IEEE Access
Multidisciplinary ⋮ Rapid Review ⋮ Open Access Journal

Received February 6, 2020, accepted February 13, 2020, date of publication February 17, 2020, date of current version February 27, 2020.

Digital Object Identifier 10.1109/ACCESS.2020.2974699

A Position-Adjustable Multi-Point Synchronizing Biopsy Tool for Intratumor Heterogeneity: A Proof-of-Principle Study

BAIQUAN SU[1], HAO YAN[1], LIAOLIAO LIU[1], SHI YU[1], YIDA HU[2,3], GANG WANG[4], WEI YAO[5], JIE TANG[6], AND SHAOLONG KUANG[7]

[1]Medical Robotics Laboratory, School of Automation, Beijing University of Posts and Telecommunications, Beijing 100876, China
[2]Brigham and Women's Hospital, Boston, MA 02115, USA
[3]Harvard Medical School, Boston, MA 02115, USA
[4]General Surgery Department, Peking University Third Hospital, Beijing 100191, China
[5]Gastroenterology Department, Peking University Third Hospital, Beijing 100191, China
[6]Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing 100053, China
[7]Robotics and MicroSystems Center, School of Mechanical Engineering, Soochow University, Suzhou 215021, China

Corresponding authors: Wei Yao (ywei@yeah.net), Jie Tang (tangjiett@163.com), and Shaolong Kuang (slkuang@suda.edu.cn)

This work was supported in part by the National Natural Science Foundation of China under Grant 91748103 and Grant 61573208, in part by the Beijing Natural Science Foundation under Grant Z170001, and in part by the China Postdoctoral Science Foundation under Grant 2014M560985 and Grant 2015T80078.

ABSTRACT A biopsy needle is a tool employed to fetch a portion of tissue at a point in the volume of diseased tissue, i.e., a *Single Sample* with a *Single Spoon* (SS-SS). Using this tool, the pathological status of the unhealthy tissue is generally represented by that of the specimen. However, for the tumor growing heterogeneously, like brainstem glioma, its inner constituent is heterogeneous. Therefore, the histological status of the specimen cannot precisely represent that of other points except the sampled point itself. The common principle of the existing solutions to this problem is to design the needle that fulfills biopsy operation by obtaining *Multiple Samples* with a *Single Spoon* at different points (MS-SS). The drawback of the designs following this principle is that during one biopsy operation, the latter samples are contaminated by their formers. The reason for the shortcoming is that the same spoon grabs all samples. To solve this problem, we design a novel biopsy tool that implements a single insertion to obtain *Multiple Samples* in multiple desired points with *Multiple Spoons* (MS-MS). The detailed system structure design, the motion procedure of the needle spoon, and the critical stress on the crucial mechanical parts are explicitly presented. Experiments using a built prototype is carried out on agar phantom and ex vivo porcine tissue, respectively. The results demonstrate the feasibility of the novel position-adjustable multi-point synchronizing biopsy tool for investigating intratumoral heterogeneity.

INDEX TERMS Biopsy needle, intratumor heterogeneity, synchronizing biopsy, multiple samples, minimally invasive surgery.

I. INTRODUCTION

A biopsy is a medical procedure that involves taking a small sample of body tissue so it can be examined under a microscope [1]. The biopsy is the de facto gold standard of medical diagnosis in modern medicine. A biopsy needle is a tool employed to fetch a portion of tissue at a point in the volume of diseased tissue, namely, obtaining a *Single Sample with a Single Spoon* (SS-SS) with an insertion, e.g., [2]. By using this tool, the growing pathological condition of the unhealthy tissue is generally represented by that of the specimen. However, All biopsy results are based on the assumption that the histopathologic status of sample tissue at any spot inside the suspected spatial contour is qualified to represent that of the whole tissue enclosed by the shape. In many cases, the assumption is acceptable for diagnostic purposes.

Nevertheless, revealed by the pioneering works [3]–[5], for some fast-growing tumors, like brainstem glioma, its internal constituent is heterogeneous. Intratumor heterogeneity is one of the central problems in tumor studies and recognized in

The associate editor coordinating the review of this manuscript and approving it for publication was Tao Wang.

both basic medical research [6], [7] and clinic medicine [8], [9]. Therefore, the histological status of the specimen sampled at a single spot cannot precisely explain that of other points except the sampled point itself.

One of the indispensable steps for studying intratumor heterogeneity is to get multiple samples at different positions of a tumor. This step will help to reconstruct the growing status of lesion tissue, especially for the lesion with a large volume. The universal principle of the existing solutions to this problem is to fetch multiple tissue samples with several repeated insertions, namely, obtaining Multiple Samples with a Single Spoon at different points (MS-SS). Moon et al. design a novel end-effector for an automated teleoperating robotic biopsy system that can take multiple samplings during a biopsy [10]. Franke introduces a needle with a round tip. When the needle is withdrawn from tissue, it extracts large tissue samples that adhere to the tip of the probe's distal end [11]. Another design is an endoscopic biopsy needle with internal flexures that enables tissue to enter the hollow needle, and then the tissue is severed from the surrounding tissue when the needle is withdrawn [12]. A Multiple Core Biopsy (MCB) device acquires multiple tissue biopsy samples during a single endoscopic procedure, by using a substantially cylindrically-shaped core and a sharp forward-facing cutting edge [13]. A needle with a novel Enhanced Cutting Edge (ECE) tip also fulfills multiple biopsy sampling, and it uses a stylet with a sample opening and a longitudinal cutting member with a cutting edge, and the relative motion between the stylet and cutting edge will cut a tissue sample from a host [14]. Besides the conventional biopsy needles, all these biopsy needles take multiple tissue samples through a few repeated insertions. In other words, it is unable to provide multiple samples at different locations in one insertion. While multiple insertions with a single spoon will not only increase overall treatment time and workload, it may also result in cross-contamination between biopsy insertions, i.e., giving rise to the symptom of needle track implantation.

Thus, biopsy needle with multiple-sample within one insertion is a preferable choice for obtaining information of intratumor heterogeneity. A rounded tip endoscopic tool is designed for Multiple Specimens with a Single jawed Spoon (MS-SS) [15], and the biopsies are collected up to 25 and stored in a plastic chamber inside the removable metal tip. A biopsy needle instrument is designed to capture a plurality of discrete specimens without being withdrawn from pathological tissue [16]. Based on the modification of the needle [16], a revised biopsy needle is built using multiple spring design accompanying by the advantage of no reloading requirement [17]. Another surgical biopsy device comprises an automatic rotation of the probe, a frame, and an elongated piercing element attached to the distal end of the frame for harvesting at least one tissue sample from a surgical patient [18]. Also, a single-insertion biopsy device includes a cannula having an extraction position at a distal end and a recovery opening at a proximal end, and the tool provides a realization of multiple samples without more than one needle insertion [19]–[21]. A core needle biopsy device, including a needle assembly, a cutter drive assembly, a piercer drive assembly, and a piercer retraction assembly, is designed for collecting multiple samples in a single insertion [22]. However, the drawback of the designs following this principle is that during one biopsy operation, the latter samples are contaminated by their formers. The reason for the shortcoming is that the same spoon grabs all samples. When picking multiple samples, the front distal ends of the existing biopsy needles must move between desired spots. It should be noted that each of these biopsy needles picks specimens at multiple diseased volumes, not multiple places inside one unhealthy volume.

On the other side, a little attention is paid to another type of biopsy tool, which can not only fetch multiple samples in one single puncture but doesn't need adjusting any mechanical parts while gathering samples. Yu designs a kind of multiple punch biopsy sampler for a tumor of breast minimally invasive surgery [23], and this type of needle is equipped with an array of dozens of position-fixed spoons along the cylindrical surface of the cone-form frontal end. However, this design leads to many unnecessary samples, and the occurrence probability of Needle Track Implantation (NTI) [24] is increased compared to the non-redundant spoon design. NTI usually means implantation metastasis [25]. Thus, the needle, which harvests multiple samples during one insertion, satisfies the requirements for studying intratumor heterogeneity, e.g., investigating the distribution of different types of lesion tissue inside brainstem glioma.

