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研究課題名（和文）Development of a hybrid tomosynthesis and acoustic imaging modality for early detection of breast cancer

研究課題名（英文）Development of a hybrid tomosynthesis and acoustic imaging modality for early detection of breast cancer

研究代表者
彭　浩（PENG, HAO）

北海道大学・国際連携研究教育局・招へい教員

研究者番号：７０７９０１９５

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研究成果の概要（和文）：乳がん早期検出のため乳房トモシンセシスとX線音響乳房画像（XABI）を融合した新たな画像撮像法の開発を目的とする。本手法は3次元乳房画像を取得できるだけでなく、微小石灰及び病変のコントラスト分解能が高い画像が得られる。トモシンセシスで照射されるX線は同時に高減弱体（微小石灰または造影剤）からの音波を発生させる。従来法と同等の特異度を示しながら微小病変を正確に検出できると期待される。本研究では特に2つの目的に着目する。1）性能評価を行うため包括的実験体系を構築し、最適なシステム設計を検討する。2）マンモグラフィとXABIを同時に撮像できる試作機を開発し、ファントムを使用して実現可能性を実証する。

研究成果の学術的意義や社会的意義
This study introduced, for the very first time, the principle and implementation of x-ray induced acoustic imaging technique for breast cancer. The novel imaging modality work synergistically with breast tomosynthesis to produce images that would otherwise be impossible to attain.

研究成果の概要（英文）：This proposal aims to develop a novel hybrid imaging strategy of breast tomosynthesis and x-ray acoustic breast imaging (XABI) for early detection of breast cancer. It will not only provide additional spatial information in three dimensions but also enhance contrast recovery of micro-calcifications/lesions. With the proposed platform, x-ray for tomosynthesis will stimulate simultaneously the production of acoustic signals from x-ray absorbing targets (either micro-calcification itself or injected contrast agents). We expect that it has the potential to detect small lesion while demonstrating comparable specificity to other methods currently used in breast molecular imaging. The proposal focuses on two specific aims: 1) Develop a comprehensive framework to characterize the performances of a XABI system and optimize the system design ; 2) Develop a XABI prototype to realize simultaneous mammography and x-ray induced acoustic imaging and demonstrate the feasibility using phantom studies.

研究分野：Molecular Imaging

キーワード：Breast Imaging

1. Background

Mammography scans are performed about 36 million times each year and are considered as the standard-of-care for detection of breast cancer. While the technique has a high intrinsic spatial resolution, it struggles with achieving contrast resolution sufficient to differentiate small structures from background tissue[1-2]. Breast density and tissue heterogeneity further add to the complexity of interpretation of imaging data[3-5]. For instance, the positive predictive value of an abnormal mammogram is strikingly low ranging from 1.2-15.0%, and the positive predictive value for biopsies generated from an abnormal mammogram stays in the range of 3.4-48.7%[6-9]. An imaging platform that is capable of providing not only high-resolution anatomical information but also high-contrast molecular features is needed. This proposal purports to address the above challenge from two aspects. First, breast tomosynthesis is leveraged to to help mitigate tissue overlapping and enhance contrast of micro-classification.[10-12] Second, we aim to integrate x-ray acoustic breast imaging (XABI) with a breast tomosynthesis for simultaneous imaging. In this system, x-ray stimulates simultaneously the production of acoustic signals "for free", which are subsequently collected using a dual-panel acoustic detection system to provide complementary 3D information of tissue characteristics together with high-resolution morphological information. Broadly speaking, x-ray acoustic imaging is an extension of photoacoustic imaging (PAI)[13-15], which relies on the photoacoustic effect which describes conversion between light and acoustic waves. However, a well-known drawback of traditional PAI is its shallow imaging depth due to the limited penetration of optical and/or infrared photons. On the opposite, x-ray acoustic imaging enables us to harness the useful features of PAI without concerning the depth limitation. For example, the penetration depth is about 60 mm for 100 keV energy x-rays and 140 mm for acoustic wave of 2 MHz frequency. As a result, our proposed technique extends breast tomosynthesis beyond morphologic imaging with structural/functional/biological imaging capacity, providing a critically needed solution for breast cancer research and management.

