Ultrasound Molecular Imaging for Early Breast Cancer Detection: RPCA-Based Filtering for Enhanced Separation of Free and Bound Targeted Microbubbles

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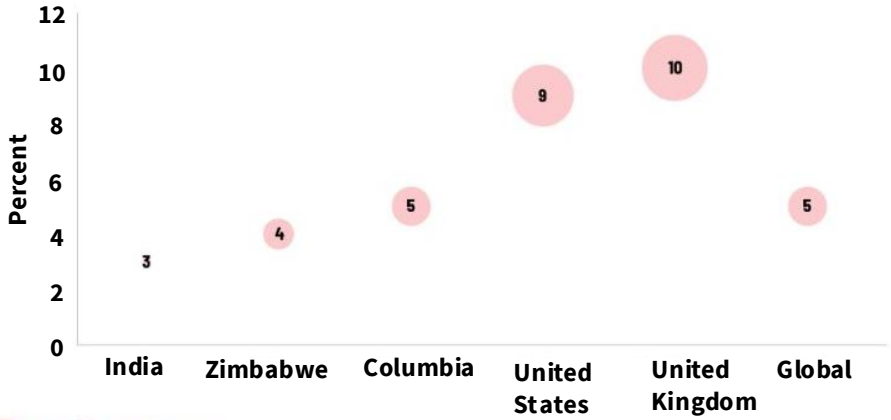
Some of the pictures are from Dr. Dahl's RAD 235 course slides.

Outline

- Overview:
  - Ultrasound molecular imaging
  - Ultrasound harmonic imaging
- Preclinical method: DTE
- Proposed method: RPCA
- Simulation results
- In vivo experiment

Background

Cumulative risk of being diagnosed with female breast cancer by age 75 years, globally and in selected counties:



- Breast most frequently diagnosed cancer in women.
- Countries where breast cancer is the most frequently diagnosed cancer in women in 2018:

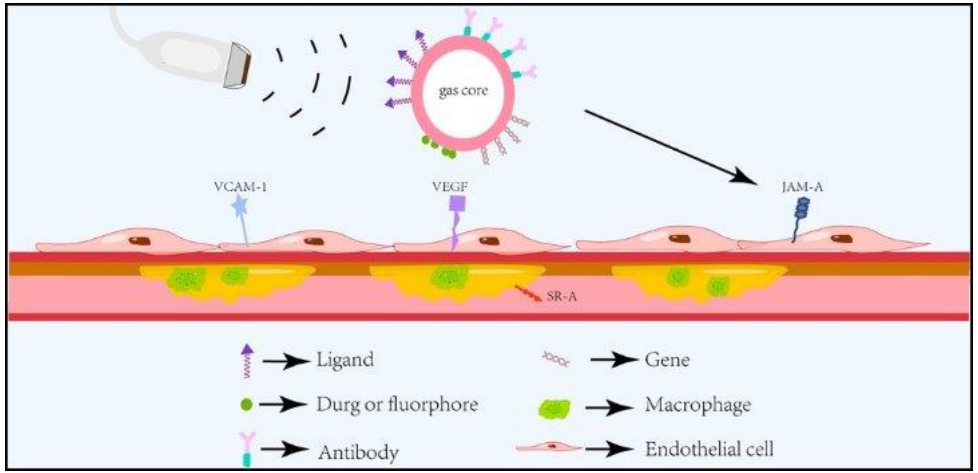
Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Lyon, France: IARC.

Motivation: Ultrasound Molecular Imaging

- An alternative to conventional ultrasound for the **early detection of breast cancer,**
- By introducing **contrast agents**, such as microbubbles.

- **Microbubbles**: tiny air bubbles that can produce a **large reflection** when injected into the body, improving the **contrast** of the image.

