Image-Guided Robot System for Small Animal Research

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Abstract – **We developed an image-guided robot system to achieve highly accurate placement of thin needles and probes into in-vivo rodent tumor tissue in a predefined pattern of about 1 mm granularity that is specified on a preoperative image. This development is part of a collaborative project between Johns Hopkins University (JHU) and Memorial Sloan-Kettering Cancer Center (MSKCC). This paper presents the design and validation of the robot system that we constructed and delivered to MSKCC.**

I. Introduction

We developed an image-guided robot system to achieve highly accurate placement of thin needles and probes into in-vivo rodent tumor tissue in a predefined pattern of about 1 mm granularity. The multiple uses of the needles/probes are (1) oxygen tension (pO_2) measurement, (2) biopsy, and (3) injection of adenoviral sequences in form of a liquid agent. This development is part of a collaborative project between Johns Hopkins University (JHU) and Memorial Sloan-Kettering Cancer Center (MSKCC). This paper focuses on the engineering design and validation of a robot system developed at JHU that will initially be used by MSKCC to insert pO_2 probes in a three-dimensional (3D) grid pattern defined with respect to a Positron Emission Tomography (PET) scan of a tumor. The design is compatible with Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), which could be used to drive the biopsy and injection applications in the future.

II. Background

Researchers at MSKCC are performing experiments to validate a non-invasive method of identifying hypoxic (oxygen-deficient) cells in tumors. This is important for cancer research because hypoxic cells are resistant to radiation treatment and therefore treatment can be improved by tailoring the radiation dosage directed at them. By measuring the tissue oxygen tension (pO_2) level of the cells (using an Oxylite probe) [1] and correlating these measurements with PET scan data, researchers can verify the efficacy of PET scans in locating hypoxic cancer cells for radiation treatment [2].

Initially, the researchers used manual methods to verify the correlation between PET scan data and pO_2 measurements for tumors on rodents. The procedure was to place the anesthetized rodent inside a foam-filled bed (see Fig. 1) that contained a template with PET-compatible markers. After the PET scans, the entire rodent and bed assembly were placed beneath a passive fixture that held the Oxylite probe. The researcher selected a set of measurement targets (a "track") on the PET image and located the corresponding template hole. After puncturing the skin and tumor with a needle, the researcher manually advanced the Oxylite probe through the template hole to measure the pO_2 level at each point along the track. This procedure was repeated for multiple template holes (tracks).

The manual procedure described above has the following disadvantages:

1. It is time consuming and labor-intensive.
2. Needle placement is restricted by the location and configuration of the insertion template and its mounting posts.
3. The setup on the rodent bed fixture is operator-dependent and not highly repeatable.
4. The PET intensity value and corresponding pO_2 measurement are manually recorded and therefore more prone to error.
5. Resolution of the needle tracks is limited by the hole pattern on the insertion template.
6. The insertion template is mounted directly above the tumor, limiting the researcher's visibility.

Our goal was to design and build a robot system that would address all these concerns.

III. System Design

The robot system consists of a mobile cart that houses the electronics, provides a table top for the four axis robot and display monitor, and contains a pull-out drawer for the

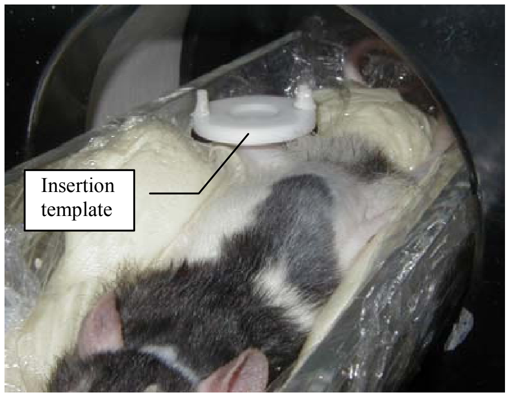

Fig. 1. Rodent in foam-filled bed

Fig. 2. Robot System

keyboard and mouse (see Fig. 2). The four axis robot is composed of a two degree-of-freedom X-Y horizontal platform and two vertical slides (Z1, Z2). The horizontal platform contains a mounting mechanism for the rodent bed. A horizontal aluminum arm is mounted on the first vertical slide (Z1) and provides an attachment for either a registration probe or a cannula. The second vertical slide (Z2) is attached to the first vertical slide and contains a probe holder. This allows the system to insert the Oxylite probe through the cannula and into the tumor, as shown in Fig. 3. Note that in this case, the Z1 axis positions the cannula near the skin surface and the Z2 axis drives the measurement probe to the target.

