, in this case 19.6cm on-axis distance between magnet and probe.*

angular rotation of the actuator =
*atan((3cm location offset - target offset) / 19.6cm)*180degrees/pi radians*

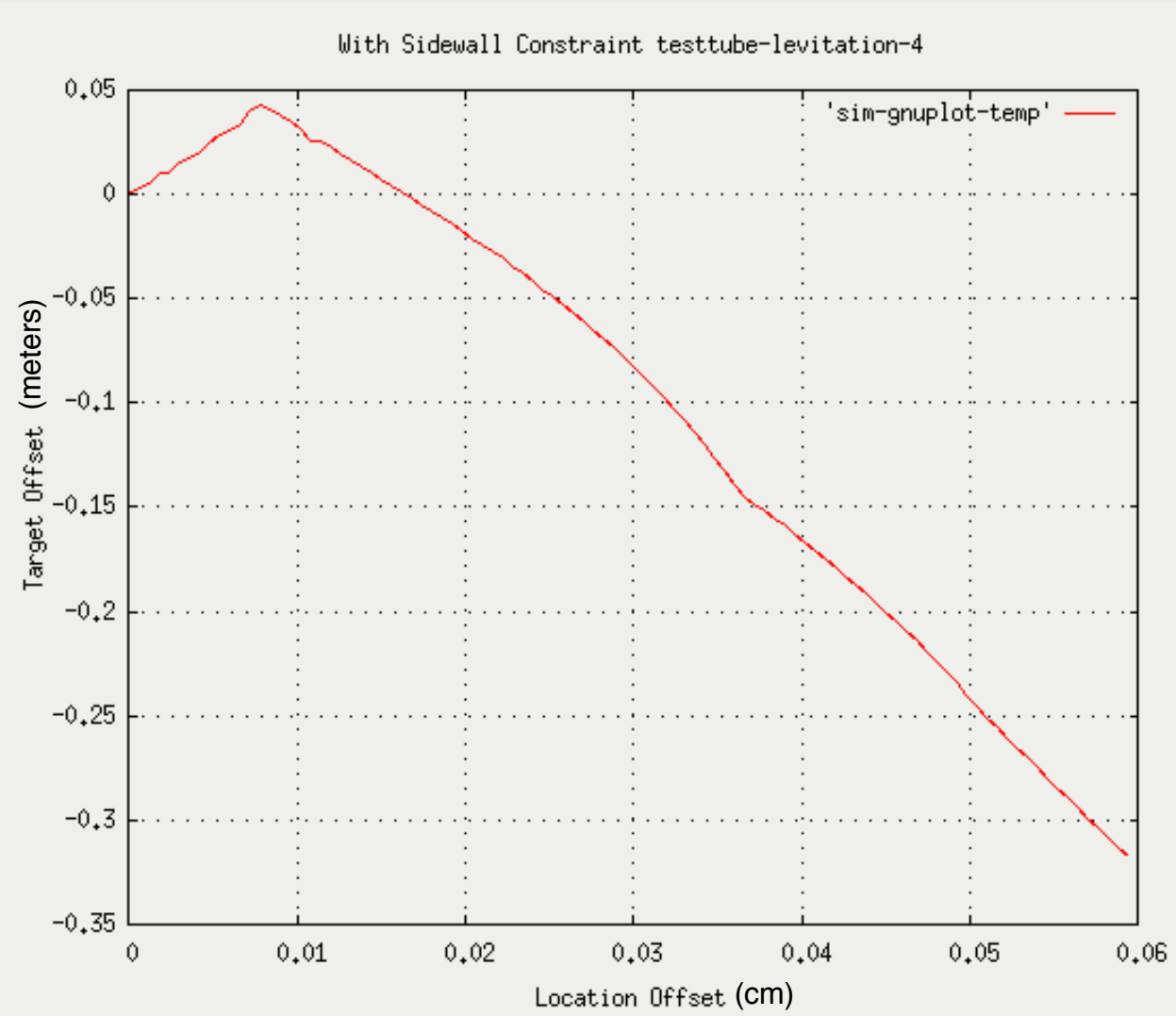


Figure 9: Optimal rotation (vertical axis) to maximize the *operating region size,* as as a function of lateral offset (horizontal axis). By comparison to Figure 8, use of the optimal rotation (specified by *target offset)* with a lateral offset of 0.03m will achieve an impressive maximum working distance (on-axis) of 13.3cm, with an operating region size in excess of 4cm. These parameters are within the range of what modern control systems should be able to achieve, with a 4cm *operating region size* at **5g** maximum propulsive acceleration corresponding to a control system bandwidth on the order of 10Hz.