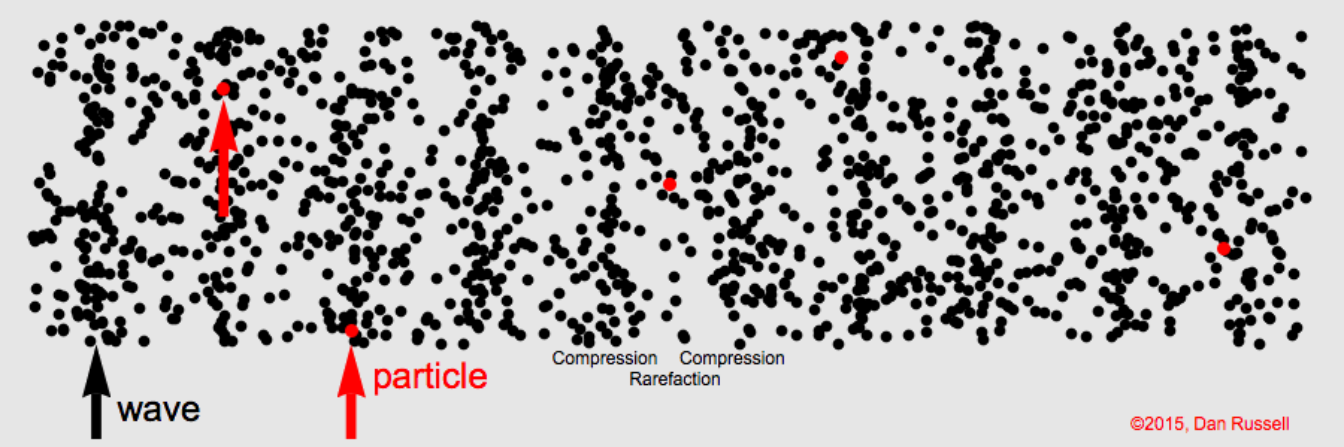
- These air bubbles can be **chemically modified on their surface** to attract to and bind with cancer cells (**Targeted microbubbles**).
- **Goal**: to detect bound microbubbles with ultrasound to identify the **cancer cells.**
- **Challenge**: Free microbubbles



Yao, et al., Frontiers in Cardiovascular Medicine, 2023.

Ultrasound Wave Propagation

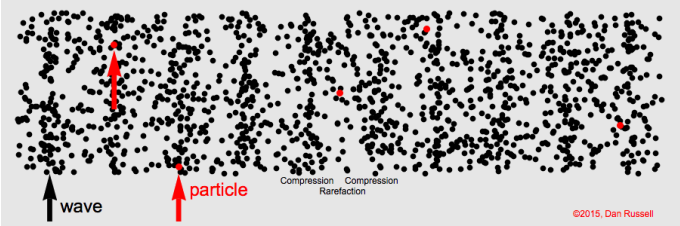
- Ultrasound is a longitudinal wave.
- Considered as a sinusoidal wave.
- There are regions of compression and rarefaction on sinusoidal wave.



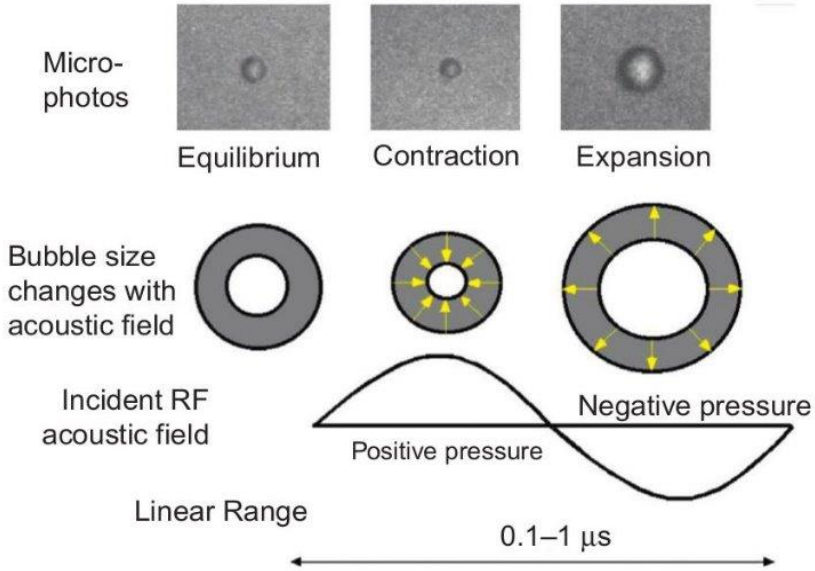
https://www.acs.psu.edu/drussell/demos/waves/wavemotion.html

Microbubble Oscillation

- When an ultrasound wave interacts with a microbubble,
- And the ultrasound pressure is very small:
  - Based on these regions of compression and rarefaction,



  - The bubble linearly contracts and expands
  - Causes the bubble to resonate at ultrasound fundamental frequency (f_0)
  - Sends the echos back to transducer (f_0).

