31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

Minimally Invasive Localization of Light Source in Tissue with an Equidistant Measurement

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Abstract—**Bioluminescence techniques permit a way of observing biological processes in vivo, and they are considered to have a promising application on guiding tumor resection. But now, the related techniques, like bioluminescent imaging and bioluminescent tomography, have a common problem on imaging depth limitation. In this paper, a minimally invasive method was introduced to detect the emission of light source beneath the deep tissue. An equidistant measurement that derived from the diffusion equation and spherical light source model was proposed to localize the light source. Using this method, we obtained the analytic solution for 3D position of light source allowing the insertion penetrating the center of light source and unknowing parameters of the tissue. In the end, we put forward a feasible design of minimally invasive probe for clinic use.**

I. Introduction

IN the last century, medical imaging techniques were well developed and widely used. However, cancer resection surgery continues to be performed "blindly": without intraoperative confirmation of tumor extension, sensitive detection of microscopic metastases, or real-time confirmation whether resection is complete or not. The main reason why intraoperative cancer detecting techniques have not been widely used is that the available techniques with problems of tissue specification, spatial & temporal differentiation, safety, bulk, expense, *etc*., are not the optimum intraoperative technique for the surgeons [1].

Bioluminescence refers to the enzymatic generation of visible light by living organisms, which permits a way of observing biological processes in vivo. With advancements in detectors and in vivo methodology, it is now possible to quantitatively examine tumor growth with great sensitivity in vivo using bioluminescent imaging (BLI) [2]. BLI technique is able to detect the light from labeled tumor directly using a cool CCD camera without external excitation, thus, with a lower background and higher signal-to-noise ratio comparing with fluorescent imaging (FLI) techniques [3]. This makes BLI technique have the potential to solve the problem of "blindness" in cancer resection surgery. However, BLI can only give planar location of light source with a low precision, because of highly scattering nature of the biological tissues, and without depth information. To acquire the depth information, researchers have developed some useful algorithms on analyzing planar distribution of light intensity, and which have demonstrated their ability on reconstructing the depth of light source [4, 5]. Moreover, bioluminescent tomography (BLT) technique was developed in view of CT theory not only to acquire the depth information but also to construct 3D profile of light source [6, 7]. However, the related techniques require that the pathology under investigation must not lie at a depth where the attenuation of the signal gives poor signal-to-noise ratio and resolvability. This limits BLI, a promising intraoperative technique, only to small animals for the low penetrating ability of light, even using a near infrared wavelength [8]. In view of biopsy technique, Li [9] developed a computational optical biopsy (COB) technique to detect the depth of light source that could be used to both FLI and BLI. In their work, fiber-optical probe was assumed to detect the light source directly in the subject along one or multiple biopsy paths and next to compute the parameters or features of the embedded light source. They also demonstrated that a single insertion with two detection angles was enough to measure the parameters of light source. However, their method needs the exact parameters of tissue and fails to get the solution in the case when the insertion penetrates the center of light source.

In this paper, we have proposed a minimally invasive method and an equidistant measurement to localize the bioluminescent source beneath the deep tissue. This minimally invasive technique permits a deeper detecting depth and simultaneously less multi-layer tissue effect and operating space restriction. The equidistant measurement offers a feasible way of detecting 3D location under the surface of anatomical region. Moreover, this method permits the insertion to penetrate the center of light source comparing with COB, and also permits a way of detecting without parameters of the tissue, which are always unknown in histo-optics because these parameters are not only based on the types of tissues but also on their states. At last, we put forward a structure of probe for clinic use. The technique we described in this paper is more like making the surgeons directly "see" the 3D location of the tumor beneath the deep tissue, and the technique has deep penetrating ability, has no spatial confining, is relatively inexpensive, and is easy to use. We hope this work contributes to a sensitive, specific, and real-time intraoperative guiding system for cancer resection.

Manuscript received April 20, 2009. This work was supported by: Shenzhen Science Technology Project (ZD200806170041A), Chinese Academy of Sciences "the 100 Talent People" Program, GuangDong Nature Science Foundation（8178922035- X000002）, National Nature Science Foundation of China（60772105).