In this paper, based on our previous experience in neurosurgical field and the resultant systems [26]–[30], we design a novel biopsy tool that comprises a needle and an actuation system, and it implements a single insertion to obtain Multiple Samples in multiple desired points along the needle tube with Multiple Spoons (MS-MS). This is the first biopsy tool that is explicitly created for studying intratumor heterogeneity. The operation procedure of the proposed biopsy tool is as follows. According to preoperative multi-modality images, a surgeon first finds a volume of suspected tissue, then selects the entrance point of the needle tip and the attitude of the needle body, further plans the locations of the biopsy spoons on the needle, and finally inserts the tool into soft tissue to take multiple samples with multiple spoons synchronously.

II. SYSTEM CONFIGURATION

A. OVERALL STRUCTURE

The biopsy tool comprises a Front Biopsy Unit (FBU), an Intermediate Connecting Segment (ICS), and a Back Transmission Part (BTP), see Figure 1 for the overall mechanical configuration of the biopsy tool proposed. The front biopsy unit consists of a group of biopsy spoons, a cover, a needle tip, and a biopsy mechanism that includes a Fixed Bar (FB), an Inserting Bar (IB), a set of mobile rotational bars, a group of Fixed Rotational Joint Bar (FRJB), a group of Mobile Rotational Joint Bar (MRJB) and a sliding rail. The intermediate connecting segment comprises

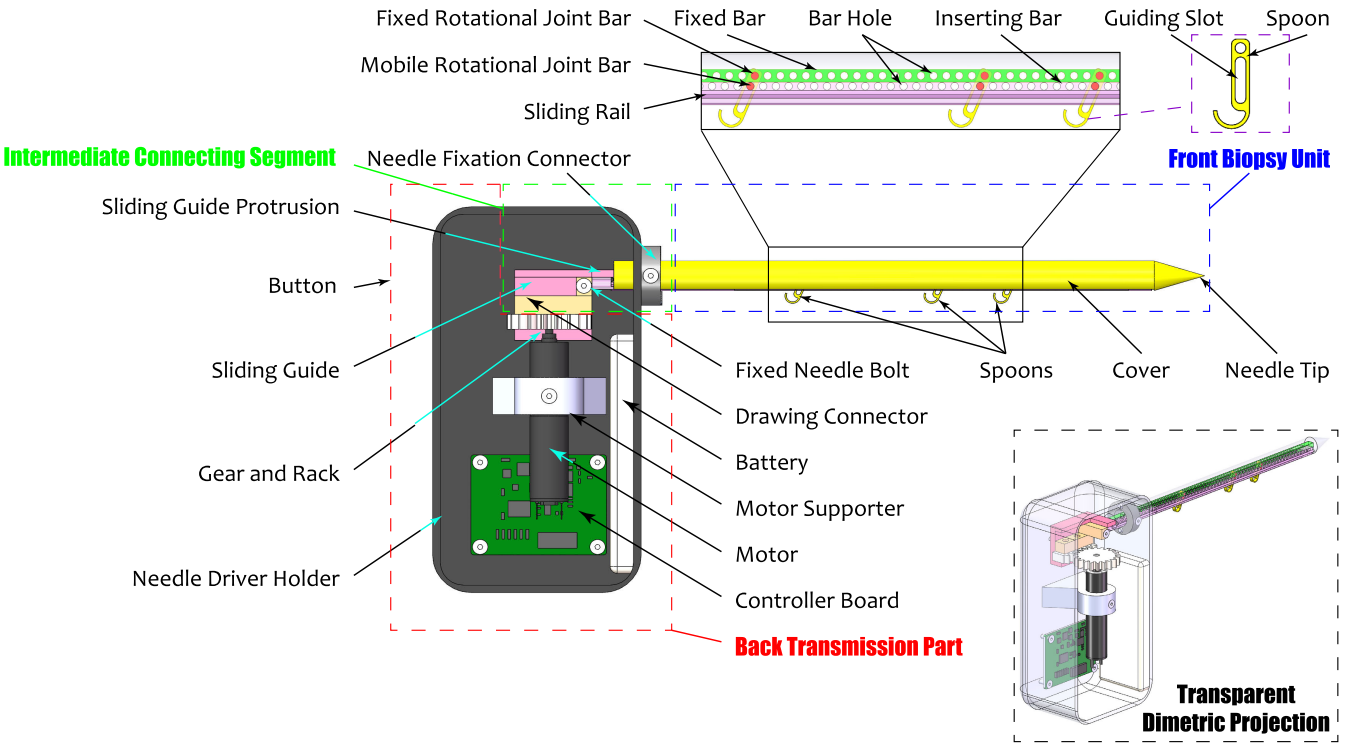


FIGURE 1. System structure of the biopsy tool, a single insertion obtaining *Multiple Samples* in multiple desired points via a group of *Multiple Spoons* (MS-MS).

several components including a Needle Fixation Connector (NFC), a Fixed Needle Bolt (FNB), a Drawing Connector (DC), a sliding guide, and a sliding guide protrusion. The back transmission part includes a motor, a motor supporter, a controller board, a block of battery, a Needle Driver Holder (NDH), a set of gear and rack, a drawing connector, and a button. Other trivial connecting elements are omitted in Figure 1. Due to the proof-of-principle nature of the study, that is to say, to verify the function of the design, the needle driver holder is not optimized according to the surgeon's hand following ergonomics guidelines.

The mechanical connections between the components of the biopsy tool are specified in the following. The motor drives the gear that moves the rack, and the rack is secured to the drawing connector. The inserting bar is attached to the drawing connector by the fixed needle bolt in Figure 1. The combination of the rack and the drawing connector slides under the direction of the sliding guide. The sliding guide is mounted onto the handle box. The sliding guide protrusion stops the fixed bar. The cover of FBU and the needle driver holder of BTP are connected by the needle fixation connector and the fixed needle bolt of ICS. When the biopsy spoons are set to desired depths, the biopsy operation is automatically completed by the controlling system. The trajectory of the frontal end of the spoon is offered in the next subsection, where the adjusting method of the spoons for adapting to various tissue layers is presented. The form of the spoons determines the volume of the sampled lesions gathered from the target regions.

B. BIOPSY MOTION PROCEDURE

The motion of the biopsy tool is realized by the relative sliding motion between the fixed bar and the inserting bar. The slide rail is fixed on the inserting bar, and it controls the inserting bar to move along a straight line that is parallel to the axis of the cover. The mobile rotational joint bar travels in the guide slot of the spoons, and it is also installed to one of the bar holes of the inserting bar. Except for a relative rotational displacement, there is no translational displacement between the mobile rotational joint bar and the inserting bar. These mechanical components and the lesion tissue function together to realize a lever mechanism. That's to say, each of the spoons rotates around a fixed rotational joint bar, and it excavates a portion of the suspicious tissue from a target region. In detail, the rotational center of the spoon is fixed, i.e., the point O in Fig. 3, and the location of the spoon is controlled by the Sliding Bar, i.e., the Sliding Bar pushes the spoon to rotate around the center point O. The fixed bar does not slide along the needle, and it is in a fixed position of the needle.

The motion procedure of the biopsy spoon and the trajectory of the frontal end of the spoon are shown in Figure 2. The initial phase of the biopsy procedure is shown in Figure 2(a), where the biopsy needle is inserted into the target organ and lesion tissue before taking lesion samples. Further, the intermediate stage is represented in Figure 2(b), that's to say, the group of the biopsy spoons is driven by the inner mechanism and severs some lesion tissue. Finally, the last phase is shown in Figure 2(c), where the collected

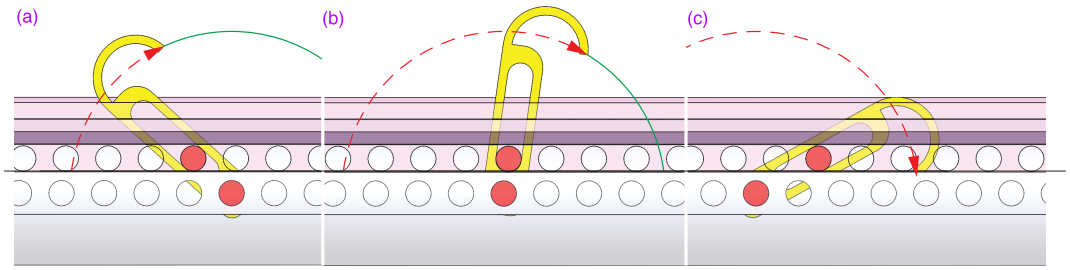


FIGURE 2. Trajectory of the frontal end of each spoon.