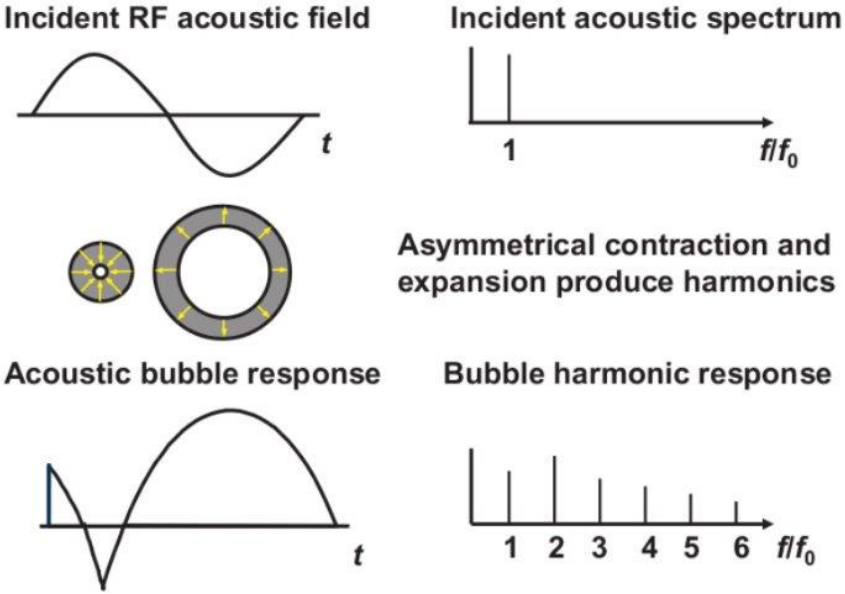


Szabo, Diagnostic Ultrasound Imaging: Inside Out. 2014.

Nonlinear Microbubble Oscillation

However, within the regular pressure range for the ultrasound imaging:

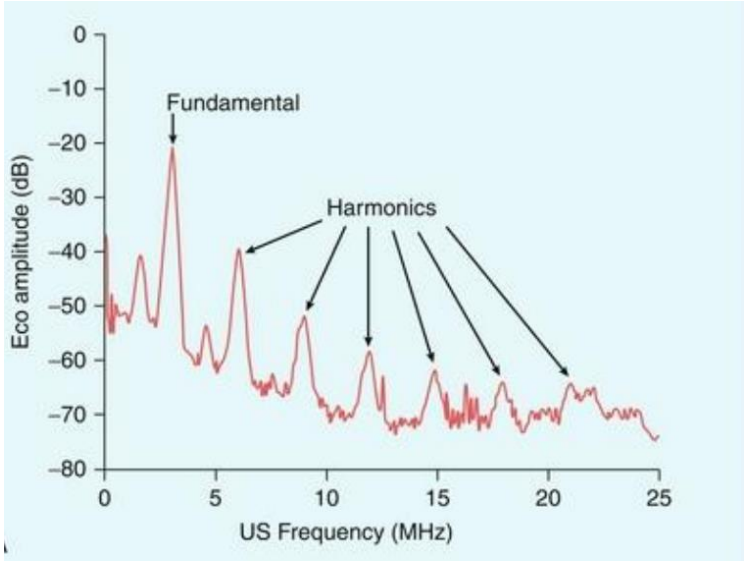
- Expansion and contraction are not symmetric.
  - Can **expand** with the pressure field
  - A **limit in contraction**
- So **asymmetric** expansion and contraction
- Changes the bubble acoustic response
- Causes the bubble to **resonate at a harmonic frequency** to the incident US wave,
- And emitting harmonic frequency waves back to the US transducer.

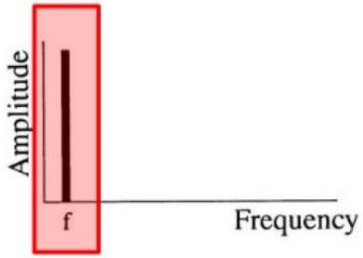


Szabo, Diagnostic Ultrasound Imaging: Inside Out. 2014.