2. Purpose

This proposal aims to develop a novel hybrid imaging strategy of breast tomosynthesis and x-ray acoustic breast imaging (XABI) for early detection of breast cancer. It will not only provide additional spatial information in three dimensions but also enhance contrast recovery of micro-calcifications/lesions. Our hypothesis is that this imaging technique will overcome the limitations of traditional imaging methods and substantially improve the sensitivity and specificity in breast cancer detection. With the proposed platform, x-ray for tomosynthesis will stimulate simultaneously the production of acoustic signals from x-ray absorbing targets (either micro-calcification itself or injected contrast agents). We expect that it has the potential to detect a cancerous lump of ~300 micrometric dimensions while demonstrating comparable specificity to other methods currently used in breast molecular imaging, such as Positron Emission Tomography (PET). The proposal focuses on two specific aims: 1) Develop a comprehensive framework to characterize the performances of a XABI system and optimize the system design with respect to image quality, detection limit and spatial resolution; 2) Develop a XABI prototype to realize simultaneous mammography and x-ray induced acoustic imaging and demonstrate the feasibility using both phantom and in-vivo mice studies.

3. Methods

3.1 System design: optimize the overall system design, including the collimation of x-ray photons and a dual-panel system comprising two PZT (lead zirconate titanate) detector arrays.

3.2 Simulation of x-ray interaction and acoustic wave propagation: to perform simulations under a variety of situations, using Monte-Carlo simulation tools. Find the optimal trade-off between radiation dose, output, filtration, and mammography contrast. On the acoustic side, we will simulate the detection of acoustic signals by the PZT ultrasound transducer in order to boost detection efficiency.

3.3 Signal analysis framework: develop a noise-equivalent-pressure (NEP) framework dedicated for breast cancer imaging (i.e., micro-calcification, gold nanoparticle for contract enhancement), to quantitatively study/predict the minimal required dose under different conditions. Our goal is to differentiate between subgroups of different contrasts, for micro-calcification sites with and without fiducial markers. The minimal required dose and detection limit with and without fiducial markers will be quantified.

3.4 Image reconstruction: use two commercial PZT array detectors and develop an accurate model that accounts for non-uniform x-ray attenuation. The signal-limited nature of the measurements will be modeled using a statistical reconstruction approach. Iterative expectation maximization (EM) method will be applied to solve for the elemental concentration with the highest likelihood of providing the measured signals.

3.5 System integration: we will assemble the components into a clinical breast tomosynthesis system. The necessary mechanical support for fixture will be designed and machined. Data acquisition, tube operation,

interlocks and jaw motion will be synchronously controlled by a National Instrument control station. The x-ray tomosynthesis measurements will be processed in the same manner as in clinical settings.

3.6 Phantom imaging and in-vivo imaging: validate the quantitative results with phantom imaging and mice imaging at Stanford University (see the proposal for more details).

4. Results

4.1 Simulation framework

The tasks 3.1, 3.2 and 3.3 are successfully accomplished.

A comprehensive model about X-ray induced acoustic model was developed during the implementation of this project, which will be of great use for future research and can be applied to other formats of radiation as well such as proton therapy or carbon therapy. As shown in Fig. 1, our model consists of the following components: X-ray beam transfers its kinetic energy to the format of heat energy after Coulombic interactions within the media it traverses. The heat energy consequently causes local pressure increase via thermoelastic expansion [A1-A2]. Thermal diffusion can be neglected as the rate of heat deposition induced by the radiation pulse is extremely fast (10^{-6} to10^{-12} s). With respect to the temporal profile of a pulse, a delta-function proton pulse is considered to produce acoustic pressurization and propagation, while the effect of finite pulse duration can also be considered. The GATE tool is used to calculate dose deposition within the tissues in three dimensions.