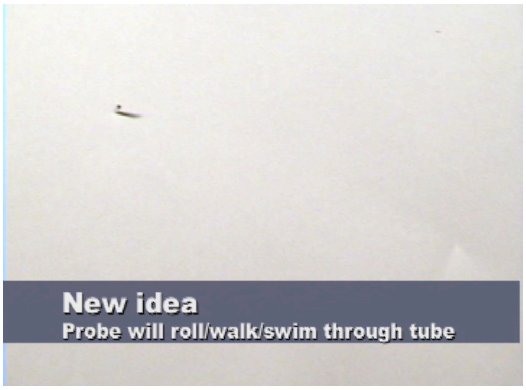
An Alternative Approach: Locomotion Gaits

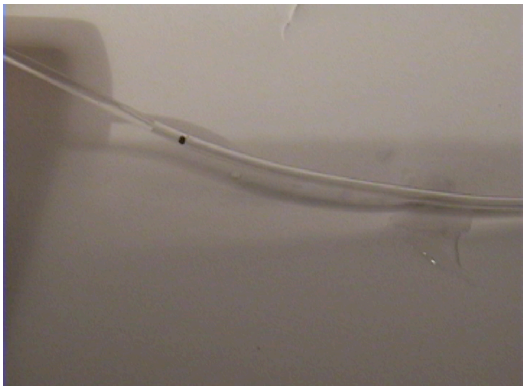
An alternative to magnetic-induced propulsion of the probe via direct repulsion/attraction is to induce probe motion via a locomotion gait, such as a walking, swimming, or crawling motion. In gait-based locomotion, forward propulsion is achieved through interaction of the probe's motion with its surroundings, such as transforming rotary motion into forwards motion by 'rolling' along the wall of a tube.

The advantage to employing locomotion gaits is that gaits can enable tradeoffs between rotational motion and propulsive motion. Thus, for example, 1g propulsive acceleration can be achieved vertically against the force of gravity, even if sufficient magnetic *attractive* force is not available, by using *torque-induced interaction* with the channel wall to rotate the probe end-over-end, or 'roll' a circular probe up the tube. Interaction with cilia, with channel walls, with viscous fluids (corkscrew-like swimmers), and use of inchworm actuators or vibratory motors are just a few of the options available.

Gait-based locomotion effectively extends the *maximum working distance* constraint by providing an indirect means to achieve forward propulsion against the force of gravity, without requiring a full 1g of direct propulsive acceleration. The *minimum working distance* constraint must be still be observed to ensure that magnetic forces do not grow large enough to harm tissues.

As locomotion gaits typically depend heavily on forces such as stiction that can be difficult to model, the potential to use locomotion gaits as an augmentation to the magnetic propulsion approach was explored through the construction of physical models. Below are two frames from a video that documents the magnetically-driven gait-based locomotion experiments. On the left is a magnet rotating end over end under torque-induced forces, while on the right is a small magnet fragment being rolled through a fluid-filled tube without displacing the fluid. Experimental results (see the video for more information) showed that under ideal conditions, use of gait-based locomotion can increase the effective range of magnetic actuation by roughly 50% relative to direct magnetic attraction-based locomotion.





Conclusions

Through a combination of simulation and physical experimentation, we have shown that under ideal conditions it is possible to remotely couple energy fields in a way that will propel a magnetic probe through a fluid filled tube, using actuators located a significant (8-inch) distance away. This can be achieved without displacing (pumping) the fluid, using very gentle forces, at modest cost, and with practical control and timing constraints. The introduction and optimization of the design metrics *operating region size* and *minimum working distance* effectively capture the interplay between proportional, translational, and rotational forces, force limitations, and control bandwidth considerations. The use of locomotion gaits have been shown to extend the *minimum working distance* and open the door to many creative design opportunities. The key question moving forward is: How do the physical parameters of a fallopian tube, or other biological structure of interest, compare to the ideal parameters used in this study? How much force is required to move a probe forward through a dilated fallopian tube? Will pushing forward with that amount of force cause damage?

This project started initially based on the premise that existing endoscopes are not sufficiently narrow or flexible to probe the fallopian tube effectively, based in part on the reported 5% rate of puncture of the fallopian tube when using state of the art endoscopic devices. 5% is a high enough complication rate to make the endoscopic procedure unacceptable for routine early cancer detection screening, even in high risk women. After reviewing the literature in-depth, speaking with surgeons, and gaining insights from the design metrics developed as part of this study, it is not clear whether endoscope flexibility is in fact the limitation, or whether the physical properties of the fallopian tube's force limitations are such that no endoscopic probe, no matter how flexible, could ever traverse the tubes of certain patients without damage. In that case, sensing when damage is about to occur, and stopping the procedure, could make both the endoscopic and the untethered probe approach more effective.