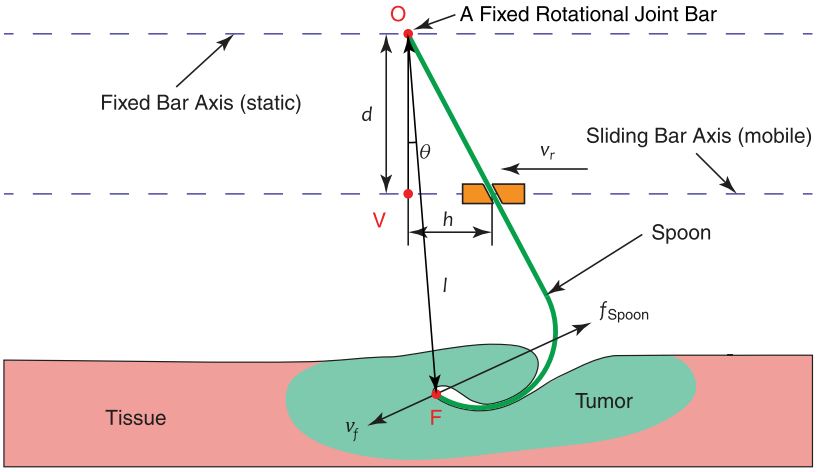


FIGURE 3. Schematic of biopsy mechanism.

lesion samples are deposited in the spoons, and the spoons are hidden in the cover. During insertion or removal of the device, the spoons are not on the external surface of the needle. In both cases, the spoons are hidden concealed in the needle cover. For example, the spoon is concealed in the needle during it is withdrawn from the tissue as shown in the subfigure (c) of Fig. 2. Thus, there is no traumatic from the spoons during insertion or removal of the device. After the final phase, the biopsy needle is pulled back from the target region of a patient. Thus, very roughly, the biopsy task using this tool is accomplished by the relative motion between the inserting bar and the fixed bar.

The method to retrieve the biopsy specimens is as follows. After the spoons are positioned, via the actuation mechanism in Fig. 1, to the location in the subfigure (b) of Fig. 3, one can retrieve the biopsy specimens by using a long slim bar or a similar object to push the biopsy specimens out of the spoon. While in this study, we disassembled the mechanism and took the spoon and its inner biopsy specimens out of the needle cover together.

C. METHOD FOR POSITION DETERMINATION

The features of the biopsy tool are twofold including synchronization of multi-spot biopsy and adjustability of the spoons' positions. These features bring two advantages compared to other biopsy needles. One of the strengths is the avoidance of needle track implantation, and the additional reward is the saving of time-cost. According to preoperative Magnetic Resonance (MR) or Computerised Tomography (CT) images, a surgeon chooses the optimal direction and position for the entrance of the biopsy tool's tip. Then with only one insertion, the biopsy tool fetches samples to provide the histopathologic diagnosis in suspicious locations inside one heterogeneous lesion.

The multiple bar holes enable the biopsy tool to be with the adjustability of the sampling locations of the spoons. The fixed rotational joint bar can be inserted into any one of the bar holes, shown in Figure 1. The center of the fixed rotational joint bar represents the position of the sampled tissue. The distance between two neighboring bar holes, in the inserting bar or the fixed bar, determines the positioning precision of the tool, and thus the maximal error of the positioning precision is half of the distance. In addition, we can change the distance by redesigning the structure to match a positioning precision required by a customized clinic condition before it is manufactured. The method determining the spoon position is the procedure below: a) Take medical images of the biopsy area; b) Select the insertion direction and position of the needle system; c) Determine the biopsy spots and record the positions along the needle longitudinal axis; d) Select the nearest hole to each position marked in the step c). We present the adjustment method of the spoons

position in the following. Case I: Alter the spoon's position before the sliding bar and the fixed bar are inserted into the needle cover. First, a biopsy surgeon disassembles the needle fixation connector from both the cover and the needle driver holder. Then, the fixed needle bolt is also unloosed from the drawing connector shown in Figure 1. Next, all of the Fixed Bar, the inserting bar, the fixed rotational joint bars, the mobile rotational joint bars, and the spoons are pulled out from the cover. In the following step, a few spoons are fixed by a set of fixed rotational joint bars at the desired positions. Last, the biopsy surgeon reloads the fixed bar and the inserting bar back into the cover and secures the fix needle bolt. Case II: Alter the spoon's position after the sliding bar and the fixed bar are inserted into the needle cover. We first remove the needle cover from the fixed bar and the sliding bar, and then follow the step in Case I. Besides the reusable way, the needle can be made to be disposable and thus, no alternation of the spoon positions is required.

The general working flow for the biopsy tool system is stated in the following. To start with, a surgeon determines the entry position of the tool's tip and the direction of the axis of the cylindrical biopsy tool. Then, the surgeon gives the number and positions of biopsy sites in the tumor of a patient. Afterward, the surgeon loads a group of spoons to the front biopsy unit at the desired locations. Next, the biopsy tool is installed on the distal end of a robotic arm. After that, the robotic system inserts and pushes the needle into the patient's tissue and stops when the tip reaches a goal position in the tumor. Last, the biopsy needle automatically takes some tissue samples by the spoons.

III. ANALYSIS ON THE NEEDLE SYSTEM

In this section, we address the motion analysis and derivation of the force of the sample spoon during the biopsy procedure, and these results determine the theoretical feasibility of the biopsy tool.

A. CUT FORCE ANALYSIS

Basically, to get a sample by a biopsy device is equal to using a mechanical tool to cut a portion off from the suspected soft tissue. Whether the action of the biopsy tool can be accomplished or not depends on its mechanics relative to several factors, including mechanical structure parameters, cutting speed, cutting volume, and the form and sharpness of the edge, et al. [31]–[35]. Design of a biopsy tool means to select its structural parameters. The schematic diagram for motion analysis of biopsy procedure is shown in Figure 3. Before acquiring the structural parameters of the biopsy tool, we should know in advance the force f_{spoon} applied to the biopsy spoon from the tissue.

When the needle is inserted, either by a surgeon or by an automatic puncture system, into the desired position, the velocity v_r between the inserting bar and the fixed bar is crucial for calculating the force f_{spoon}. The force f_{spoon} is defined by the cutting speed v_f of the frontal end of a sample spoon [36], i.e.,

$$f_{spoon} \propto v_f, \quad \text{namely}, f_{spoon} = k \cdot v_f + f_{cut}. \tag{1}$$

We explain the parameters in Eq. (1) in detail. k, experimentally measured, is a positive constant determined by the properties of the specific tissue. f_{cut} is the cutting force on the front end of the spoon, and it depends on the properties of the sampled tissue and the edge form of the spoon. For a given spoon, f_{cut} is mainly related to the sharpness of its edge, namely, Blade Sharpness Index (BSI), and these variables can be experimentally obtained [37]. In this paper, the explicit form of f_{cut} is omitted for space consideration.

In the rest of this part, f_{spoon} is derived. Let d be the distance between the inserting bar and the fixed bar. Denote by l the distance between the center of a fixed rotational joint bar and the distal end of the spoon. Let θ be the angle between line OV and line OF connecting the front end point F of the spoon and the rotational center O. Thus, the geometric relationship in Figure 3 yields

$$\theta = \arctan \frac{h - v_r t}{d}. \tag{2}$$

Accordingly, the rotational velocity $\dot{\theta}$ of the spoon bar with respective to the rotational center O is

$$\dot{\theta} = -\frac{dv_r}{d^2 + (h - v_r t)^2}. \tag{3}$$

Hence, the velocity of the front end of the spoon v_f is

$$v_f = -\frac{ldv_r}{d^2 + (h - v_r t)^2}. \tag{4}$$

Eq. (4) explains how to control the velocity v_f by regulating the input speed v_r.

