Bringing “the sixth sense” for surgeons using light and sound

Jeeun Kang, Ph.D.

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Evolution of my personal interest

• One-dimensional advances towards smaller clinical ultrasound (US) imaging

• Higher spatiotemporal-spectral contrast

• Multi-modal imaging

Could be more colorful?

Could be more colorful?

Fractional change in FL intensity [%]

[Fig. 10 AX]

Could be more catching subtle temporal changes?
Defining the right form of “the sixth sense”

Knowledge in human anatomy & body memory of surgical procedures

Vision: a dynamic input

Crisp perception is a must for the new sixth sense
- High spatiotemporal resolution
- High contrast resolution
- Wide volumetric field-of-view
- Real-time feedback
- No surgical interruption

Current state-of-the-art in intra-operative guidance

Current state-of-the-art in intra-operative guidance

**Fluorescence imaging**

- Only 2-dimensional perception with en face imaging FOV

**Confocal / multiphoton microscopy & Raman spectroscopy**

- Slow imaging
- Limited imaging depth & FOV

**Optical coherence tomography (OCT)**

- Small FOV in few mm diameter
- Limited contrast resolution

**X-ray**

- Ionizing effect
- Interrupt the surgical procedure

**Prostate MRI**

- Challenging for intra-operative use

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**Medical ultrasound**

- **Anatomical**
  - Static 2D compound
  - 1D array (e-scan)
- **3D/4D imaging**
- **Synthetic aperture focusing**
- **Functional & Molecular**
  - Flow
  - CA
  - Elastography
  - Photoacoustics

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References:

Prostate Cancer (PCa)

- PCa is a leading organ for new cancer cases for males, (21% in total cancer diagnosis) resulting second highest cancer deaths †

- High survival rate when localized, but survival rate drops with metastasis

- Early PCa detection & accurate surgery for negative tumor margin are the best defense strategy


Clinical US imaging of PCa

...
**PCa management in healthcare**

![Diagram of PCa management process]

- **Prostate-Specific Antigen (PSA)**
  - High false-positive rate (75%)†

- **MRI PET/CT**
  - The prevalence of nearly invisible PCa on TRUS ranges from 25 to 42%‡

- **Transrectal US-guided biopsy**

- **Histopathology**
  - Post-operative complications: erectile dysfunction (59.9% at 18M); incontinence (8.4% at 18M)

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**Mission**

![Diagram showing mission goals]

- **Higher spatial resolution**

- **Molecular contrast**

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Limited aperture, but desire to see more – What shall we do?

Synthetic aperture focusing?
Synthetic “lateral” aperture focusing in medical ultrasound

Forget about something?

Synthetic “radial” aperture focusing (rSAF)

Acoustic field expression of single transmission

\[ \Phi_\alpha (y, z, t) = e^{-j\alpha} \frac{1}{j\lambda ||R||_2} \Psi_\alpha (y, z) \]

Continuous transmit beam pattern at a depth of \( R \)

\[ \Psi_\alpha (y, z) = e^{j\alpha} = e^{j\lambda, \sqrt{(y-R)^2 + (z-R')^2}} \]

Synthetic transmit aperture focused beam pattern at \((y_f, z_f)\)

\[ \Psi_{TSAF}(y_f, z_f) = c_0 \int_{-\alpha}^{\infty} p_2(\alpha)e^{-j\lambda, \sqrt{(y_f-R)^2 + (z_f-R')^2}} \Psi_\alpha (y, z) d\alpha \]

Scale factor

\[ c_0 = \frac{1}{j\lambda ||R||_2} \]

Synthetic focusing delay

\[ \tau(\alpha) = e^{-j\lambda, \sqrt{(y_f-R)^2 + (z_f-R')^2}} \]

Analytical solution for synthetic radial aperture focusing (rSAF)