The measurement procedure is physically decoupled from the imaging procedure for maximum flexibility; therefore, fiducial markers are used for the registration between image coordinates and robot coordinates. The system uses the Acustar® marker system, donated by Z-Kat Inc., for the CT, MRI and robot markers and a separate set of support tubes (offset by a known amount) for the radioactive PET markers. During the robot registration procedure, the cannula is replaced by a registration probe, which is guided to the markers using a force control mode [3]. Force control is possible because the system contains a two-axis sensor (XY) beneath the rodent bed and a single-axis sensor (Z1) near the attachment mechanism for the registration probe and cannula.

Fig. 3. Oxylite probe inserted in rodent

The rodent bed design, including multi-modal imaging markers, was challenging due to the limited bore of the small animal imaging scanners. The final design (Fig. 4) includes an adjustable bridge that allows the researcher to move the markers so that they cover the target region (tumor), are within the scanner field of view and maintain the geometrical relationship necessary for accurate registration results. The bridge is removed after registration to enable access to the rodent.

The operation procedure is as follows: a) place anesthetized tumor-bearing rodent in rodent bed; b) place rodent bed in scanner and obtain image data; c) move rodent bed to robot system and load image data into computer; d) register image data to robot by manually guiding robot's registration probe into contact with each marker and using a semi-automatic image processing procedure to locate the corresponding image marker; e) remove registration probe from Z1 axis and attach cannula; f) attach measurement probe to Z2 axis and zero its position; g) identify target regions (sets of vertical tracks) in the image; h) command robot to move to each target position and record measurements.

We developed the application software using the 3D Slicer package [4], which provides visualization, registration and segmentation capabilities. The researcher first loads the image data and uses a semi-automatic procedure to locate the markers in the image. The researcher then manually guides the robot's registration probe to each marker. This manual guidance feature is achieved by a force control algorithm that uses nonlinear gains to provide fine positioning without sacrificing maximum motion speed, as reported in [3] (though a different nonlinear function is used). The software computes the registration transformation by matching the marker positions in the image to the marker positions located by the robot.

Fig. 4. Rodent bed with fiducial bridge

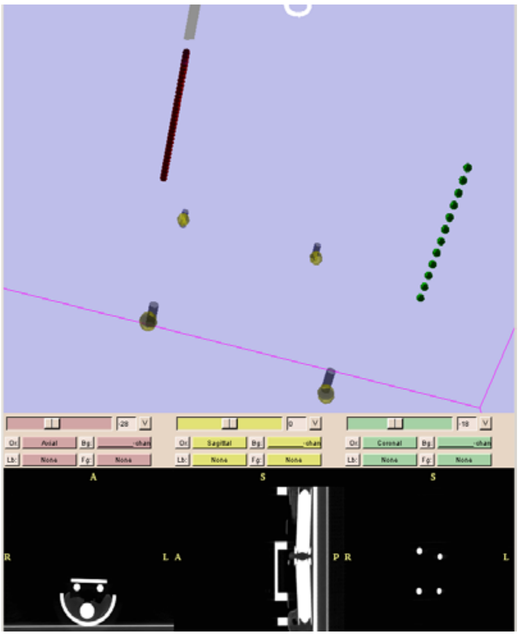

Fig. 5. Defining needle tracks in 3D Slicer software

Once registration is completed, the researcher defines measurement tracks in the image space (see Fig. 5). The software transforms track points to robot coordinates and drives the robot so that it positions the cannula at the entry point of the first probe track. After the skin is manually punctured, the robot drives the Oxylite probe through the cannula and into the tumor. The Oxylite probe moves vertically inside the tumor in user-defined increments (typically 1mm). At each position, the Oxylite probe measures the tissue oxygen tension of the tumor and sends the result to the software that stores all measurements in an array. When the Oxylite probe reaches the end of the track, the robot retracts the probe back inside the cannula. Next the software drives the cannula and Oxylite probe upward, pulling them out of the tumor. The software then moves the cannula to the starting point of the next track and repeats the cannula insertion and probe measurement sequence described above until the entire grid pattern has been traversed.