Finally, replacing Eq. (1) by Eq. (4) yields

$$f_{spoon} = \frac{k \cdot ldv_r}{d^2 + (h - v_r t)^2} + f_{cut}. \tag{5}$$

In next part, we analyze the critical stress using f_{spoon} in Eq. (5). The critical stress analysis is crucial for parameter selection of mechanical configuration.

B. CRITICAL STRESS ANALYSIS

For a given mechanical system, an oversized force on the critical mechanical structure often results in its failure. Thus, considering operational safety of the biopsy tool, we should take the critical stress of its vital parts into account. A fixed rotational joint bar, a mobile rotational joint bar, a spoon, and a block of tumor tissue, shown in Figure 3, form a lever mechanism together. Thus, according to Figure 4, the force f_{pull} between the fixed rotational joint bar and the spoon is determined by

$$f_{pull} = f_{spoon} \frac{\lambda_{spoon}}{\lambda_{pull}} \tag{6}$$

where f_{spoon} is same to that in Eq. (5). λ_{spoon} and λ_{pull} are the force arms of f_{spoon} and f_{pull}, respectively. Further, according to the Hertz theory for contact analysis between a cylinder and

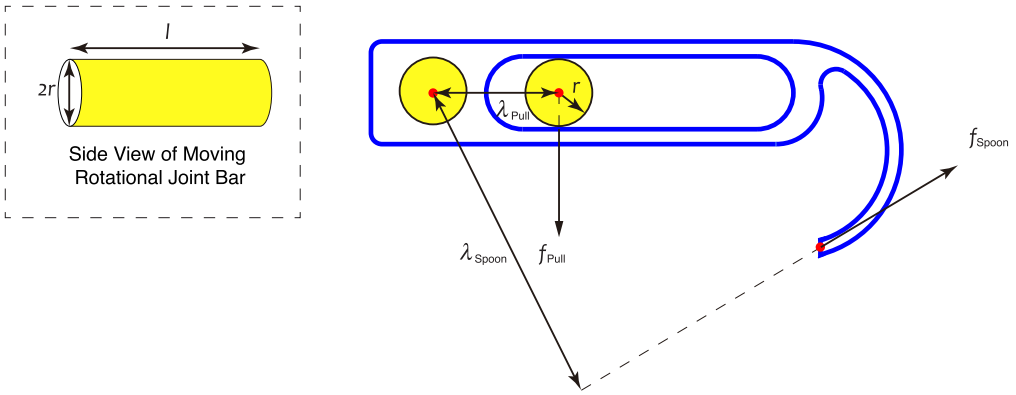


FIGURE 4. Schematic of the load on a fixed rotational joint bar.

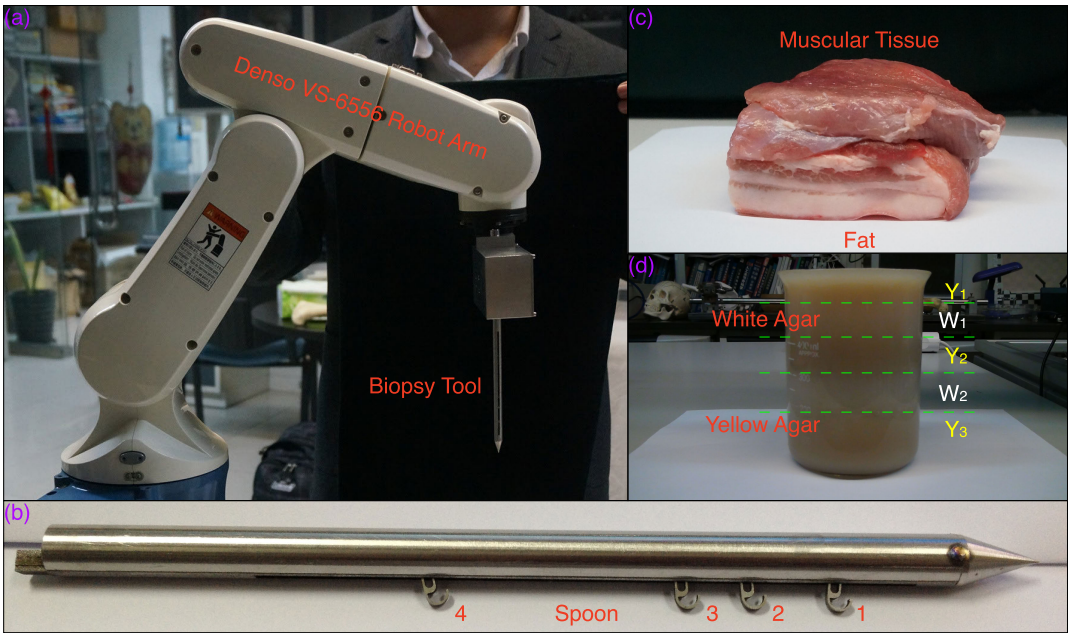


FIGURE 5. Biopsy experimental preparation. The experimental setup (a), the biopsy tool (a), the agar phantom (c), and the ex vivo porcine tissue (d).

a plane [38], the maximal contact stress κ at the center of the contact surface is calculated by

$$\kappa = \left(\frac{E^* f_{pull}}{\pi r l}\right)^{1/2} \tag{7}$$

where E is an elastic modulus, and ν denotes a Poisson's ratio. r and l are the radius and the height of the mobile rotational joint bar, respectively. E^*, an equivalent elastic modulus, is determined by

$$E^* = E/(1-\nu^2). \tag{8}$$

Thus, by substituting Eq. (5) and Eq. (6) into Eq. (7), we can obtain the relationship between f_{spoon} and κ, i.e.,

$$\kappa = \left(E^* \frac{k \cdot l d v_r + f_{cut}(d^2 + (h - v_r t)^2)}{\pi r l (d^2 + (h - v_r t)^2)}\right)^{1/2} \tag{9}$$

where f_{cut} is a variable that is independent from the control input v_r. Thus, κ only depends on v_r, which is the drawing speed of the inserting bar in Figure 3. For safety consideration, the drawing speed v_r of the inserting bar should not be bigger than a critical value, say $v_{r\max}$, i.e., $v_r \leq v_{r\max}$. $v_{r\max}$ is determined by the material of the mobile rotational joint bar. The diameters of clinic biopsy needles are often small in dimension. For example, the diameters of the neurosurgery biopsy needles are less than 3mm. Therefore, the dimensions of the components inside a neurosurgery biopsy tool are often of small sizes. Thus, the selection of mechanical parameters is one of the keys that differentiate either success or failure of biopsy tool design. So, the constraint in Eq. 9 is crucial when the diameter of the proposed biopsy needle is scaled down to the dimension of less than 8 Gauge (4.191mm).

IV. EXPERIMENTAL VERIFICATION

A. EXPERIMENTAL SETUP

In this section, we set up an experimental biopsy system, shown in the subfigure (a) of Figure 5, to verify the feasibility of the biopsy needle. The biopsy system comprises a six

DOF VS-6556 robotic arm by DENSO Robotics, a built prototype of the biopsy needle tool, and two biopsy targets, namely, a multi-layer agar phantom and an ex vivo swine tissue. In Figure 5, the biopsy needle system is shown in the subfigure (a), and in the subfigure (b), the biopsy tool is installed to the end effector of the DENSO robotic arm.

In this study, our goal is to check the feasibility of the design of the biopsy tool and the biopsy method using the device. Thus, to reduce high manufacturing cost, the diameter and the length of the biopsy tool, shown in the subfigure (b), are 8mm and 153mm, respectively. It's necessary to clarify that the manufacturing factory confirmed that the dimension and all parts of the needle of the biopsy tool can be scaled down to that of an 8 Gauge biopsy needle with a much higher charge than the current double-size version. We use two types of layered material in two groups of experiments to check the feasibility of the multi-point synchronizing biopsy tool. The first material is a sandwich structure phantom with five layers of the C12H12O9 agar, Biosharp CO., LTD, shown in the subfigure (d), Figure 5. The agar phantom comprises the three slight yellow layers denoted by Y1 and Y2 and Y3 and the two white layers marked by W1 and W2. The other is a piece of ex vivo swine tissue that is naturally layered, shown in the subfigure (c), Figure 5.