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II. THEORY AND METHOD

A. Light Diffusion Theory

In BLI, the luciferase generates light through the oxidation of an enzyme-specific substrate, and then bioluminescence signal be quantified by optical detectors to estimate the position of the cancer. The main problem with such quantification is the highly scattering nature of the biological tissues, which results in the dispersion of the photon path lengths, loss of localizing precision and spatial resolution. So, complicated diffusion-like models of photon migration should be developed to analyze the experimental data [10]. Always, bioluminescent materials with a near-infrared (NI) emission are well favorable because the NI wavelengths are ideal since there is wave-range called optical window with a little absorption either by hemoglobin or by water. In this region, the bio-tissue can be regarded as a high scattering and low absorbing medium, and photons propagate in this medium can be described by

$$\frac{\partial \phi(r,t)}{v\partial t} - D\nabla^2\phi(r,t) = -\mu_a\phi(r,t) + S(r,t), \quad (1)$$

where, $\Phi(r, t)$ is diffusion intensity at time t, μ_a is absorbing coefficient of medium, v is the propagating velocity of photons, and $S(r,t)$ is the function of light source, $D=[3(\mu_a+\mu'_s)]^{-1}$ is diffusion coefficient, $\mu'_s=(1-g)\mu_s$, where μ_s is the diffusion coefficient of medium and g is the factor of anisotropy. In the infinite medium, when $S(r,t)$ is a continuous point light source, the solution of (1) is:

$$\phi(r) = \frac{1}{4\pi Dr}\exp(-\frac{\sqrt{\mu_a/D}}{r}) = C\frac{\exp(-\mu_{eff}r)}{r}, \quad (2)$$

where $C=(4\pi D)^{-1}$, and $u_{\text{eff}} =(u_a/D)^{1/2}$ is effective extinction coefficient. To continuous spherical light source $S(r')$, when the power of light source equals to P for $0\le r'\le R$ and equals to 0 for others, then

$$\phi(r)=\frac{P}{2Dr\mu_{eff}}e^{-\mu_{eff}r}[\frac{R}{\mu_{eff}}(e^{-\mu_{eff}R}+e^{\mu_{eff}R})+\frac{1}{\mu^2_{eff}}(e^{-\mu_{eff}R}-e^{\mu_{eff}R})]. \quad (3)$$

It can be rewritten as

$$\phi(r)=C'\frac{\exp(-\mu_{eff}r)}{r}, \quad (4)$$

where

$$C'=\frac{P}{2D\mu_{eff}}[\frac{R}{\mu_{eff}}(e^{-\mu_{eff}R}+e^{\mu_{eff}R})+\frac{1}{\mu^2_{eff}}(e^{-\mu_{eff}R}-e^{\mu_{eff}R})]. \quad (5)$$

B. An Equidistant method

From (2) and (4), we can see that diffusion intensities of single point source and spherical light source in the scattering medium have direct ratios to $\exp(-u_{\text{eff}}r)/r$. If the direction of insertion v goes through the center of light source S, and the distances from three measuring points A_1, A_2 and A_3, which are on the line of insertion, to centre of light source are r_1, r_2 and r_3, respectively, and r_3-r_2 = r_2-r_1 = d, then, the diffusion light intensities $\Phi(r_1)$, $\Phi(r_2)$ and $\Phi(r_3)$ of A_1, A_2 and A_3, respectively, have the relationship as

$$\frac{\phi(r_1)\phi(r_3)}{\phi(r_2)^2} = \frac{r_2^2}{r_2^2 - d^2}. \quad (6)$$

In this Equation, there are only relations about light intensities, the interval of measuring points and distances from measuring points to the light source, but without parameters of the tissue. In practice, the measurement of optical parameters is complicated and difficult, because these parameters are not only based on the types of tissues but also on their states. So, without parameters of tissues in the equation, the calculation of r will be much easier, because the interval of measuring points is always known and light intensities are measurable in the probing process.

III. EXPERIMENTS AND DISCUSSION

A. Experimental result using equidistant method

We designed an experiment to verify the equidistant method. In the experimental setup, light source was a semiconductor laser with a wavelength at 650nm and power at 20mw, the light from the laser was collimated by a lens and chopped by a chopper with a frequency at 1658Hz. Then the light passed a diaphragm and a multi-model fiber with a spherical diffusion ball on the exit, and went into a 5L 6.667% Intralipid tissues simulator liquid. The 3D movement was controlled by an electric stage with a precision of 0.01mm. The diffusion light was collected by a probing fiber to a photoelectric diodes, the signal was read out by Lock-in Amplifier after pre-amplifier.

