

# Multispectral Photoacoustic Imaging for Breast Cancer Detection and Hysterectomy Guidance

Muyinatu A. Lediju Bell<sup>a,b,c,d</sup>

<sup>a</sup>Department of Electrical & Computer Engineering, Johns Hopkins University, Baltimore, MD

<sup>b</sup>Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD

<sup>c</sup>Department of Computer Science, Johns Hopkins University, Baltimore, MD

<sup>d</sup>Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD

## ABSTRACT

This invited contribution discusses recent applications in breast imaging and hysterectomy guidance from the Photoacoustic & Ultrasonic Systems Engineering (PULSE) Lab at Johns Hopkins University. Challenges with breast imaging and hysterectomy guidance are discussed. Solutions to the discussed challenges that incorporate multispectral photoacoustic imaging are summarized. In particular, diagnostic imaging innovations in coherence-based beamforming ultimately enabled molecular imaging innovations for surgical guidance, relying on training data, principal component analyses, and acoustic-based approaches to spectral unmixing. These new innovations are promising for breast imaging and hysterectomy procedures.

## 1. INTRODUCTION

Ultrasound and photoacoustic imaging are two complementary techniques that are promising for multiple applications in diagnostic imaging and surgery.<sup>1-4</sup> Two particular women's health applications include breast cancer detection and surgeries to remove the uterus (known as hysterectomies). Breast cancer is typically diagnosed after a biopsy procedure, which employs ultrasound image guidance.<sup>5</sup> There are multiple treatment options following a diagnosis, including surgery.<sup>6</sup> Similarly, endometrial, cervical, or uterine cancers can be treated with surgery to remove the uterus, which is known as hysterectomy.<sup>7-9</sup>

During the diagnostic, surgical, and interventional procedures noted above, several common challenges arise. With respect to breast cancer detection, breast ultrasound is often used as a supplement to mammography, particularly in women with dense breast tissue.<sup>5,10</sup> When breast tissue is dense, the surrounding tissue can often obscure diagnostic features. In addition, dense breast tissue can cause distortions in the propagation of acoustic waves. These distortions include off-axis scattering, reverberation, and phase aberrations, resulting in artifacts such as acoustic clutter, which appears as a diffuse haze overlaying masses of clinical interest.<sup>11</sup>

One method to reduce acoustic clutter is coherence-based beamforming.<sup>12</sup> Previous work has demonstrated image quality improvements in a variety of clinical areas using coherence-based beamforming. Building on this foundation, coherence-based ultrasound breast imaging can be used to characterize the content of breast masses as fluid or solid.<sup>13-18</sup> Once a mass is identified as solid, an outstanding imaging challenge is to non-invasively determine whether the solid mass is benign or malignant.

With respect to hysterectomy (i.e., the surgical removal of the uterus), transection of the uterine artery is required, while the nearby ureter needs to remain intact to preserve urinary function.<sup>19</sup> Due to the proximity of the ureter and uterine arteries, gynecologic surgeries such as hysterectomy account for 75% of all intraoperative injuries to the ureters.<sup>20</sup> These injuries can cause increased hospital re-admissions, sepsis, or even patient death.<sup>21</sup> For these reasons, it is important for surgeons to both visualize and differentiate between the ureter and uterine artery during hysterectomy procedures.

The spatial coherence of received photoacoustic signals from both the ureter and uterine artery, as well as the surgical tool, can be used to assist with associated signal identification. Once identified, it becomes a technical challenge to choose the best approach to correctly associate the identified signals with their originating structures. The outcome can then be used for higher-order tasks, such as measuring the distance from the tool to the ureter and converting this distance into an auditory signal that can alert surgeons to an impending risk of ureteral injury.<sup>22</sup>