For the position of the target spot determines that of the spoon, thus, in these experiments, the positions of spoons are determined by the distances between the layers of the agar phantom and that of the layered swine tissue. The distances between the needle tip and the spoons are 32.52mm, 45.84mm, and 55.74m, respectively.

B. EXPERIMENTAL RESULTS AND ANALYSIS

We implemented six groups of experiments to testify the biopsy performance of the biopsy tool for investigating intratumor heterogeneity. The experimental setup is shown in the subfigure (a) of Figure 6. Because an ex vivo tumor from a patient is hard to be fixed, we use an agar phantom and a piece of ex vivo porcine tissue to test the feasibility of the biopsy tool.

1) EXPERIMENTS ON MULTI-LAYER PHANTOM TISSUE

An agar phantom with several layers simulates a block of heterogeneous tissue, and the layers are the cascade yellow and white sandwich structure shown in the subfigure (b) and (c) of Figure 6. Nos. 1, 3, 4 spoons in the subfigure (b) of Figure 5 are employed to take samples. Then a microbalance measures all the sampled tissue. Because the form of a sampled tissue in a spoon is irregular, it is hard to measure its volume. Thus, the mass of the sampled tissue is used to analyze the results, and the weights of the samples are shown in Figure 7.

From the results in Figure 7, the average masses of the sampled tissue collected by Nos. 1, 3 and 4 spoons are 133.05μg, 108.80μg, and 114.60μg, respectively. The average mass of all the sampled tissue is 123.82μg. From the observation of all groups of the agar experiments, the interiors of the spoons are filled with agar phantom. The reason may be that the agar phantom is granulous and fiberless, and it is easy for the spoons to cut off.

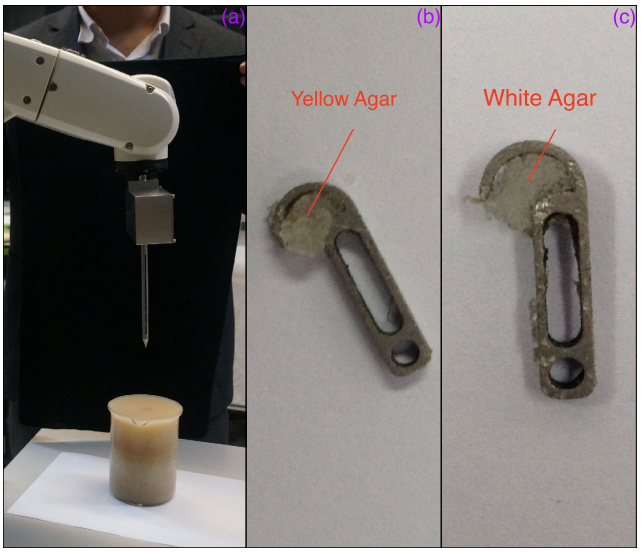


FIGURE 6. The agar phantom experimental scenario and the sampled specimens with the corresponding spoons.

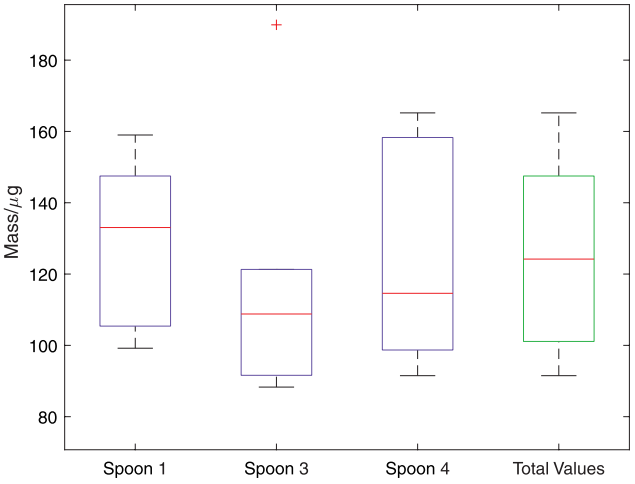


FIGURE 7. The statistical result on the masses taken by the Nos.1, 3 and 4 spoons on the agar phantom.

2) EX VIVO EXPERIMENTS ON SWINE TISSUE

In this part, we implemented several groups of biopsy experiments on ex vivo porcine tissue. The swine tissue is naturally layered and is appropriate to verify the multiple layer sampling of the needle system. We also carried out six groups of biopsy experiments with the experimental environment shown in the subfigure (a) of Figure 5. The bottom layer is a subcutaneous layer of fat and others are muscular tissue.

Similar to agar phantom, it is also difficult to measure the grabbed volume of swine tissue by each spoon, and we measured the mass of the specimen cut by the spoons. According to the thickness of the porcine tissue, Nos. 1, 2 and 3 spoons in the subfigure (b) of Figure 5 are used. And the

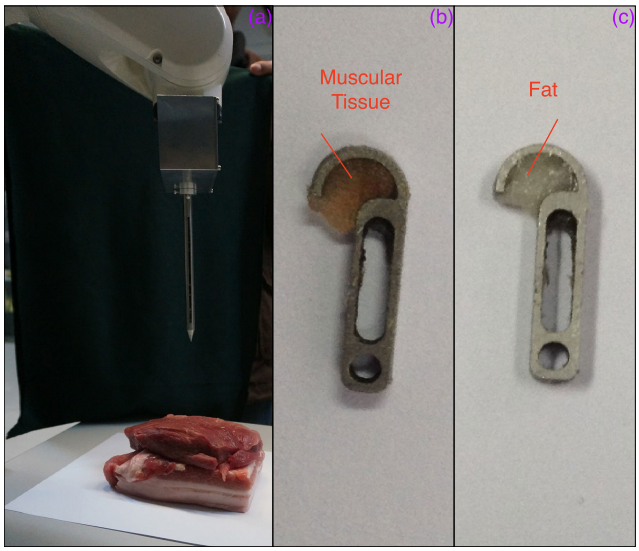


FIGURE 8. The ex vivo swine tissue experimental scenario and the sampled specimens with the corresponding spoons.

mass of the sampled tissue is measured, and the weights measured in the spoons are shown in Figure 9. The data in the first column are the collected masses by the No. 1 spoon in Figure 5, and the tissue is fat. The data in the second and third columns are the gathered masses of muscular tissue by the No. 2 and No. 3 spoons, respectively. From the results in Figure 9, the average masses of the sampled tissue collected by Nos. 1, 2 and 3 spoons are 64.40μg, 81.45μg, and 87.10μg, respectively. The total average of the sampled masses is 77.65μg. The sampled muscular tissue and fat are shown in the subfigure (b) and (c) of Figure 7.

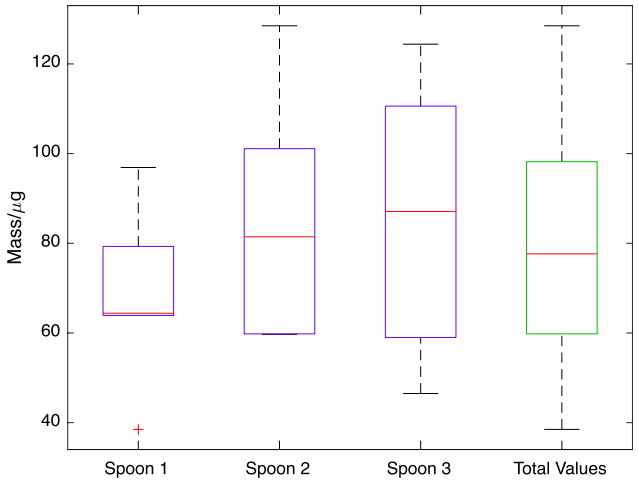


FIGURE 9. The statistical result on the masses taken by the Nos.1, 2 and 3 spoons on the ex vivo swine tissue.