The pressure distribution, due to thermoelastic expansion can be related to a number of physical parameters, such as ρ [unit: kg/m^3] the mass density, $\Gamma = \alpha_V c^2 / C_p$ is the dimensionless Grüneisen coefficient dependent on the volumetric thermal expansion coefficient, α_V [unit: K^{-1}], the speed of sound, c [unit: m/s], and the isobaric specific heat capacity, C_p [unit: J/(K kg)]. Due to tissue heterogeneity, these physical parameters (ρ, α_V, c and C_p) for pressure distribution calculation at each pixel need to be converted through multiple calibration curves we developed based upon HU information (Fig. 2).

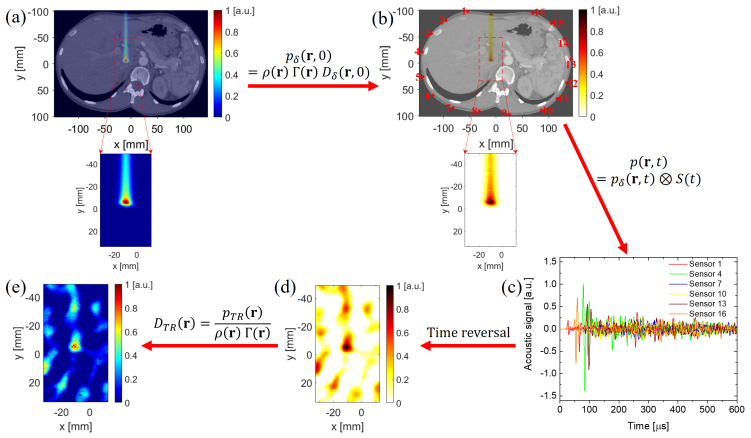

Fig. 1. Schematic diagram of CT-based image reconstruction for pressure/dose distribution using the time-reversal method.

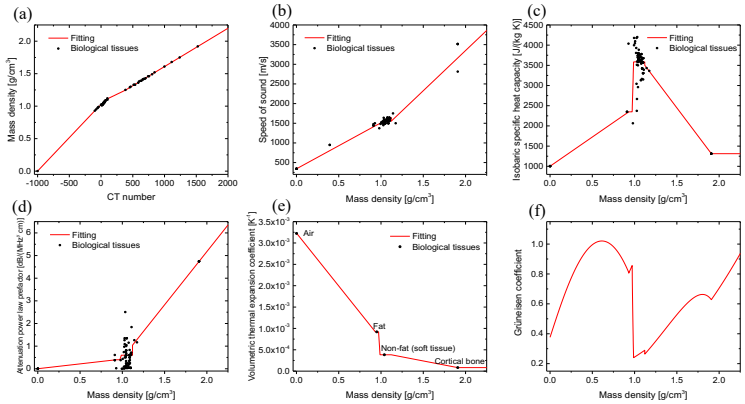

Fig. 2. (a) The calibration curves for the conversion between CT number and mass density. The calibration curves for the conversion between mass density and (b) speed of sound, (c) isobaric specific heat capacity, (d) attenuation power law prefactor, (e) volumetric thermal expansion coefficient and (f) Grüneisen coefficient.

We successfully implemented the acoustic pressure detection, using the k-Wave MATLAB toolbox. It utilizes a k-space pseudospectral method to help improve computation efficiency, compared to finite difference and finite element methods. To avoid committing "inverse crime", the acoustic propagation was conducted with a different grid and a different pitch from, from the grid and pitch settings in the subsequent image reconstruction. An absorbing boundary layer, defined as a perfectly matched layer (PML) in the k-wave toolbox, was added to enclose the computational domain for preventing waves leaving one side of the domain to reappear at the opposite side. To take finite pulse duration, also known as spill time, into account, the time-dependent pressure distribution was convolved with the temporal profile of proton pulse. Such a convolution provides the final pressure distribution to be detected and thus allows us to study noise- NEP, pulse width, dose, transducer center frequency and bandwidth, image SNR and contrast-to-noise ratio (CNR). In addition, the study regarding of how gold nanoparticles may enhance contrast and improve imaging performance has also been conducted [A3].

