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Registered laser speckle imaging analysis of cerebral tumor

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Abstract

Laser speckle imaging (LSI) has been widely used for in vivo detecting cerebral blood flow (CBF) under various physiological and pathological conditions. So far, nearly all literature on in vivo LSI does not consider the influence of disturbances due to respiration and/or heart beating of animals. In this paper, a registered laser speckle contrast analysis (rLASCA) method has been proposed which first registers raw speckle images with a 3×3 convolution kernel, normalized correlation metric and cubic B-spline interpolator, and then constructs the contrast image for CBF. rLASCA not only significantly improves the distinguish ability of small vessels, but also efficiently suppresses the noises induced by respiration and/or heart beating. In an application of imaging the angiogenesis of rat's brain tumor, rLASCA providing a much higher resolution for new small vessels.

IndexTerms—Cubic B-spline interpolation, laser speckle imaging (LSI), normalized correlation registration, registered laser speckle contrast analysis (rLASCA

1. INTRODUCTION

As a 2-D and noninvasive optical imaging technique, laser speckle imaging (LSI) has been widely used to study rat's cerebral blood flow (CBF) under a variety of physiological and pathological conditions, focal cerebral ischemia , hypotension , peripheral electrical stimulation , hypothermia , and brain tumor . When the tissue contains scattering moving particles, blood cells, sequentially recorded raw speckle images { $I_i(x, y)$}(i = 1, . . . , N) are analyzed by laser speckle contrast analysis (LASCA) to obtain both CBF and vessel structure information.

According to the theory of LASCA, the contrast value K2 , defined as the square of ratio of standard deviation σ to mean intensity _I_, is inversely proportional to velocity v K2 can be estimated in either spatial (K2)temporal (K2) formalism. For each frame of the acquired speckle images, K2 s for each pixel is calculated based on the intensities in a small window (typically 7×7), and therefore loses the spatial resolution.Similarly,K2 t at each pixel is estimated using the intensities of the pixel in continuously recorded raw speckle images.

$$K^2=(-)^2\propto 1/ \quad \text{——————} \quad (1)$$

In practice, 50 or more frames are used for statistical efficiency. As a result, K2 t retains the spatial resolution but temporal resolution is compromised. Like other optical imaging techniques, LSI is also susceptible to kinds of mechanical vibrations within the workspace. Such mechanical vibrations can be minimized by using vibration isolated optical platform and other precautions. In rodent in vivo experiments, the animals are always anesthetized and constrained in a stereotaxic frame to suppress movements.

However, there are still some inevitable disturbances in raw speckle images due to respiration and/or heart beating of the animals.

Such global disturbances could lead to the following problems in LASCA:

- The loss of spatial resolution, the output of LASCA is going to be blurred, and thus it is more difficult to distinguish small vessels from tissue.
- Inaccurate estimation of contrast values, disturbances change the statistic property of the speckles and lead to inaccurate estimation of CBF by LASCA.

In order to overcome these problems, propose to register the raw speckle images before LASCA, or called registered LASCA (rLASCA) here after. Since the raw speckle images are usually too noisy to find a stable pattern for registration, develop a novel automatic registration technique, using a 3×3 convolution kernel, a normalized correlation metric and a cubic B-spline interpolator, to register raw speckle images accurately. RLASCA is shown to enhance the small vessels and alleviate noises in both tissue area and vessels. As an application, studied the angiogenesis in rat's brain tumor by LSI, and showed how rLASCA

improves the resolution of cortical vascular structure of the angiogenesis.

2. METHODS

rLASCA involves two steps,

1) registering raw speckle images { I_i (x, y)}(i = 1, . . . , N) .

2) calculating LASCA based on the registered raw speckle images { I_i (x, y)}(i = 1, . .N).

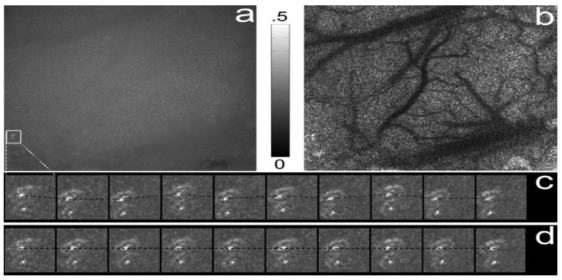

Figure.1 Typical raw speckle image

A. Registering raw speckle images by modified registration technique:

Traditional registration techniques are incapable of processing raw speckle images {I_i(x, y)}(i = 1, . . . , N), because the random speckles indicate no stable pattern, which could be used for registration [see Fig. 1.1]. Occasionally, there are some isolated pixels overexposed due to strong reflection [white boxed area in Fig. 1.1], in which case, the continuously acquired speckle images can be registered based on these overexposed pixels. However, in practice, the existence of such overexposed area is neither guaranteed nor desired.