V. DISCUSSION

From the experimental results available, it is confirmed that the biopsy needle tool can take samples at multiple positions in the simulated lesion tissue through one single insertion. Therefore, the effectiveness of the needle is verified for studying intratumor histological heterogeneity. However, the obtained results are the pilot studies, and more points should be strengthened on the proposed needle design, the built prototype, and the experiments in future work.

From the mechanical point of view, first, the form of the spoons is designed on the considerations of the spoon volume and the edge sharpness. The ratio of the sampled tissue volume to the spoon volume is about 60% averagely. Thus, the form of the spoons could be optimized by analyzing the current results, which concentrate on the relationship between the parameters of the spoon edge and the volume of the sampled tissue. The tradeoff will be made between the sharpness of the spoon edge and the mechanical structural strength of the spoon. Then, the optimized spoon form should be measured experimentally by sampling various types of phantom and animal tissue.

Second, the multi-hole changing mechanism gives the biopsy tool the advantage of the multi-point synchronizing biopsy over the existing biopsy needles. However, unless the biopsy device is manufactured as a disposable one, the benefit is realized at the cost of the structural adjustment involving disassembly and assembly of its components. The solution for reducing or removing the inconvenience may be the auxiliary adjusting device, which is a challenging task.

Third, due to the existence of a distance between two neighboring bar holes shown in Figure 1, two adjoining biopsy spots with an interval smaller than the gap cannot be sampled simultaneously. Thus, before using the biopsy tool, its user should check whether the distance between two adjacent biopsy spots is greater than that between two abutting bar holes. Further, the biopsy tool can be designed as several versions with the different distances between two contiguous bar holes. There are some solutions for reducing the spacing between the sampling positions. For example, based on some optimization of the mechanical structure, e.g., partially overlapping the needles with the fixed rotation centers, we can get a closer spacing between the sampling positions.

Fourth, the design task of the biopsy tool roots in the study of the intratumor heterogeneity by the neurosurgery department. In the next, the system structure and parameters of the biopsy needle may be modified or redesigned according to the specific requirement from multiple medical departments.

Fifth, after the feasibility study in this paper, the shape and structural parameters of most parts can be redesigned and scaled down to an 8G size. For example, the shape of the needle driver holder of the tool can be redesigned with a smooth form according to the ergonomics. The needle driver holder with an optimized shape is shown in Figure 10. Sixth, for the current sharpness of the spoon tip in Fig. 5, the agar, the porcine fat, and the porcine muscle can be taken without difficulties. While if the spoon has a sharper cutting edge, it is easier to biopsy by cutting the tissue off. In future, we would compare the amount of the sampled tissue grabbed by both the current edge and a sharper cutting edge. Seventh, unlike the flexible biopsy needles, the offered needle belongs to the

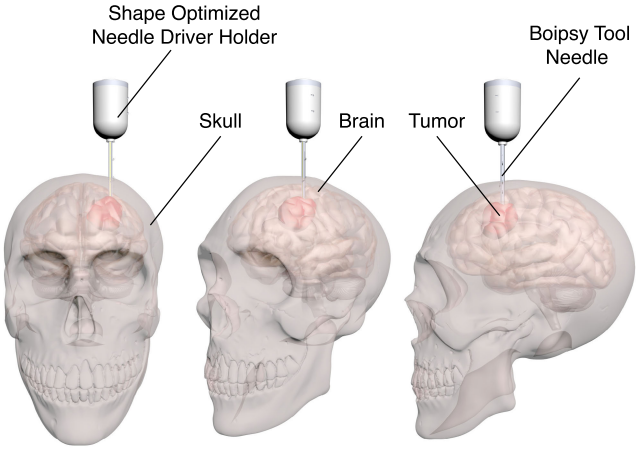


FIGURE 10. **An inferential clinical scenario of the biopsy tool in sampling a brain tumor.**

rigid type and the selected positions of the spoons are not adjustable after insertion into soft tissue. If the actual final position is different from the planned position or there are relative distances between sampling positions changed after insertion, one solution for these cases is that we select a group of predicted positions before insertion the needle into soft tissue. The anticipated positions are calculated using a fitting curve determined by the experiments that measure the position changes of desired spots after the needle is inserted into soft tissue. Alternatively, we may test various flexible materials that are used by the flexible type needles for our design in future, and thus this limitation may be solved thoroughly. Eighth, for the current design, when needing samplings from different positions and directions, one can rotate the needle along the longitude axis of the frontal needle after the spoons are hidden in the needle cover. This is a way for the task without re-insertion with a rotated pose. At the same time, it is suggested that, for the presented system, the best way to take samples is to select the best facing direction before insertion.

From the experiment angle of view, first, according to the observation and the measured experimental results, the agar phantom is comparatively convenient to be sampled than the swine tissue is. The reason for the result is that no fibrous tissue exists in the agar phantom, and abundant fibrous tissue exists in the swine tissue, including muscular tissue and fat. Besides, considering gradients and mechanical properties, various types of tissue differ from the agar and the swine muscle and fat tissue. Thus, multiple kinds of experimental tissue should be sampled to get a comprehensive understanding of the appropriate environment of the biopsy tool.

Second, animal and pre-clinic experiments are planned using a small-scale version of the biopsy tool. During these experiments, neurosurgeon feedback on the usage of the biopsy tool is of fundamental importance for optimizing its structural design. Besides the mechanical design, biopsy time cost, operation convenience, and other factors should be considered as well. Third, traumatic injury is always a side effect of biopsy procedures for harming both the channel and tumor-surrounding healthy tissue. Although most of the new biopsy needle designs, e.g., [11]–[14], [16]–[23], didn't study traumatic injury on healthy tissue, from some studies, e.g., [39], there are clear examples where apparent innovation in biopsy needle tip has caused great harm to patients compared to older technology by producing lower quality specimens for pathologic analysis. Thus, after this study, we would scale down the dimension of this biopsy needle and study the traumatic injury by the proposed system and then optimize its mechanical design. One of the possible methods is to obtain live tissue, e.g., brain biopsies immediately from euthanized mice or rats, using the biopsy needle and formalin-fixed paraffin-embedded (FFPE) samples that are sectioned and stained with hematoxylin and eosin (H&E). Next, the device is compared to a biopsy device that is commonly used clinically for the selected organ. Then the tissue damage is evaluated by excising the rest of the brain and assessing the biopsy site margins by FFPE H&E staining. Fourth, the hardness values of various types of diseased tissues vary. Thus, for an excellent biopsy needle system, it should cover a broad spectrum of human tissue. To this end, in future, this device would be tested to penetrate hard tissue, like bone or tumors with stone/calcium deposits. Fifth, the samples taken by the No. 2 and No. 3 spoons are both white agar and thus, we omitted the No. 2 spoon for avoiding repetition in Fig. 7. Because the thickness of the ex vivo tissue is not enough for the No. 4 Spoon to take a sample, the spoon is not used and thus omitted in Fig. 9. The main reason why there exist some variations in tissue biopsy masses is that we use the different pieces of ex vivo porcine tissue and the agar phantoms with the various ratios of water and agar powder. The groups of the porcine tissue are from different swine blocks from supermarkets. Also, the mass is not a good evaluation criterion for the amount of the porcine tissue, while the volume is a better criterion than mass. However, the volume is not an easy quantity that can be directly measured. We may try other quantities to compare the grabbed tissue.

VI. CONCLUSIONS AND FUTURE REMARKS

A position-adjustable multi-point synchronizing biopsy tool is designed, and the position adjustment method of the spoons is developed based on the multiple-hole mechanism. Then, the analysis of the motion of the biopsy spoon and the critical stress of the vital motion components are implemented. Furthermore, we built an 8mm diameter prototype and carried out multiple groups of experiments to evaluate the effectiveness of the biopsy needle on the agar phantom and the swine tissue. The experimental results demonstrated that the tool could synchronously take biopsy samplings at different positions in one single insertion. Thus, the device contributes to the study of intratumor histological heterogeneity.