4.2 System development

The tasks 3.4 and 3.5 are successfully accomplished. The task 3.6 is only partially accomplished and needs additional efforts. The original plan is to apply an iterative expectation maximization (EM) method for image reconstruction, modeling the linear shift-varying response of the system. The system matrix will include three separable components, namely a diagonal depth-dependent attenuation matrix, a geometric matrix representing the collimation process, and a depth-dependent blurring kernel modeling the resolution loss due to the finite detector pixel size. Due to the complicated nature of the signal prorogation in a 3D mode, the initial method in the proposal was too challenging to be realized. Therefore, we worked out the following alternative: time reversal reconstruction method [A1, A2]. All the recorded pressure time series were organized in a time-reversed order and re-emitted at the respective sensing positions. The reversed pressure signals were then focused at the original source at t=0. The reconstructed pressure distribution in the whole region can then be obtained, with a positivity condition applied (i.e. setting the negative reconstructed pressure to be zero). The TR-based reconstructed dose distribution can then be derived from the reconstructed pressure distribution. The TR-based reconstructed results are found to be further improved by using an iterative procedure. The basic idea behind it is to use first reconstructed pressure distribution as a new emitting source for propagation simulation, and the residual between the original and the new recorded pressure time series signals is assigned as input for another round of TR reconstruction. This loop can be repeated until there is no noticeable improvement in the reconstructed result. The dependency of the reconstruction results on other parameters such as the number of sensors, pulse duration and noise, are also investigated. Moreover, we have participated two different research projects involving CT image reconstruction, one cone beam CT and the other one dual energy CT [A4-A6].

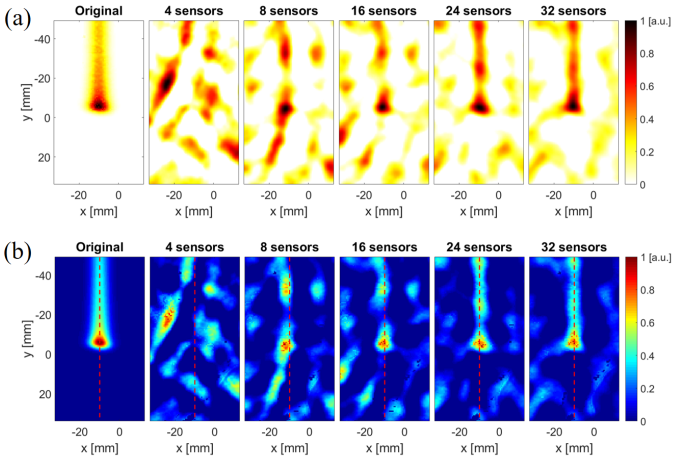

Fig. 3. (a) The normalized original pressure distribution and reconstructed pressure distributions using 4, 8, 16, 24 and 32 sensors, respectively, and (b) The normalized original dose distribution and reconstructed dose distributions.

We successfully assembled two commercial PZT array detectors (from iThera Medical) and developed the required experimental platform for the next of our research. The necessary mechanical support for fixture has been designed and machined (Fig. 4). Data acquisition and tube operation (the XRS-3 X-Ray Kit for pulsed x-ray generation) was realized by a National Instrument control station. The station communicates with the iThera system to manage data transfers and provide an interface for adjusting operation parameters (exposure time, tube voltage/current, pulse width, duty cycle, etc.) How the system is to be integrated with a breast tomosynthesis is also currently being considered (Fig. 4).

Fig. 4. (left) The experimental platform and acoustic sensors in a water tank. (right) Possible candidates of mechanical design and fixture support, similar to the concept of breast ultrasound imaging (GE Invenia ABUS) and a typical MRI breast coil. This task is in collaboration with colleagues at Wuhan University (China) and Stanford University (USA).