In this paper, propose a novel registration technique to register the raw speckle images. First, each raw speckle image I_i(x, y)(i = 1, . . . , N) is preprocessed by a 3×3 convolution kernel as described in the following to reveal vessel structure pattern. Then a rigid translation parameter (Δx_i ,Δy_i) is estimated for each preprocessed image S_i(x, y)(i = 1, . . . , N) by a normalized correlation metric. Finally, the raw speckle images { I_i (x, y)}(i = 1, . . . , N) are registered (resampled) by a cubic B-spline interpolator based on their rigid translation parameters (Δx_i ,Δy_i) to obtain the registered rawspeckle images {$\hat{I}_i$(x, y)}(i = 1, . . . , N).

1)Preprocessing with 3×3 convolution kernel:

A 3×3 convolution kernel is implemented to preprocess each raw speckle image to obtain the spatial standard deviation at each pixel, which is related to vessel structure information .

$$\text{Kernel} = 1/9 \begin{matrix} 1 & 1 & 1 \\ 1 & 1 & 1 \\ 1 & 1 & 1 \end{matrix} \qquad (2)$$

$$= (\quad \otimes \quad) - (\quad \otimes \quad)^2 \qquad (3)$$

Here for a given matrix A with pixel index (x, y), A2 represents A2 (x, y) = (A(x, y))2.Based on , the size of image S_i is equal to that of I_i .Since the convolution kernel size is 3×3, only the information at the four borders (the first row, the first column, the last row,and the last column) of Si is lost. Therefore, the average loss of spatial resolution in this preprocessing step is very small and always less than one pixel. The preprocessed images, i.e., S_i(x, y)(i = 1, . . . , N), reveal the same vessel structure pattern which, therefore, can be used for registering { I_i (x, y)}(i = 1, . . . , N) with aminor loss of spatial resolution.

2) Obtaining rigid translation parameters based on the normalized correlation metric:

In this step, each image S_i(i =2, . . . , N) is to be registered to the first image S1 in accordance with a proper rigid translation. The optimized rigid translation parameter (Δx_i,Δy_i) for each S_i(i = 2, . . . , N) is determined by maximizing the normalized correlation metric using a gradient descent optimization procedure with a variable step length

Metric = x,y S1 (x, y)S_i(x – Δx_i, y – Δy_i)-(4)

Among various registration metrics, have chosen the normalized correlation metric for its advantages of low computational cost and well-defined maxima (sharp peaks) in the cost function. All rigid translation parameters (Δx_i ,Δy_i) are used to register (resample) the corresponding raw speckle images { I_i (x, y)}(i = 1, . . . , N) in the next step.

$$\text{Metric} = \frac{\sum_{x,y} S_1(x,y) S_i(x-\Delta x_i, y-\Delta y_i)}{\sqrt{\sum_{x,y} S_1^2(x,y) \sum_{x,y} S_i^2(x-\Delta x_i, y-\Delta y_i)}}. \qquad (4)$$

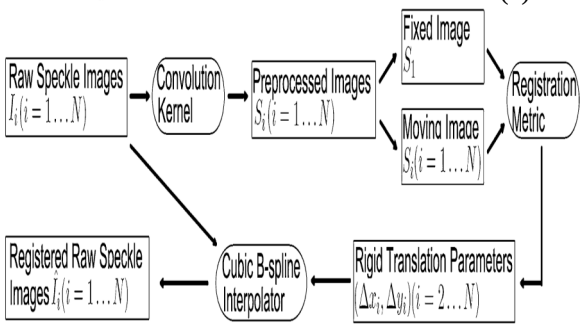

Figure. 2. block diagram

3) Resampling raw speckle images using cubic b-spline interpolator:

The displacement due to disturbances need not conform to integral pixels, so the rigid translation parameters(Δx_i ,Δy_i) always have subpixel precision. Therefore, a resampling interpolation is needed to register the raw speckle images { I_i (x, y)}(i = 1, . . . , N).In this study, the cubic B-spline interpolator is used to calculate the intensity of nongrid position in a two dimensional piecewise polynomial way based on the cubic B-spline function which is smooth, continuous and bounded . Although the computational cost of B-spline interpolation is not very low, it is used in this study because cubic B-spline interpolation utilizes the non-integer parameters which is preferable over the nearest neighbor interpolation. In addition, cubic B-spline interpolation prevents the effect of degeneration in linear interpolation

$$\beta^3(d) = \begin{cases} 2/3 - |d|^2(2 - |d|)/2, & 0 \le |d| < 1 \\ (2 - |d|^3)/6, & 1 \le |d| < 2 \\ 0, & 2 \le |d| \end{cases} \quad (5)$$

After resampling, the registered raw speckle images I_i (i =1, . . . , N) are obtained. The above registration procedures are summarized .After registration as described earlier, the registered raw speckle images I_i (i = 1, . . . , N) are then analyzed by conventional temporal LASCA to obtain maps of blood vessels and flow. The whole procedure as described earlier is then called registered LASCA (rLASCA).