The advantage of the needle includes avoidance of multiple motions in lesion and tissue enclosing lesion targets,

especially those in vital locations, like the brainstem. Also, another value of the tool is timesaving when multiple position biopsies are required to obtain detailed tissue distribution of an inner lesion. Further, a decrease of biopsy operation time will reduce the negative effect of a hand tremble because of a long time grasping on biopsy precision. Thus the proposed needle may contribute to improving the diagnostic result.

In the next work, the form of the biopsy spoons will be optimized based on several factors, including the relationship between spoon edge and the mechanical structure strength, the cutting performance of spoon edge on target tissue with different fibrous constituents, and the obtained experimental results. The outer form of the handle box will be redesigned according to ergonomics to suit for surgeons holding. An auxiliary adjustment device will be developed which changes the positions of the needle's spoons by a simple operation. The changing method of the spoon positions by multiple holes changing mechanisms may be redesigned to realize arbitrary locations of the biopsy spoons. Based on current and further experiments, a smaller-scale version of the design will be built, and an ex vivo experiment on tumor specimen, in vivo animal, and clinic biopsy experiments will be implemented to test the effectiveness of the needle. Then, the feedback from surgeons will be summarized and integrated into the next version of the biopsy needle tool.

ACKNOWLEDGMENT

The authors would like to thank Associate Professor J. Wang and W. Liu for their support on some mechanical parts and the experiments in this study, and gratefully acknowledge the insightful and very constructive comments from the anonymous reviewers.

REFERENCES

[1] C. Fisher, E. A. Montgomery, and K. Thway, *Biopsy Interpretation of Soft Tissue Tumors* (Biopsy Interpretation), 3rd ed. Norwell, MA, USA: Kluwer, 2011.

[2] J. C. Briggs, O. A'amar, I. Bigio, J. E. Rosen, S. L. Lee, A. Sharon, and A. F. Sauer-Budge, "Integrated device for *in vivo* fine needle aspiration biopsy and elastic scattering spectroscopy in preoperative thyroid nodules," *J. Med. Devices*, vol. 8, no. 2, Jun. 2014, Art. no. 021003.

[3] T. A. Yap, M. Gerlinger, P. A. Futreal, L. Pusztai, and C. Swanton, "Intratumor heterogeneity: Seeing the wood for the trees," *Sci. Transl. Med.*, vol. 4, no. 127, p. 12710, Mar. 2012.

[4] C. E. Meacham and S. J. Morrison, "Tumour heterogeneity and cancer cell plasticity," *Nature*, vol. 501, no. 7467, pp. 328–337, Sep. 2013.

[5] J. Zhang *et al.*, "Intratumor heterogeneity in localized lung adenocarcinomas delineated by multiregion sequencing," *Science*, vol. 346, no. 6206, pp. 256–259, Oct. 2014.

[6] R. Gyanchandani, N. Priedigkeit, A. Basudan, and A. V. Lee, "Chapter 2 - intratumor heterogeneity: Biological and clinical implications," in *Oncogenomics*, F. Dammacco and F. Silvestris, Eds. New York, NY, USA: Academic, 2019, pp. 17–30.

[7] J. H. Rasmussen, G. Lelkaitis, K. Håkansson, I. R. Vogelius, H. H. Johannesen, B. M. Fischer, S. M. Bentzen, L. Specht, C. A. Kristensen, C. von Buchwald, I. Wessel, and J. Friborg, "Intratumor heterogeneity of PD-L1 expression in head and neck squamous cell carcinoma," *Br J Cancer*, vol. 120, no. 10, pp. 1003–1006, May 2019.

[8] G. Stanta and S. Bonin, "Overview on clinical relevance of intra-tumor heterogeneity," *Frontiers Med.*, vol. 5, p. 85, Apr. 2018.

[9] P. L. Bedard, A. R. Hansen, M. J. Ratain, and L. L. Siu, "Tumour heterogeneity in the clinic," *Nature*, vol. 501, no. 7467, pp. 355–364, Sep. 2013.

[10] Y. Moon, J. B. Seo, and J. Choi, "Development of new end-effector for proof-of-concept of fully robotic multichannel biopsy," *IEEE/ASME Trans. Mechatronics*, vol. 20, no. 6, pp. 2996–3008, Dec. 2015.

[11] K.-J. Franke, G. Nilius, K.-H. Ruehle, M. D. Enderle, W. Linzenbold, and C. H. von Weyhern, "The Cryo-Needle: A new tool for histological biopsies. A feasibility study," *Lung*, vol. 191, no. 6, pp. 611–617, Dec. 2013.

[12] S. L. Figueredo, W. R. Brugge, and A. H. Slocum, "Design of an endoscopic biopsy needle with flexural members," *J. Med. Devices*, vol. 1, no. 1, pp. 62–69, Mar. 2007.

[13] R. Clements and A. R. Face, "Device, system and method for multiple core biopsy," U.S. Patent 20 110 125 054 A1, May 26, 2011.

[14] J. Z. Moore, P. W. McLaughlin, and A. J. Shih, "Novel needle cutting edge geometry for end-cut biopsy," *Med. Phys.*, vol. 39, no. 1, pp. 99–108, Dec. 2011.

[15] D. S. Zimmon, F. B. Smith, F. Manheimer, C. Fan, C. Njiwaji, S. Aksenov, and P. Chattoo, "Endoscopic multiple biopsy and rapid diagnosis by in situ fixation and histopathologic processing," *Gastrointestinal Endoscopy*, vol. 86, no. 2, pp. 333–342, Aug. 2017.

[16] Y. Chin and M. Chu, "Biopsy needle instrument for storing multiple specimens," U.S. Patent 5 195 533 A, Mar. 23, 1993.

[17] N. Erlich, "Single puncture multi-biopsy gun," U.S. Patent 5 595 185 A, Jan. 21, 1997.

[18] R. R. Stephens, J. A. Kretchman, M. D. Hileman, and D. N. Ladd, "Surgical biopsy device having automatic rotation of the probe for taking multiple samples," U.S. Patent 6 620 111 B2, Sep. 16, 2001.

[19] J. Taylor, S. Thompson, T. Coonahan, and G. Gray, "Single-insertion, multiple sample biopsy device with integrated markers," U.S. Patent 8 267 868 B2, 2012.

[20] J. Taylor, S. O. Thompson, T. J. Coonahan, and G. A. Gray, "Single insertion, multiple sample biopsy device with integrated markers," U.S. Patent 8 728 003 B2, Sep. 18, 2014.

[21] S. O. Thompson, T. J. Coonahan, and J. Taylor, "Single-insertion, multiple sampling biopsy device with linear drive," U.S. Patent 20 180 338 748 A1, Sep. 11, 2018.

[22] A. P. Nock, "Core needle biopsy device for collecting multiple samples in a single insertion," U.S. Patent 20 190 231 325 A1, Aug. 1, 2019.

[23] Z. Yu, "A kind of multiple punch biopsy sampler for tumor of breast minimally invasive surgery," China Patent 109 498 070 A, Mar. 22, 2019.

[24] T. Hayashi, M. Hirokawa, M. Higuchi, T. Kudo, Y. Ito, and A. Miyauchi, "Needle tract implantation following fine-needle aspiration of thyroid cancer," *World J. Surg.*, vol. 44, no. 2, pp. 378–384, Feb. 2020.

[25] M. Kara, "Implantation metastasis caused by fine needle aspiration biopsy following curative resection of stage IB non-small cell lung cancer," *Eur. J. Cardio-Thoracic Surg.*, vol. 20, no. 4, pp. 868–870, Oct. 2001.

[26] B. Su, J. Tang, S. Kuang, M. Jin, H. Wu, L. Liu, H. Liu, J. Wang, H. Sun, L. Lam, and Y. Li, "Extensible and compressible continuum robot: A preliminary result," in *Proc. Symp. Adv. Robot. Autom. (WRC)*, Aug. 2019, pp. 44–49.

[27] Y. Zhang, H. Sun, Y. Jia, D. Huang, R. Li, Z. Mao, Y. Hu, J. Chen, S. Kuang, J. Tang, X. Xiao, and B. Su, "A continuum robot with contractible and extensible length for neurosurgery," in *Proc. IEEE 14th Int. Conf. Control Autom. (ICCA)*, Jun. 2018, pp. 1150–1155.