## 2. MULTISPECTRAL PHOTOACOUSTIC IMAGING SOLUTIONS

Multispectral photoacoustic imaging is one solution to the challenges outlined above, as demonstrated in a few recent publications from the PULSE Lab. With respect to breast imaging, intraoperative multispectral photoacoustic pathology assessment presents a promising approach to guide biopsy resection. Recent work<sup>23,24</sup> developed and validated a novel photoacoustic technique to differentiate between healthy and cancerous tissues, with the ultimate goal of intraoperative deployment. After calculating photoacoustic image contrast as a function of wavelength, the photoacoustic spectrum was normalized and projected into a two-dimensional space using principal component analysis. Representative spectra were then identified to characterize healthy and cancerous tissues and correlated with spectra in a test set from tissue sections that were not included in the characterization process. The test healthy tissue region had 0.967 mean correlation with the representative healthy tissue spectrum and lower correlation (0.801) with the cancer tissue spectrum. The test cancer tissue region had 0.954 mean correlation with the cancer tissue spectrum and lower correlation (0.762) with the healthy tissue spectrum. Example results are shown in Fig. 1 (adapted from Zhang *et al.*<sup>23</sup>), relative to a photograph of a microscopy slide of the same tissue section and a H&E stain result from an adjacent section of the same tissue block. This label-free multispectral photoacoustic imaging approach has the potential to enable real-time tumor margin determination during surgery.

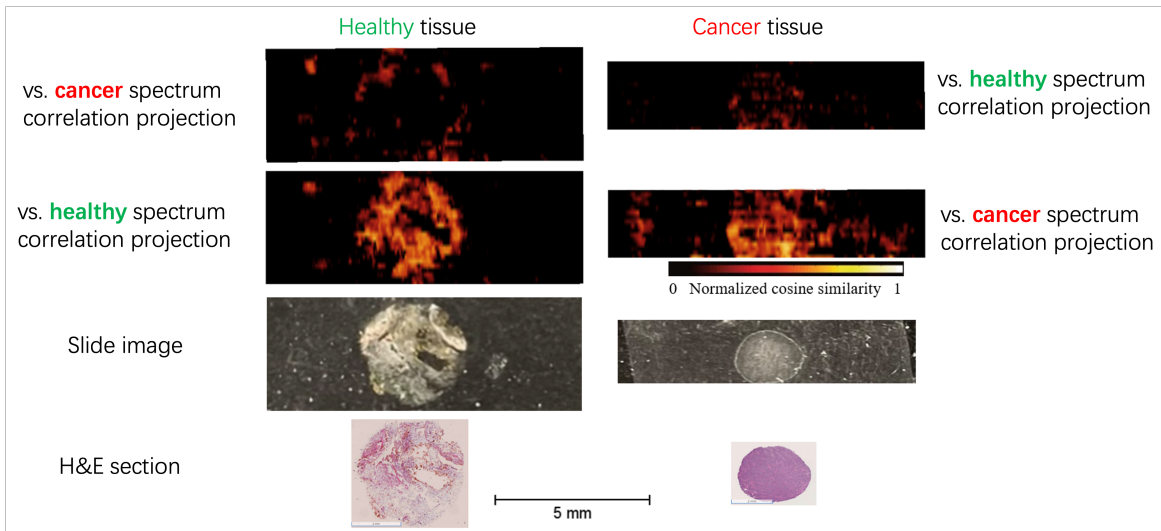


Figure 1. Maximum correlation projections and comparison with slide images and H&E stain images (adapted from Zhang *et al.*<sup>23</sup>)

To address the noted challenges with hysterectomy guidance using multispectral photoacoustic imaging, methylene blue (MB) is an exogenous contrast agent that has the potential to assist with visualization and penetration challenges in photoacoustic imaging, such as ureter visualization and distinction from the uterine artery to avoid accidental damage during surgery. An acoustic-based atlas method<sup>25</sup> was employed to estimate concentration levels from a mixture of MB and the hemoglobin (Hb) in human blood, after two laser wavelength emissions.<sup>26</sup> An algorithm to perform linear regression of the acoustic frequency response from an atlas composed of pure concentrations of each component. The overall mean absolute error (MAE), coefficient of determination (i.e.,  $R^2$ ), and Spearman's correlation coefficient (i.e.,  $\rho$ ) between the estimated results and ground-truth labels were 12.68%, 0.80, and 0.89, respectively, for the human Hb dataset. Results were additionally tested on an independent porcine Hb dataset, with example results shown in Fig. 2 (reproduced from Gonzalez and Bell<sup>26</sup>). The strong potential for minimal data acquisition times with only two wavelength emissions is highly advantageous toward real-time implementation in the operating room.