Synthetic transmit aperture focused beam pattern

\[ \Psi_{TSAF}(y_f, z_f) = c_0 \int_{-\alpha}^{\infty} p_2(\alpha)e^{j\lambda, \sqrt{(y_f-R)^2 + (z_f-R')^2}} \Psi_\alpha (y, z) d\alpha, \]

\[ \tau(\alpha) = e^{-j\lambda, \sqrt{(y_f-R)^2 + (z_f-R')^2}} \]

\[ \Psi_\alpha (y, z) = e^{j\alpha} = e^{j\lambda, \sqrt{(y-R)^2 + (z-R')^2}} \]

\[ \Psi_{TSAF}(y_f, z_f) = c_0 \int_{-\alpha}^{\infty} p_2(\alpha)e^{j\lambda, \sqrt{(y_f-R)^2 + (z_f-R')^2}} \Psi_\alpha (y, z) d\alpha. \]

Fresnel approximation

\[ R - R_f = \frac{y^2 - y_f^2}{2f} + \frac{r(y - y_f)}{z_f} \]

\[ y' = y - y_f \]
Analytical solution for synthetic radial aperture focusing (rSAF)

\[ \Psi_{\text{rSAF}}(x_f, y_f, z_f) = \frac{c_0 e^{j k \frac{r^2 - y_f^2}{2 z_f}}}{R_f} \mathcal{F}[p_0(a)] e^{j k r_y y_f} \]

Discrete synthetic transmit aperture focused beam pattern

\[ \Psi_{\text{rSAF}}(y_f, z_f) = c_0 e^{j k \frac{r_y^2 - y_f^2}{2 z_f}} \mathcal{F}[p_0(a)] e^{j k r_y y_f} \]

Null-to-null beam width

\[ y_{n, \text{ML}} = \frac{\lambda a_f}{r_n \Delta a} = \frac{\lambda a_f}{r_{a_{\text{max}}}} \]

Grating lobe positions

\[ y_{n, \text{GL}} = \frac{\lambda a_f}{r_n \Delta a} n \]

(n = 1, 2, ...)

Practical implementation strategy

Virtual source-based SAF technique

\[ \Psi_{\text{rSAF}}(x_f, y_f, z_f) = \frac{c_0 e^{j k \frac{r^2 - y_f^2}{2 z_f}}}{R_f} \mathcal{F}[p_0(a)] e^{j k r_y y_f} \]

Synthetic aperture focusing delay calculation

\[ \tau_f(i, z) = \frac{d_i(z)}{c} \]

(i.e., \( R_f \))

Radial aperture synthesis

\[ l_{\text{rSAF}}(\theta_n, z) = \frac{1}{N_{\text{syn}}(z)} \sum_{i=-N_{\text{syn}}(\theta_n, z)/2}^{N_{\text{syn}}(\theta_n, z)/2} l_i(\theta_n, \tau_f(i, z)) \]
**Design framework**

- Sagittal axis, \( z \)
- Frontal axis, \( y \)
- TRUS array design
  - Acoustic frequency
  - Elevation f-number
  - Scanning radius
  - Radial scanning interval
  - Imaging depth

**Spatial resolution & grating lobe**

\[ y_{SL}^f = \frac{\lambda x_f}{r \Delta \alpha} \]  
\[ y_{GL}^f = \frac{\lambda x_f}{r \Delta \alpha} n (n = 1, 2, 3, \ldots) \]

- \( d_{YS} = 5 \text{ mm}; h = 7 \text{ mm} \)

\[ y_{SL}^f \quad (r = 5 \text{ mm}) \]
\[ y_{SL}^f \quad (r = 10 \text{ mm}) \]
\[ y_{SL}^f \quad (r = 15 \text{ mm}) \]

- **(a)** Sagittal axis
- **(b)** Synthetic aperture width (mm)
- **(c)** FWHM (mm)
- **(d)** ΔSNR (dB) vs. TRUS-CON

\[ \Psi_{RAF}(x_f, y_f, z_f) \]

- Proportional
- Inversely proportional

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\[ ^{†} \text{H. Song, J. Kang, J Comput Des Eng 9, 1774-1787 (2022).} \]

\[ ^{‡} \text{J. Kang, et al., US Patent 63/355,525 (2022).} \]
2D Field-II simulation – Frontal-sagittal plane


Comparison to clinical standard

What's next?