Flexible guidewire-based catheters employ guidewires in the 0.3mm-0.8mm range, with a teflon cannula having outer diameter up to 1.3mm. A dilated fallopian tube has diameter on the order of 1mm over most of the region of interest. Balloon-based falloscopes, fully inflated, have diameters that range from 2 to 5 mm over lengths of 2 cm [10]. based on these dimensions, there does appear to be room for a small (~1mm) untethered probe, particularly if coupled with a tube-dilating drug, to be more gentle on fallopian tubes than the current generation of endoscopes is. Moving forward, pursuing the untethered (or perhaps a very lightly tethered magnetic probe with a highly flexible emergency retrieval cable) approach represented by Snooperscope, while starting a parallel track to explore ways to reduce the 5% puncture rate of endoscopic procedures (such as creating endoscopes with integral force-limiting sensors) could be quite worthwhile.

The long-term goal of this work to provide a method to access fluid and cell samples in the direct vicinity of potentially cancerous tissues holds significant promise for improving biomarker-based screening relative to blood-based assays, since access to the direct vicinity of disased tissues can dramatically reduce the 'body background' signal of a biomarker assay. The next step towards achieving this goal is to initiate a series of biophysical experiments to gather properties of tissues of interest that can inform the next generation of probe design, considering both magnetic actuation and potential improvements to conventional endoscopes.

Recommendations for next steps

1. Engage a medical research center to perform a series of biophysics experiments to obtain physical properties of fallopian tubes that will inform the next generation of actuation experiment design. Of specific interest are:

    1. Typical tube diameter under normal conditions.
    2. Typical tube diameter when dilated through local action of a drugs.
    3. Physical properties of fallopian tube fluid, such as viscosity, density, volume present, pressure, flow rate, and direction of flow.
    4. Maximum permitted force per unit area that may be exerted without tube damage
        a) Force normal to tube
        b) Force parallel to tube
    5. Tube mechanical properties, such as modulus of elasticity, and yield strength, at various length scales. For instance, at the local length scale, measure properties of the tube wall itself; at a larger length scale, measure the elasticity and range of motion of ligaments holding tube in place.

2. Perform a sensing feasibility study to determine how closely a probe can be tracked in 3-dimensions.

3. Take a second look at falloscopy as used in fertility treatments and whether that approach could be modified to gather proof-of-concept data for early diagnosis via molecular analysis of fallopian fluid. Specifically, explore whether a modification to an existing falloscope would permit fluid lavage samples to be acquired locally.

4. Consider adding an optical imager, radiation detector, or electrical impedance spectrometer to an existing falloscope for use in conjunction with imaging biomarker experiments.

5. Informed by the biophysics results, pursue a second-generation design of the actuation subsystem that accounts for the mechanical properties of the fallopian tube and fluid.

6. Explore complementary applications in addition to the fallopian probe application, that can potentially provide earlier/lower hanging fruit starting points for the untethered probe concept. Examples to look into: saliva ducts, ear canal (delivery of antibiotics), biliary ducts, brachytherapy, prostate seed therapy, etc.

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Appendix 1: Project Status Tracker

Objective	Deliverable	Status
Literature survey to identify state of the art in endoscopy. Is existing technology good enough?	Summary of findings.	Done.
Literature survey to identify state of the art in direct-contact fallopian tube cancer detection techniques, such as tubal lavage.	Summary of findings.	Done.
Identify challenges and potential design solutions associated with the problem of designing a probe capable of obtaining fluid, cytological, and/or optical samples of information from fallopian tubes	Summary of findings	Done.
Feasibility analysis for magneticaly actuated probe system	Simulation model capable of modeling a magnetic probe moving through fallopian tubes under actuation from an array of magnets.	Done. Full-motion (1-D through tube under 3-D force action) simulator implemented.
	Physical experimentation with permanent magnets to calibrate the simulation model.	Done.
	First level of optimization of magnetic actuation system design. Vary number, position, and type of actuator. Compare design options via simulation.	Done. Design metrics and optimization code that works with simulation model have been developed.

Objective	Deliverable	Status
Magnetic Propulsion Experimental Demonstration	Report on a small scale magnetic actuation experiment designed to propel a 1mm diameter cylinder, 3mm-10mm in length, through a 2-3mm diameter tube. Measurements will be collected to indicate whether this magnetic propulsion approach is effective. Report will include assessment of the outcome and recommendation as to whether this propulsion approach is worthy of further investment.	Done. Working prototype created demonstrating propulsion of small (~1mm) magnetic probe through a narrow fluid-filled tube. Video documenting results was produced and presented to the Canary Foundation SAB and to the Canary 2007 Symposium.