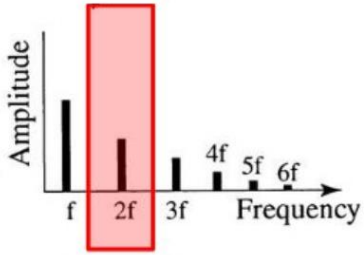
Nonlinear Microbubble Oscillation

Goal: Receive the first harmonic (2f) echo instead of the fundamental frequency (f)





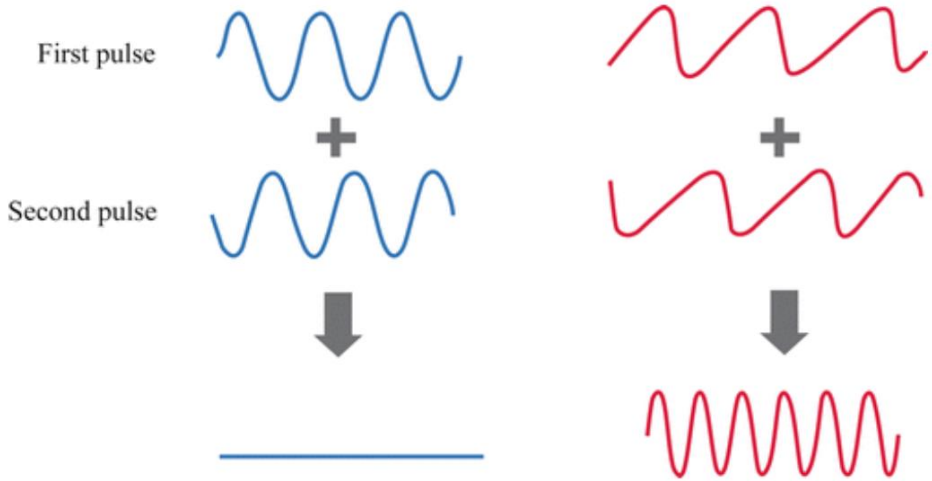
Transmit here:



“Receive” or form image here

Pulse-Inversion Harmonic Imaging

- A pulse is transmitted.
- An **inverted** pulse is transmitted.
- Echoes from the “positive” pulse are **added** to the echoes of the “negative” pulse.
- Eliminates **odd** harmonics and preserves **even** harmonics.
- Preserves **resolution** and increases **SNR**, but loses **frame rate**.



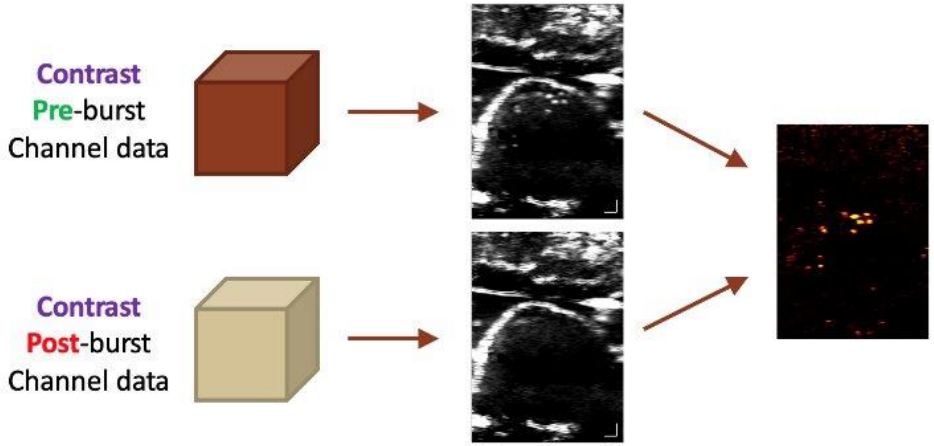
Anvari et al. “A Primer on the Physical Principles of Tissue Harmonic Imaging” Radiographics 35(7) :1955–1964, 2015.

Differential Targeted Enhancement (DTE)

- The preferred preclinical approach to detect microbubbles.
  - A strong acoustic pulse is used to destroy (burst) microbubbles.
  - Images acquired post-burst are subtracted from images acquired pre-burst.
  - Removing the background signals and leaving the targeted microbubbles.