3. EXPERIMENT AND DATA ANALYSIS

A. Animal preparation:

The experimental protocol used in this study has been approved by the Animal Care and Use Committee of Johns Hopkins Medical Institutions. The female Sprague-Dawley (SD) rat(∼ 325 g) was anesthetized with intraperitoneal (IP) injection of a mixture of 90 mg/kg of ketamine and 10 mg/kg of xylazine. The rat was constrained in a stereotaxic frame (model 975, Kopf Instruments, Tujunga, CA). A midline incision was made over the scalp and the tissues over the bones were cleaned with a blade. A 6×6 mm2 cranial window overlying the right somatosensory cortex (centered at 3.5 mm lateral and 2.5 mm posterior to the bregma) was thinned with a high speed dental drill (Fine Science Tools, Inc., North Vancouver, Canada) with 1.4 mm steel burr until half transparent. Saline was used to cool down the scalp during the surgery. Rectal temperature was maintained at 37 ◦C throughout the experiment using a Gaymar Heat Therapy System (model TP-500 T/Pump, Gaymar Industries,Inc., New York, NY).

In the brain tumor angiogenesis experiment, the female Fisher 344 rats (∼ 170 g) were similarly prepared for imaging. In addition, a 6×6 mm2 cranial window was thinned on the contralateral left cortex (centered at 3.5 mm lateral and 3 mm posterior to the bregma). After recording the baseline raw speckle images on day 0, a hole was drilled carefully at the center of the cranial window with a 1 mm steel burr until the dura was reached. Then 100 000 cells of 9 L glioma were injected into the cortex using a 26 gauge Hamilton syringe at a depth of 2mmbelow the surface of the cerebral cortex to induce brain tumor. The skin was closed with surgical clips and the rat was housed in the animal facility, as the tumor was allowed to grow. A 12-bit, cooled CCD camera (Sensicam SVGA, Cooke, MI)with a 60 mm macro (1:1 maximum reproduction ratio) f/2.8 lens was focused on the blood vessels in the cranial window.

Exposure time of the CCD was set to 5 ms. Frame rate was 11 ft/s. The imaging field was illuminated with a 632 nm He–Ne Laser beam source (1508P-O, Uniphase, CA). The laser beam
was reshaped by a lens to illuminate the entire thinned skull window. The field of view recorded by the CCD camera was 704×704 pixels corresponding to an imaging area of 4.7 × 4.7 mm2 on the rat's brain. . The skin was closed with surgical clips and the rat was housed in the animal facility, as the tumor was allowed to grow. A 12-bit, cooled CCD camera (Sensicam SVGA, Cooke, MI)with a 60 mm macro (1:1 maximum reproduction ratio) f/2.8 lens was focused on the blood vessels in the cranial window.

B.Data recording and processing:

In the SD rat experiment, a white light reflectance image (40-ms exposure time) was obtained first for reference. Following that, a stack of 80 raw speckle images were acquired sequentially.In the brain tumor experiment, the baseline recordings(a) Contrast image based on original unregistered raw speckle images. (b) Contrast image of rLASCA. The white arrows in (a) and (b) indicate the same small vessel which can be seen more clearly in (b) than in (a). (c) and (d) Zoomed out images of the white box area in (a) and (b), respectively. The black arrows in (c) and (d) show the suppression of blur effect. (e) White light image of the corresponding area. were performed on the day of tumor inoculation (day 0). After that, on day 10, the Fisher rat was imaged again to investigate the angiogenesis. All data were analyzed by both traditional LASCA and rLASCA.

4. CONCLUSION

In this project, rLASCA has been proposed to eliminate the effect of disturbances due to respiration and heart beating during imaging the rat's CBF. Then implemented a modified registration technique

containing a 3×3 convolution kernel, normalized correlation metric and cubic B-spline interpolator to register the raw speckle images accurately.rLASCA improves the spatial resolution of contrast image and alleviates the noisy effect of disturbances.In the application for investigating angiogenesis of rat's brain tumor, rLASCA shows the small vessels with a higher resolution.

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