The preliminary phantom experiments were conducted as planned, though we are still in the process of trying to achieve positive results and compare them with the simulation results. We encountered two major challenges: short of manpower and the weak amplitude of acoustic signals. The hardware development and phantom imaging tasks turned out to be more challenging than what we initially expected. The team struggled to address some engineering challenges, such as the implementation of low-noise signal amplification and synchronization of 64 channels. Various hydrophones of different gain, bandwidth and sensitivity have also been tested. For example, the simulation indicates that given a distance of 35 mm, a delivery of 2 Gy would yield a detector SNR of 15. However, this is much higher than the preliminary experimental results we obtained. This is a big hurdle we are facing right now and will continue to tackle the challenge.

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５．主な発表論文等

〔雑誌論文〕　計5件（うち査読付論文　5件／うち国際共著　5件／うちオープンアクセス　0件）

１．著者名 Yu Yajun、Li Zhongxing、Zhang Dong、Xing Lei、Peng Hao	４．巻 46(8)
２．論文標題 Simulation studies of time reversal‐based protoacoustic reconstruction for range and dose verification in proton therapy	５．発行年 2019年
３．雑誌名 Medical Physics	６．最初と最後の頁 3649-3662
掲載論文のDOI（デジタルオブジェクト識別子） 10.1002/mp.13661	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 該当する

１．著者名 Kwon Jihun、Sutherland Kenneth、Makarova Anastasia、Matsuura Taeko、Hashimoto Takayuki、Peng Hao、Toshito Toshiyuki、Umegaki Kikuo、Shirato Hiroki、Shimizu Shinichi	４．巻 429
２．論文標題 Investigation of energy absorption by clustered gold nanoparticles	５．発行年 2018年
３．雑誌名 Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms	６．最初と最後の頁 34～41
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.nimb.2018.05.033	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 該当する

１．著者名 Zhao W, Vernekohl D, Han F, Han B, Peng H, Yong Yang, Min JK, and Xing L	４．巻 45
２．論文標題 A unified material decomposition framework for quantitative dual- and triple-energy CT imaging	５．発行年 2018年
３．雑誌名 Medical Physics	６．最初と最後の頁 2964-2977
掲載論文のDOI（デジタルオブジェクト識別子） 10.1002/mp.12933|	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 該当する

１．著者名 Zhao Wei、Li Dengwang、Niu Kai、Qin Wenjian、Peng Hao、Niu Tianye	４．巻 5
２．論文標題 Robust Beam Hardening Artifacts Reduction for Computed Tomography Using Spectrum Modeling	５．発行年 2019年
３．雑誌名 IEEE Transactions on Computational Imaging	６．最初と最後の頁 333～342
掲載論文のDOI（デジタルオブジェクト識別子） 10.1109/TCI.2018.2884479	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 該当する

1．著者名 Nomura Yusuke、Xu Qiong、Peng Hao、Takao Seishin、Shimizu Shinichi、Xing Lei、Shirato Hiroki	4．巻 47
2．論文標題 Modified fast adaptive scatter kernel superposition (mfASKS) correction and its dosimetric impact on CBCT‐based proton therapy dose calculation	5．発行年 2019年
3．雑誌名 Medical Physics	6．最初と最後の頁 190～200
掲載論文のDOI（デジタルオブジェクト識別子） 10.1002/mp.13878	査読の有無 有
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2．発表標題 Feasibility of X-Ray-Induced Acoustic Computed Tomography for Breast Imaging by Monte Carlo Simulation
3．学会等名 Annual Meeting of the American Association of Physicists in Medicine 2019（国際学会）
4．発表年 2019年

1．発表者名 Y Yu , D Zhang , L Xing, H Peng
2．発表標題 Time Reversal-Based Protoacoustic Reconstruction for Range and Dose Verification in Proton Therapy
3．学会等名 Annual Meeting of the American Association of Physicists in Medicine 2018（招待講演）（国際学会）
4．発表年 2018年

〔図書〕　計0件

〔産業財産権〕

〔その他〕

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6．研究組織

	氏名 （ローマ字氏名） （研究者番号）	所属研究機関・部局・職 （機関番号）	備考