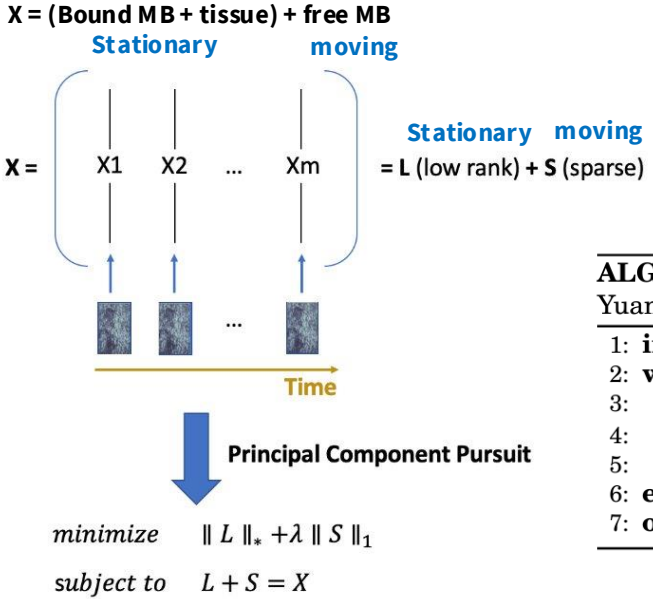
Disadvantage:

- Preclinical method, and can damage the vasculature.
- Still faces challenges in differentiating free and bound microbubbles.



Our Proposed Approach: RPCA

- We propose a **non-invasive** optimization approach using the robust principal component analysis (RPCA) to differentiate between bound and free-floating microbubbles.
- Spatial-temporal data matrix **X:**



Augmented Lagrangian multiplier:

$$l(L, S, Y) = \|L\|_* + \lambda\|S\|_1 + \langle Y, M - L - S\rangle + \frac{\mu}{2}\|M - L - S\|_F^2.$$

Alternating Directions Method of Multipliers (ADMM)

$$\arg\min_S l(L, S, Y) = \mathcal{S}_{\lambda/\mu}(M - L + \mu^{-1}Y). \qquad \mathcal{S}_\tau[x] = \text{sgn}(x)\max(|x| - \tau, 0)$$

$$\arg\min_L l(L, S, Y) = \mathcal{D}_{1/\mu}(M - S + \mu^{-1}Y). \qquad \mathcal{D}_\tau(X) = U\mathcal{S}_\tau(\Sigma)V^*$$

ALGORITHM 1: (Principal Component Pursuitby Alternating Directions [Lin et al. 2009a; Yuan and Yang 2009])

1: **initialize:** $S_0 = Y_0 = 0, \mu > 0$.
2: **while** not converged **do**
3: compute $L_{k+1} = \mathcal{D}_{1/\mu}(M - S_k + \mu^{-1}Y_k)$;
4: compute $S_{k+1} = \mathcal{S}_{\lambda/\mu}(M - L_{k+1} + \mu^{-1}Y_k)$;
5: compute $Y_{k+1} = Y_k + \mu(M - L_{k+1} - S_{k+1})$;
6: **end while**
7: **output:** L, S.

- The motion of bound microbubbles, appears as a high spatiotemporal coherence → Low-rank matrix L
- The flow of free microbubbles, has low coherence → Sparse matrix S