IV. TEST RESULTS

We performed several tests at JHU prior to delivering the system to MSKCC in January 2005. Our in-house tests focused on the robot system because we do not have small animal imaging systems. We therefore tested the performance of each individual robot axis as well as the performance of the complete robot, including the registration procedure. The system specification, finalized with MSKCC in March 2004, requires a robot motion resolution of 0.1mm and a robot registration accuracy of ±0.25mm.

A. Repeatability and Accuracy of Individual Axes

We performed small motion repeatability and accuracy tests on each of the 4 axes using a dial indicator (Mitutoyo model #543-693B) with ±0.003mm accuracy and 12.7mm travel. We positioned the dial indicator in contact with the axis and moved the robot back and forth (ten times) between two positions that were 10mm apart, recording the dial indicator reading at each position. The repeatability was computed by averaging the difference between each reading and the average of all the readings. The accuracy was computed by averaging the differences between the measured displacements and the specified travel of 10mm. Table 1 shows the raw data (dial indicator readings) for the X-axis, as well as the computed repeatability and accuracy results. Table 2 summarizes the repeatability and accuracy results for all four axes. Note that the repeatability ranges from 0.001mm to 0.030mm and the accuracy ranges from 0.015mm to 0.075mm. These results are all well within the 0.1mm motion resolution requirement.

B. Repeatability and Accuracy of Robot System

For these tests, we designed a test plate with 9 target holes on a horizontal plane and 4 more at various heights (see Fig 6). Four of the target holes on the horizontal plane were arranged in the same geometry as the four Acustar markers on the rodent bed. Each target hole had the same

Trial #	**Dial Indicator Reading**		**Travel**
	"0"	**"10"**	
1	0	9.989	9.989
2	0.006	9.987	9.981
3	0.005	9.987	9.982
4	0.005	9.987	9.982
5	0.005	9.988	9.983
6	0.005	9.990	9.985
7	0.004	9.989	9.985
8	0.003	9.990	9.987
9	0.002	9.989	9.987
10	0.002	9.991	9.989
Avg.	0.004	9.989	9.985
Repeatability	**0.001**	**0.001**	
Accuracy			**0.015**

Table 1: Repeatability and accuracy data for X axis (units: mm)

Axis	**Repeatability**		**Accuracy**
	“0”	**“10”**	
X	0.001	0.001	0.015
Y	0.003	0.007	0.048
Z1	0.005	0.004	0.044
Z2	0.011	0.030	0.075

Table 2: Repeatability and accuracy for all axes (units: mm)

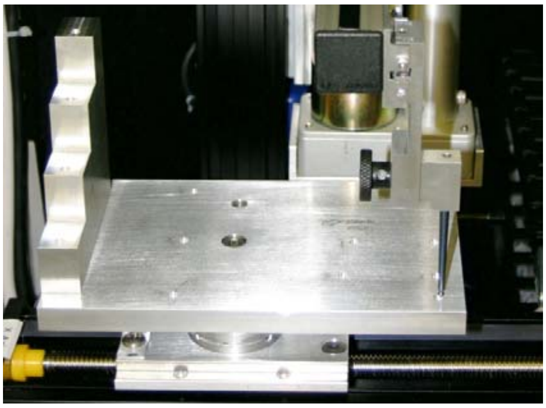

Fig 6: Registration probe on test plate

conical shape and depth that allowed the rounded registration probe tip to sit at the bottom of the cone in a repeatable manner. The test plate was 8"L x 5"W x 4.5"H in size and was machined on a CNC machine with a known accuracy of 0.0005" (0.0127mm). This plate served as the gold standard for our measurements.