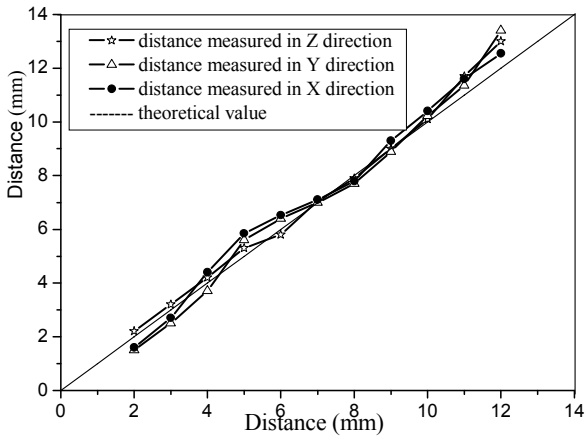

Figure.1. Experimental results of light source localizing in x, y and z axis comparing with the theoretical value.

Figure.1 shows the calculated distance r_2 using the light intensities of $\Phi_t(r_1)$, $\Phi_t(r_2)$ and $\Phi_{t(}r_3)$ at different time t when the direction of movement passing through the center of light source. Where the straight line denotes the theoretical values, and solid circle, hollow triangle and hollow star represent the calculated values from X, Y and Z directions, respectively. In the figure, the calculated values are almost equal to the theoretical ones, which seem to satisfy the practical use in most cases.

B. Excursion from the center of light source

The methodology, presented above, allows us to get quite an accurate localization of bioluminescent source that is located in tissue when the insertion penetrates the center of light source. In the former works [4, 5], localization with fine accuracy was achieved using a planar location of light source with CCD camera and a similar method as (4). However, we can not always know the exactly planar location of the light source when the bioluminescence is almost diminished to undetectable from the surface of tissue. Even though, we can "see" the planar location of the bioluminescence, it is hard to pinpoint the exact planar position when the surface is uneven and detecting angle is not regulated.

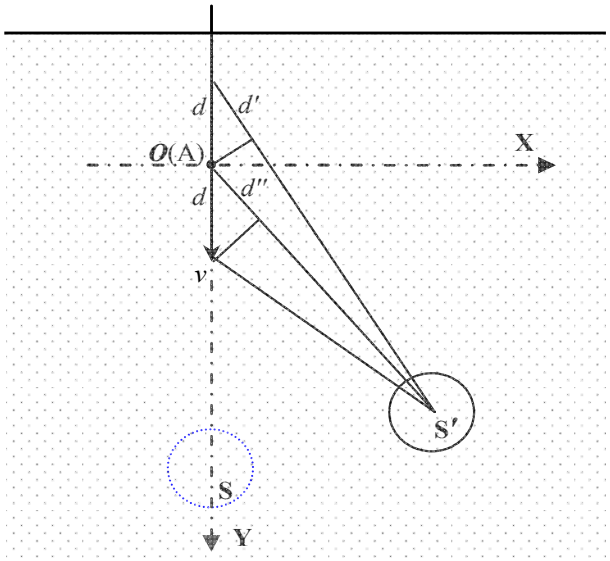

Figure.2. Illustration of localizing light source with a single insertion, which is not penetrating the center of light source, using an equidistant method. S′ is the center of light source, and *v* is the direction of insertion.

In practice, the probing orientation is always not directly to the center of light source, as shown in figure.2. *S′* and *S* are the actual light source and the calculated one using (6). *d′* (*d″*) and *d* are actual intervals of measuring points and that on the insertion direction, and $d' \neq d'' \neq d$. If the orientation of the light source is unknown, there will be many possible solutions that satisfying (6) when only knowing the ratio of relative diffusion intensities. Namely

$$r_2^2 = x^2 + y^2 = \frac{Hd^2}{(1-H)}, \tag{7}$$

where r_2 is the distance from the middle of the three measuring points *O*(A) to the center of light source, *x* and *y* are coordination of light source in Cartesian axis, *H* is a constant, which equals to $\Phi(r_1)\ \Phi(r_3)/\ \Phi(r_2)^2$. The possible solutions, namely the planar location of light source, are belonged to a track of a circle, whose center is *O*(A) and radius is $[H*d^2/(H-1)]^{1/2}$. If in the 3D space, the track of possible solutions is belonged to a sphere with a radius

$$r = \left(x^2 + y^2 + z^2\right)^{1/2} = \left(\frac{Hd^2}{1-H}\right)^{1/2}. \tag{8}$$