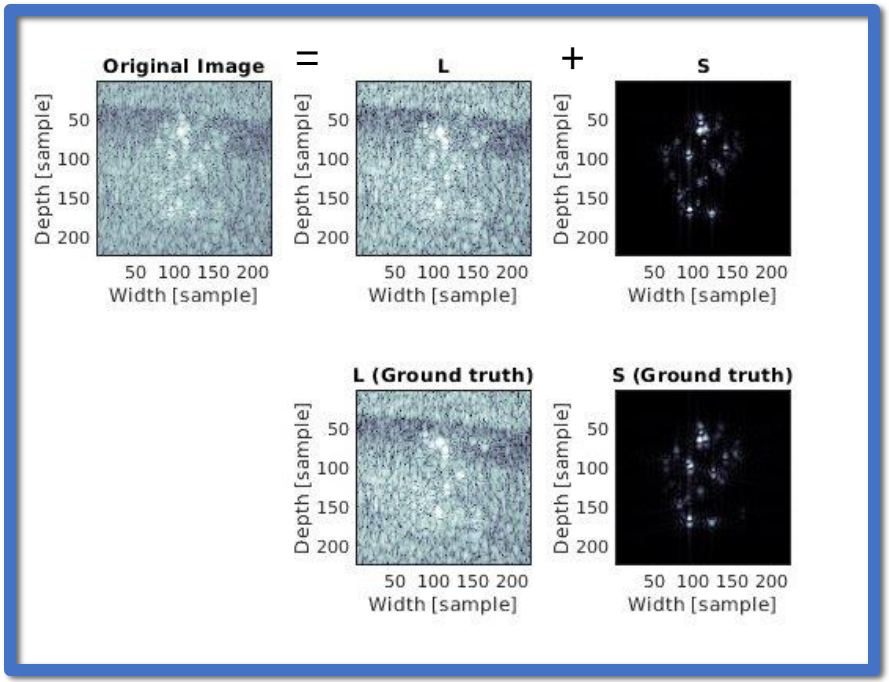
Simulation Data

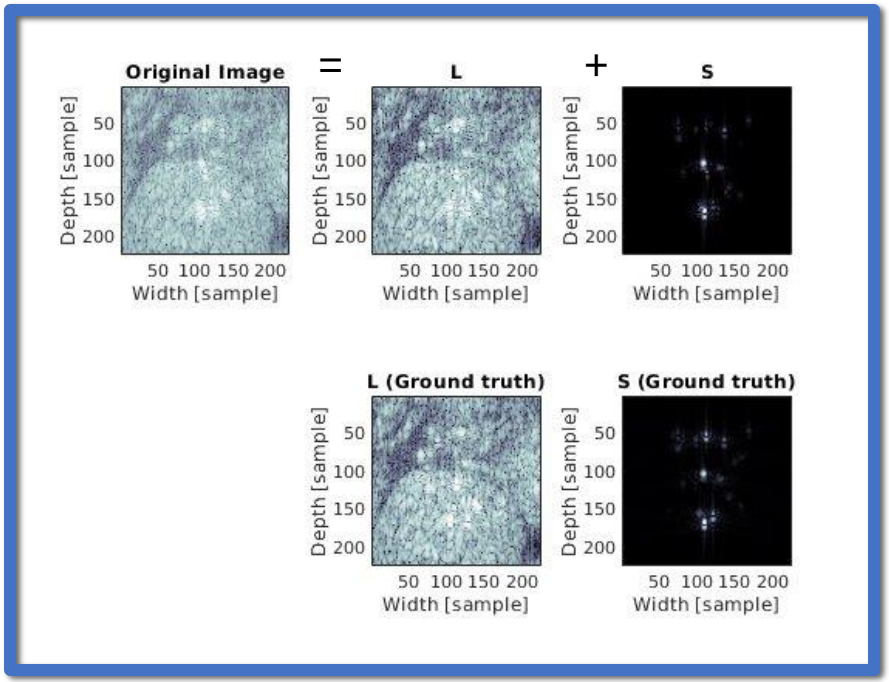
- 20 simulations, each one has 20 frames over time (Field II)
- Modelled bound and free-floating microbubbles.
- Total of 400 frames.
- L12-3v transducer.
- Images are compounded from 25 TX angles.
- 60 scatterers per resolution voxel.

Simulation Results

Original image (X) = Low rank (L) + Sparse (S)

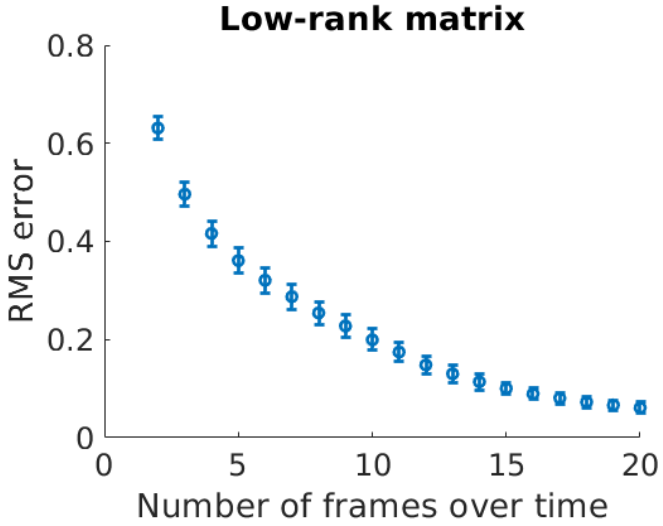
Two examples:

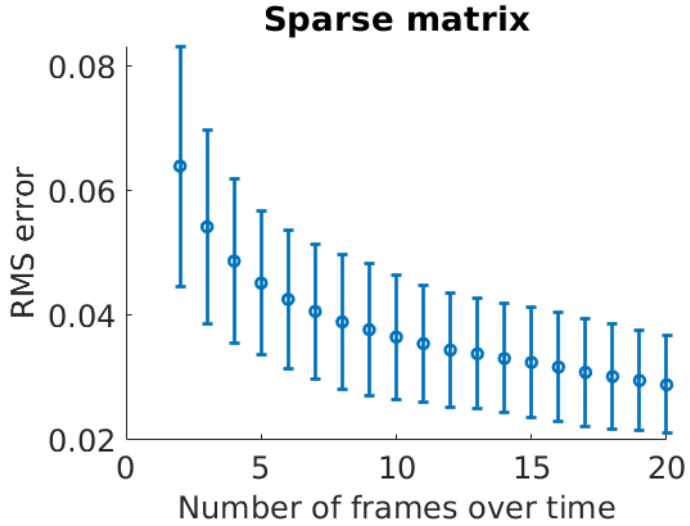




Simulation Results

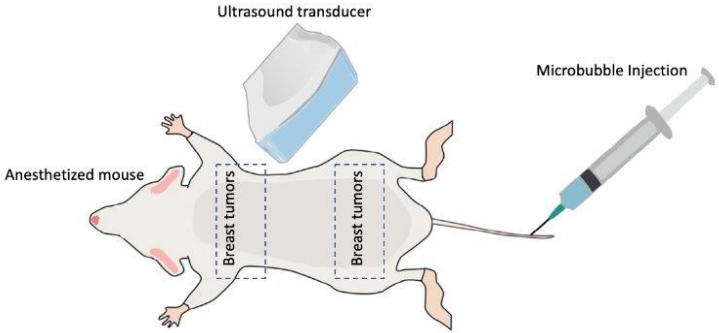
- RMS error = $\sqrt{\frac{(L_e - L_{gt})^2}{m*n}}$ RMS error = $\sqrt{\frac{(S_e - S_{gt})^2}{m*n}}$
- 20 simulations
- RMS error vs. the number of frames that we used over the time to make the spatial-temporal data matrix X