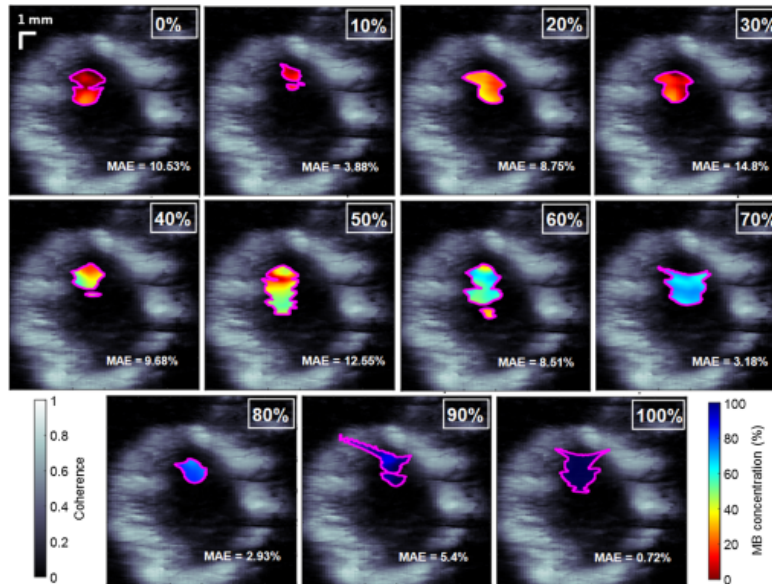


Figure 2. Examples of concentration maps of MB and porcine Hb generated by the dual-wavelength atlas method in a phantom experiment. The concentration maps (colored) are overlaid on ultrasound images generated with coherence-based beamforming (reproduced from Gonzalez and Bell<sup>26</sup>).

### 3. CONCLUSION

Multiple scales, from organ-level to molecular-level, can be effectively combined to tackle challenges in diagnostic imaging and surgical guidance. The diagnostic imaging innovations surrounding coherence-based beamforming ultimately enabled molecular imaging innovations for surgical guidance, relying on training data, principal component analyses, and acoustic-based approaches to spectral unmixing. These new innovations are promising for breast imaging and hysterectomy procedures.

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### REFERENCES

- [1] González, E. A. and Bell, M. A. L., “Photoacoustic imaging and characterization of bone in medicine: Overview, applications, and outlook,” *Annual Review of Biomedical Engineering* **25** (2023).
- [2] Wiacek, A. and Bell, M. A. L., “Photoacoustic-guided surgery from head to toe,” *Biomedical Optics Express* **12**(4), 2079–2117 (2021).
- [3] Bell, M. A. L., “Photoacoustic imaging for surgical guidance: principles, applications, and outlook,” *Journal of Applied Physics* **128**(6), 060904 (2020).
- [4] Steinberg, I., Huland, D. M., Vermesh, O., Frostig, H. E., Tummers, W. S., and Gambhir, S. S., “Photoacoustic clinical imaging,” *Photoacoustics* **14**, 77–98 (2019).
- [5] Guo, R., Lu, G., Qin, B., and Fei, B., “Ultrasound imaging technologies for breast cancer detection and management: a review,” *Ultrasound in Medicine & Biology* **44**(1), 37–70 (2018).
- [6] Waks, A. G. and Winer, E. P., “Breast cancer treatment: a review,” *JAMA* **321**(3), 288–300 (2019).
- [7] Koskas, M., Amant, F., Mirza, M. R., and Creutzberg, C. L., “Cancer of the corpus uteri: 2021 update,” *International Journal of Gynecology & Obstetrics* **155**, 45–60 (2021).
- [8] Bhatla, N., Aoki, D., Sharma, D. N., and Sankaranarayanan, R., “Cancer of the cervix uteri,” *International Journal of Gynecology & Obstetrics* **143**, 22–36 (2018).