[28] B. Su, Z. Shi, and H. Liao, *A Laser Ablation End-Effector with Multiple Degrees Freedom for Minimally Invasive Surgery*. Cham, Switzerland: Springer, 2015, pp. 223–226.

[29] B. Su, J. Tang, and H. Liao, "Automatic laser ablation control algorithm for an novel endoscopic laser ablation end effector for precision neurosurgery," in *Proc. IEEE/RSJ Int. Conf. Intell. Robots Syst. (IROS)*, Sep. 2015, pp. 4362–4367.

[30] B. Su, Z. Shi, and H. Liao, "Micro laser ablation system integrated with image sensor for minimally invasive surgery," in *Proc. IEEE/RSJ Int. Conf. Intell. Robots Syst.*, Sep. 2014, pp. 2043–2048.

[31] Z. Hu, B. Zhang, and W. Sun, "Cutting characteristics of biological soft tissues," *CIRP Ann.*, vol. 61, no. 1, pp. 135–138, 2012.

[32] P. Han, D. Che, K. Pallav, and K. Ehmann, "Models of the cutting edge geometry of medical needles with applications to needle design," *Int. J. Mech. Sci.*, vol. 65, no. 1, pp. 157–167, Dec. 2012.

[33] D. J. van Gerwen, J. Dankelman, and J. J. van den Dobbelsteen, "Needle–tissue interaction forces—A survey of experimental data," *Med. Eng. Phys.*, vol. 34, no. 6, pp. 665–680, Jul. 2012.

[34] J. A. Jones, Y.-S. Lee, and J. Z. Moore, "Parametric study for asymmetric flexure hinge design for tissue cutting," *Proc. Inst. Mech. Eng., B, J. Eng. Manuf.*, vol. 233, no. 4, pp. 1302–1309, Mar. 2019.

[35] P. Shi, B. Cheng, Y. Zong, Y. Gong, H. Yan, Y. Hu, H. Zhang, S. Kuang, W. Liu, L. Wang, and B. Su, "A soft tissue scalpel cutting robotic system with sucker fixation," in *Proc. IEEE 14th Int. Conf. Control Autom. (ICCA)*, Jun. 2018, pp. 1162–1167.
[36] T. Chanthasopeephan, J. Desai, and A. Lau, "Study of soft tissue cutting forces and cutting speeds," *Stud. Health Technol. Informat.*, vol. 98, pp. 56–62, Feb. 2004.
[37] C. T. McCarthy, M. Hussey, and M. D. Gilchrist, "On the sharpness of straight edge blades in cutting soft solids: Part I—Indentation experiments," *Eng. Fract. Mech.*, vol. 74, no. 14, pp. 2205–2224, Sep. 2007.
[38] C. Guan, "Calculation of critical parameters for hertz contact between cylinder and rigid plane," *Bearing*, no. 8, pp. 4–7, Feb. 2013.
[39] J. R. Brestoff, A. Toland, K. Afaneh, A. J. Qavi, B. Press, P. Westervelt, F. Kreisel, and A. Hassan, "Bone marrow biopsy needle type affects core biopsy specimen length and quality and aspirate hemodilution," *Amer. J. Clin. Pathol.*, vol. 151, no. 2, pp. 185–193, Jan. 2019.

BAIQUAN SU received the B.S. degree in mechatronics and the M.S. degree in control theory and control engineering from Harbin Engineering University, Harbin, in 2001 and 2006, respectively, and the Ph.D. degree from Beihang University, Beijing, in 2013. He was a Postdoctoral Scholar with the Department of Biomedical Engineering, School of Medicine, Tsinghua University, from 2013 to 2015. Since 2016, he has been an Assistant Professor and then an Associate Professor, founding the Medical Robotics Laboratory, School of Automation, Beijing University of Posts and Telecommunications. His research interests include medical robotics and artificial intelligence in clinical medicine. Dr. Su was awarded and co-awarded Best Application Award, Honorable Mentioned Award, and Nomination for Outstanding Youth Paper Award. He was a PI of Grants from Natural Science foundation of China (NSFC), and Grants from China Postdoctoral Science Foundation (CPSF).

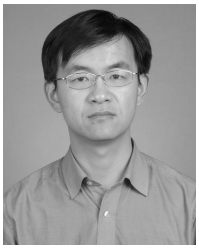
HAO YAN was born in Dezhou, Shandong, China, in 1997. He received the B.S. degree in mechanical engineering from the Beijing University of Posts and Telecommunications, Beijing, China, in 2017, where he is currently pursuing the master's degree. His research interests include medical robot and soft robot.

LIAOLIAO LIU was born in Chenzhou, Hunan, China, in 1998. He is currently pursuing the bachelor's degree with the Automation School, Beijing University of Posts and Telecommunication. His research interests include structured-light scanning systems and medical robot.

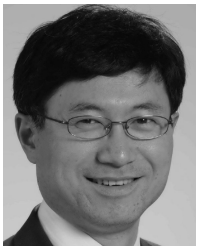
SHI YU was born in Wuhan, Hubei, China, in 1996. She received the B.S. degree in mechanical engineering from the Hubei University of Technology, Hubei, China, in 2019. She is currently pursuing the master's degree with the Beijing University of Posts and telecommunications. Her research interests include mechanical design, medical robot, and soft robot.

YIDA HU received the Ph.D. degree from Beihang University, Beijing, China, in 2006. He is currently a Faculty Instructor with the Harvard Medical School and a Clinical Physicist with Brigham and Women's Hospital, Boston, USA. His research interests include medical robotics and image-guided therapy.

GANG WANG studied in Peking Medical University, in 1992. He received the M.D. degree from Peking University, Beijing, China, in 2003. He is currently the Deputy Chief Physician with the General Surgery Department, Peking University Third Hospital, and the Director of the Animal Experiment Center. He has been involved in surgery teaching for a long time and received the second prize of Beijing teaching achievement. His research interests include surgery teaching and medico engineering cooperation.



WEI YAO received the M.D. degree from Peking University, in 2003. He is currently a Chief Physician with the Peking University Third Hospital. He is experienced with endoscopy technique, not only in diagnosis but also in practicing of endoscopy therapy, such as EMR, EMR, POEM, PEG, band ligation of bleeding esophageal varices, and digestive tract metal stent implantation. Among all the procedures, he is extremely experienced with ERCP and associated techniques, such as the extraction of common bile duct stone.



JIE TANG received the M.D. degree in neurosurgery from Peking University Health Science Center, Peking University, Beijing, in 2005. From 2005 to 2006, he was a Clinical Researcher with the Department of Neurosurgery, Louisiana State University Medical Center, where he studied surgical treatment of skull base surgery and cerebrovascular disease. As a Visiting Scholar, he went to the University of California Los Angeles Medical Center (UCLA), the Stanford Medical Center, the Hannover International Neurosurgical Institute (INI), and the University of Zurich Medical School in Switzerland for neurosurgical communication. He is currently an Associate Professor with the Department of Neurosurgery, Xuanwu Hospital, Capital Medical University. His research interests include skull base neurosurgery, multidisciplinary technology-aided diagnostics and therapeutics in skull base, and neurosurgery robots. Dr. Tang is a member of the Sixth National Youth Committee of the Chinese Medical Association Neurosurgery Branch and a member of the Asia Pacific Cranial Surgery Association (AOSBS). He received the 2nd prize of the 8th Wuyang Medical Pharmacy Research at Health Department, in 2004, the 3rd prize of the 8th Beijing Youth Science and Technology Excellent Paper, in 2005, and the 2nd prize of the 6th National Neurosurgery Conference Excellent Paper, in 2006.

SHAOLONG KUANG received the bachelor's degree in mechanical manufacturing engineering from Anhui Polytechnic University, Wuhu, China, in 1996, the master's degree in mechanical manufacturing engineering from Southeast University, Nanjing, China, in 1999, and the Ph.D. degree in mechatronics engineering from Beihang University, Beijing, China, in 2013. He is currently an Associate Professor with the Robotics and Microsystems Research Center, Soochow University, China. His research interests include medical robot and medical equipment design, and human–robot interaction.