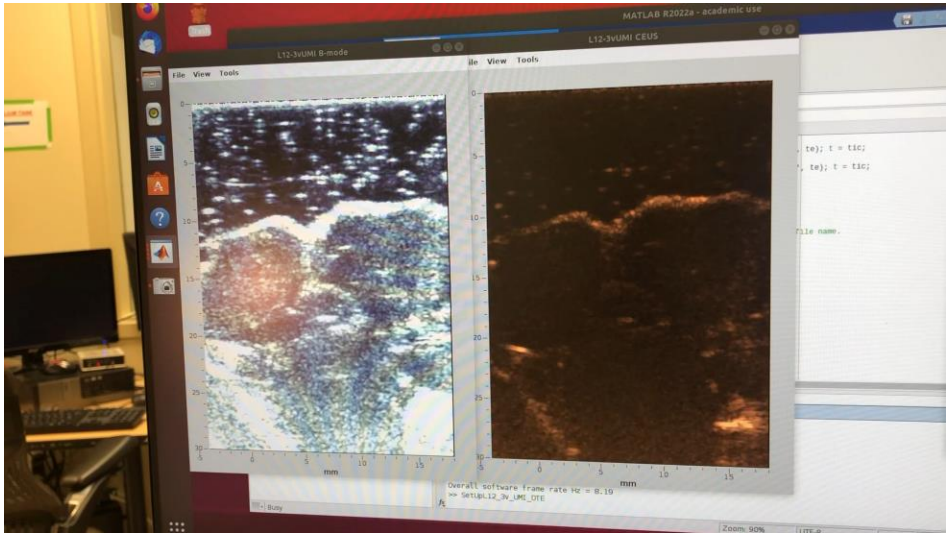




In vivo Data Collection

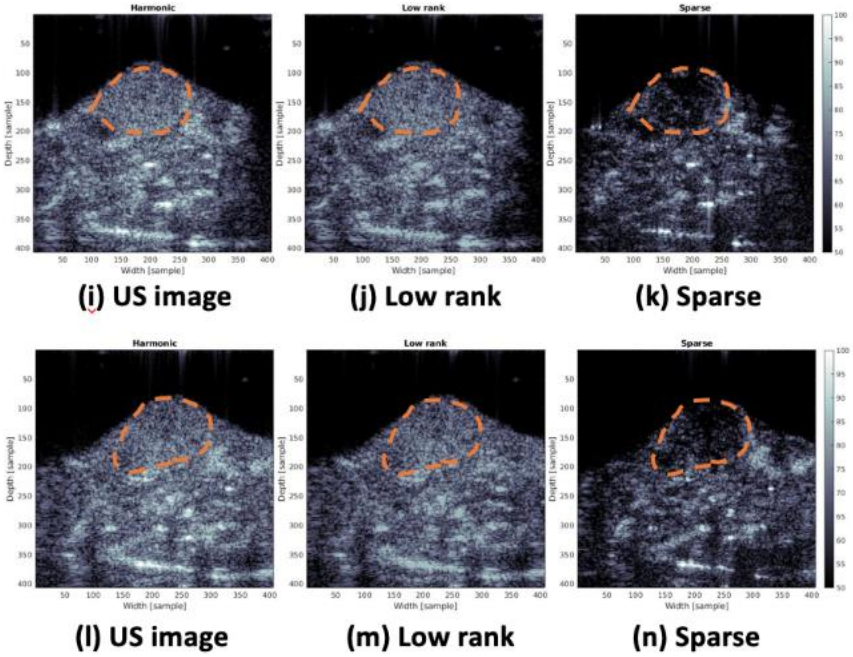
- Transgenic mouse models of breast cancer development.
- B7-H3- and PDL1-targeted microbubbles injected intravenously.
- Verasonics Vantage 256 research scanner.
- Harmonic imaging (contrast mode).





In vivo Results

Two Examples of in vivo data:

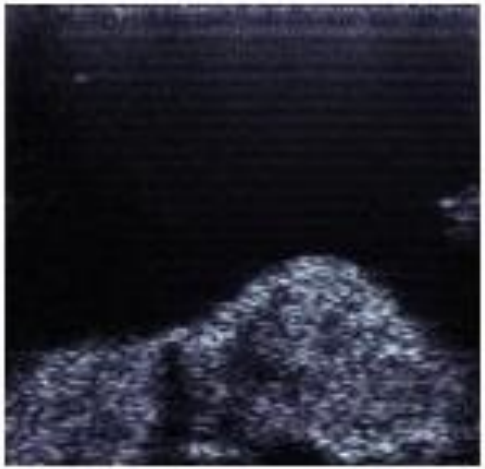


In vivo Results

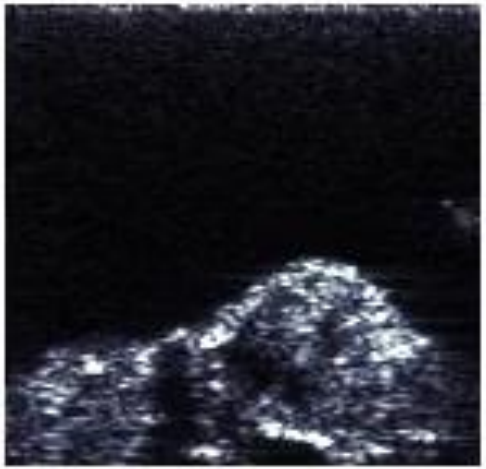
An Example of in vivo data:

Original harmonic image

Tissue + attached bubbles
(low-rank matrix)



Free-floating bubbles
(sparse matrix)



Summary

- **Ultrasound molecular imaging (UMI)** enables early detection of **breast cancer**.
- Detection of bound microbubbles is a **vital step** in UMI, which is challenging due to the presence of free microbubbles.
- We applied a **novel RPCA-based method** to separate free and bound microbubbles.
- The method was applied to **simulation** and **in vivo data** from transgenic mouse models of **breast cancer** development using targeted microbubbles.
- The stationary output of this method (tissue + bound microbubbles) can be used as input for **neural networks** to improve the differentiation of bound and free-floating microbubbles in nondestructive UMI.

Acknowledgment

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