- [9] Artioli, G., Wabersich, J., Ludwig, K., Gardiman, M. P., Borgato, L., and Garbin, F., “Rare uterine cancer: carcinosarcomas. review from histology to treatment,” *Critical Reviews in Oncology/Hematology* **94**(1), 98–104 (2015).
- [10] Jaglan, P., Dass, R., and Duhan, M., “Breast cancer detection techniques: issues and challenges,” *Journal of The Institution of Engineers (India): Series B* **100**(4), 379–386 (2019).
- [11] Lediju, M. A., Pihl, M. J., Dahl, J. J., and Trahey, G. E., “Quantitative assessment of the magnitude, impact and spatial extent of ultrasonic clutter,” *Ultrasonic Imaging* **30**(3), 151–168 (2008).
- [12] Lediju, M. A., Trahey, G. E., Byram, B. C., and Dahl, J. J., “Short-lag spatial coherence of backscattered echoes: Imaging characteristics,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control* **58**(7), 1377–1388 (2011).
- [13] Wiacek, A., Rindal, O. M. H., Falomo, E., Myers, K., Fabrega-Foster, K., Harvey, S., and Bell, M. A. L., “Robust short-lag spatial coherence imaging of breast ultrasound data: Initial clinical results,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control* **66**(3), 527–540 (2019).
- [14] Wiacek, A., Oluyemi, E., Myers, K., Mullen, L., and Bell, M. A. L., “Coherence-based beamforming increases the diagnostic certainty of distinguishing fluid from solid masses in breast ultrasound exams,” *Ultrasound in Medicine & Biology* **46**(6), 1380–1394 (2020).
- [15] Wiacek, A., Oluyemi, E., Myers, K., Ambinder, E., and Bell, M. A. L., “Coherence metrics for reader-independent differentiation of cystic from solid breast masses in ultrasound images,” *Ultrasound in medicine & biology* **49**(1), 256–268 (2023).
- [16] Sharma, A., Oluyemi, E., Myers, K., Ambinder, E., and Bell, M. A. L., “Spatial coherence approaches to distinguish suspicious mass contents in fundamental and harmonic breast ultrasound images,” *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control* **71**(1), 70–84 (2024).
- [17] Sharma, A., Gonzalez, E. A., Ambinder, E., Myers, K., Oluyemi, E., and Bell, M. A. L., “Real-time coherence imaging of suspicious breast masses recommended for aspiration or biopsy,” in [*Proceedings of the IEEE International Ultrasonics Symposium (IUS)*], 1–4, IEEE (2023).
- [18] Kokumo, K., Sharma, A., Myers, K., Ambinder, E., Oluyemi, E., and Bell, M. A. L., “Theoretical basis and experimental validation of harmonic coherence-based ultrasound imaging for breast mass diagnosis,” in [*Medical Imaging 2023: Physics of Medical Imaging*], **12463**, 95–104, SPIE (2023).
- [19] Williams, P., Bannister, L., Berry, M., Collins, P., Dyson, M., and Dussek, J., “Gray’s anatomy: the anatomical basis of medicine and surgery,” *New York: Churchill Livingstone* **38** (1995).
- [20] Dowling, R. A., Corriere Jr, J. N., and Sandler, C. M., “Iatrogenic ureteral injury,” *The Journal of Urology* **135**(5), 912–915 (1986).
- [21] Blackwell, R. H., Kirshenbaum, E. J., Shah, A. S., Kuo, P. C., Gupta, G. N., and Turk, T. M., “Complications of recognized and unrecognized iatrogenic ureteral injury at time of hysterectomy: a population based analysis,” *The Journal of Urology* **199**(6), 1540–1545 (2018).
- [22] Wiacek, A., Wang, K. C., Wu, H., and Bell, M. A. L., “Photoacoustic-guided laparoscopic and open hysterectomy procedures demonstrated with human cadavers,” *IEEE Transactions on Medical Imaging* **40**(12), 3279–3292 (2021).
- [23] Zhang, J., Arroyo, J., and Lediju Bell, M. A., “Multispectral photoacoustic imaging of breast cancer tissue,” in [*2024 IEEE Ultrasonics, Ferroelectrics, and Frequency Control Joint Symposium (UFFC-JS)*], 1–4 (2024).
- [24] Zhang, J., Arroyo, J., and Lediju Bell, M. A., “Multispectral photoacoustic imaging of breast cancer tissue with histopathology validation,” *Biomedical Optics Express* (2025).
- [25] González, E. A. and Bell, M. A. L., “Acoustic frequency-based differentiation of photoacoustic signals from surgical biomarkers,” in [*Proceedings of the IEEE International Ultrasonics Symposium (IUS)*], 1–4, IEEE (2020).
- [26] González, E. A. and Bell, M. A. L., “Dual-wavelength photoacoustic atlas method to estimate fractional methylene blue and hemoglobin contents,” *Journal of Biomedical Optics* **27**(9), 096002 (2022).