C. Localizing in 3D

Theoretically, we can get planar location of the light source using two insertions, namely, using two equations as (7). And we can also extend to get 3D location of the light source using three insertions, which are not lie in the same plane. If we have three insertions and each insertion have three detecting positions with an interval *d*, then

$$\begin{cases} \dfrac{\phi(r_1)\phi(r_3)}{\phi(r_2)^2} = \dfrac{x^2+y^2+z^2}{x^2+y^2+z^2-d^2} \\ \dfrac{\phi'(r_1)\phi'(r_3)}{\phi'(r_2)^2} = \dfrac{x'^2+y'^2+z'^2}{x'^2+y'^2+z'^2-d^2} \\ \dfrac{\phi''(r_1)\phi''(r_3)}{\phi''(r_2)^2} = \dfrac{x''^2+y''^2+z''^2}{x''^2+y''^2+z''^2-d^2} \end{cases}, \tag{9}$$

where $\begin{cases} x' = x+i \\ y' = y+j \\ z' = z+k \end{cases}$ and $\begin{cases} x'' = x+l \\ y'' = y+m, \\ z'' = z+n \end{cases}$

and light intensities $\Phi(r_n)$ are measurable, *i*, *j*, *k*, *l*, *m*, *n* and *d* are all known. It is easy to calculate the 3D location of light source.

Alternatively, we may suggest the insertion direction *v* is along Y axis and $x^2+z^2=w^2$, then

$$\begin{cases} \dfrac{\phi(r_1)\phi(r_3)}{\phi(r_2)^2} = \dfrac{y^2+w^2}{y^2+w^2-d^2} \\ \dfrac{\phi'(r_1)\phi'(r_3)}{\phi'(r_2)^2} = \dfrac{(y+d')^2+w^2}{(y+d')^2+w^2-d^2} \end{cases} \tag{10}$$

where *d′* is the distance between two measuring points at time t_1 and t_2 along Y axis. So, we can get *y* and *w* since *d*, *d′* and light intensities are known. Then, we may suggest that each insertion can detect light source with two angles in view of [9], θ_1 and θ_2, $\theta_1-\theta_2 \neq k\pi$, and $k \in N$. If let $x=w\cos\alpha$, $z= w\sin\alpha$, a proper combination of θ_1 and θ_2 can single out α. That is, we can get the value of *r*, *y*, *w* and α, namely, we can have all the spatial parameters of the light source.

D. A design of probe

In order to detect the light source in a region of interest deep inside a subject, a fiberoptical probe can be used to detect the light source directly in the subject along one or multiple insertion paths [9]. In this work, we designed a structure of probe that had an equilateral triangle-cone structure, where each facet along the insertion had at least three detectors with same interval as figure.3. With this design every two sets of data can be used to localize the light source independently, which is likely to detect the light in all directions without changing its detecting direction to fit the direction of light source. Moreover, on insertion process of the probe, the location of light source can be updated in real time and localizing accuracy can be improved.

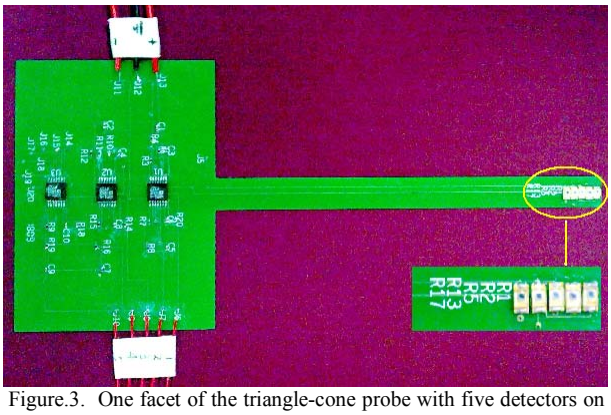

Figure.3. One facet of the triangle-cone probe with five detectors on its head.

IV. CONCLUSION

In this paper, we have put forward a minimally invasive method and an equidistant measurement to localize bioluminescent source in tissue. The minimally invasive method is very likely to permit a detection of the light source deep inside the tissue and avoid some calculating difficulty by penetrating through the multiple-layer tissue to one certain layer of interest. This equidistant measurement allows insertion penetrating the center of light source, as well as no exact optical parameters of tissues, which is favorable to bio-tissues that the optical parameters is hard to be obtained. In case of single layer, the localizing is very simple, and in case of multi-layer tissue, the location of light source will also be easily made out by assuming that the light source and detecting positions are in the same layer and a certain layer has similar optical parameters. At last, we proposed a feasible design of this probe, which enables dynamic localization of deep light source with a high spatial resolution and a free inserting angle.

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