The repeatability test was facilitated by a software program that prompted the operator to hand-guide the registration probe, in a force-feedback mode [3], to a target hole on the test plate. After seating the probe tip in the bottom of the hole, the operator pressed the Enter key to record the position. The robot automatically retracted the registration probe and moved it horizontally by a random amount. This was repeated ten times on the same hole. Four operators performed this test and the repeatability results ranged from 0.267mm to 0.389mm (Fig. 7, Test Plate line).

These results were not as good as desired and it was clear during the testing that the geometric design of the test plate holes made the registration procedure more difficult. We therefore performed the same repeatability test, with the same four operators, on an Acustar marker. These results ranged from 0.112mm to 0.159mm (Fig. 7, Acustar line), significantly better than those obtained with the test plate.

To evaluate the accuracy of the robot system, we found all 13 holes in the test plate by hand guiding the registration

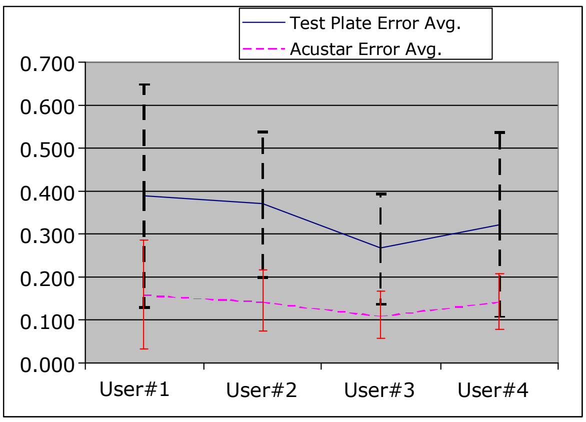

Fig. 7: Registration repeatability comparison
(with ± 1 standard deviation error bars)

probe to each hole. We compared the position of the registration probe, measured by the robot encoders, to the known locations of the machined holes. We collected three data sets and analyzed them with the following two methods:

(a) Use the four fiducials with the same geometry as the Acustar markers to register the robot coordinate system to the plate coordinate system. Transform all 13 robot points to the plate coordinate system and compute the distance between each of the 13 sets of matched points.

(b) Compute the distance between each pair of points in robot coordinates and compare that to the distance between each pair of points in plate coordinates. For example, if R_{ab} is the distance between points *a* and *b* measured by the robot and P_{ab} is the distance between points *a* and *b* in the CAD drawing, then the absolute distance error is $| R_{ab} – P_{ab}|$.

The combined average error using method (a) was 0.404mm, compared to 0.301mm using method (b), as shown in Table 3. The better result obtained with method (b) is likely due to the fact that it is not affected by registration error. These results are not within the 0.25mm specification, but we note that the test plate repeatability was the same order of magnitude as the accuracy error. Therefore, it is reasonable to expect a better accuracy result with the Acustar markers, which produced significantly better repeatability results.

Method	Data Sets			Combined Avg.
	#1	#2	#3	
(a)	0.307	0.338	0.568	0.404
(b)	0.254	0.248	0.401	0.301

Table 3: Summary of accuracy results (units: mm)

V. CONCLUSIONS

We completed the design and testing of an image-guided robot system to assist with cancer research and delivered it to MSKCC in January 2005. The repeatability and accuracy of the individual robot axes are well within specification. Our test of the robot system, including the registration procedure, produced promising results though it was negatively affected by the test plate design. This could be addressed by designing a better test plate (possibly attaching Acustar markers instead of machining holes) or by improving the software to enable more repeatable data collection on the machined holes. The next step is to measure the repeatability and accuracy of the entire system including the imaging device.

We believe that this robot system will improve the efficiency and accuracy of needle-based procedures for in-vivo measurement, biopsy, and injection in small animals. One notable feature is the support for a variety of imaging modalities, including CT, PET, SPECT, and MRI.

ACKNOWLEDGMENT

We are grateful to Clif Ling, Ph.D., Bixiu Wen, M.D., Jenghwa Chang, Ph.D. and their colleagues at MSKCC for their advice and support. The authors thank Z-Kat, Inc. for donating their Acustar® markers, Russ Taylor, Ph.D. at JHU for his advice, and Anton Deguet and Andy LaMora at JHU for assistance with the software. This work is supported by NIH RO1 CA84596 and NSF ERC 9731478.

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