Null-to-null beam width

\[ \gamma_{\text{ML}} = \frac{\lambda z/2}{\cos \alpha} \]

Anus diameter
2-3 cm

Rectal diameter
3-5 cm

What's next?

Patient
TRUS/TRPA imaging device
Passive arm
Table
Sliding base

Insertion mode
(22-mm diameter)

Waterbag
Motor and gear transmission for rotation
Piezoelectric array transducer + optical fiber
Motor and lead screw transmission for transducer extension

Imaging mode
(50-mm diameter)

Courtesy of Dr. Iulian Iordachita

**Summary**

- TRUS-rSAF technique can provide **unprecedented volumetric spatial resolution** higher than clinical convex/linear TRUS array transducer

- Analytical description and optimization framework were developed

- Mechatronic implementation will provide a next-generation TRUS imaging for higher sensitivity and specificity to detect and diagnose PCa

- Further works: prototyping & clinical translation

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**Mission**

- **Higher spatial resolution**

- **Molecular contrast**

  - The prevalence of nearly invisible PCa on TRUS ranges from 25 to 42%.

  - Post-operative complications: erectile dysfunction (59.9% at 18M) and incontinence (8.4% at 18M).

  - Prostate-specific antigen (PSA) transrectal US-guided biopsy.

  - MRI/PET/CT.

  - Histopathology.

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**References**

Prostate-Specific Membrane Antigen (PSMA)

- Type-II integral cell-surface membrane protein †

- Overexpressed in nearly all solid tumors (e.g., breast, bladder, pancreatic, testicular, or colorectal cancers) †

- High correlation to PCa aggressiveness, implying its functional role in PCa biology ‡


Targeting PSMA for early-PCa detection

PET/MRI/CT †
Pros: Wide field-of-view across whole-body; High specificity
Cons: Iodizing effects; Slow imaging speed; expensive

Optical imaging †
Pros: Real-time; easy to use
Cons: Superficial sensing depth

Extensive clinical trials stages I and II: NCT02282137, NCT02611882, NCT02488070, NCT02048150, NCT01173146 …

Clinical trials in IND stage: NCT01173146, NCT02048150


Adding light: biomedical photoacoustics

Air (medium)
Lightning (Light source)
Local heat expands volume
Acoustic propagation
Thunder (Photoacoustics)
Ear (sensor)

Competitive analysis

Multi-functional PSMA-targeted platform

Energy goes to internal conversion, rather than fluorescence.

Non-radiative relaxation in form of thermal energy.

Anti-cancer drugs
Radiolabels
MRI contrast

Multi-arm linker

Forming energy transfer within ground-state complex.

Second-generation PSMA-targeting agent

PSMA-targeting agent

Dendrimer

Control

**In vivo PA-based PSMA-targeted imaging**

In vivo PA-based PSMA-targeted imaging

![Image](image1.png)


**Potential engineering pitfalls**

Potential engineering pitfalls

![Image](image2.png)

Spectral system noise segregation

\[
\begin{align*}
\arg \min_{\mathbf{x}} & \quad \frac{1}{2} \mathbf{x}^{T} \mathbf{A}^{T} \mathbf{A} \mathbf{x} - \mathbf{y}^{T} \mathbf{A} \mathbf{x} \\
\text{subject to} & \quad \mathbf{x} \geq 0
\end{align*}
\]

In vivo validation

\[\begin{array}{cc}
\text{Pre-injection} & \text{Post-injection} \\
\text{Conventional scheme} & \text{SSE segregation scheme}
\end{array}\]

\[\begin{array}{cc}
\text{Ultrasound} & \text{Unmired contrast agent} \\
\text{10 min} & \text{Unmired noise}
\end{array}\]
In vivo validation

\[ c_{SNR} = \frac{I_{PSMA+}}{I_{BG}} \]

\[ c_{PSMA} = \frac{I_{PSMA+}}{I_{PSMA-}} \]

Summary

- PSMA-targeted imaging may endow new possibility to provide molecular contrast exclusively on aggressive PCa using TRUS/PA imaging

- Dedicated signal processing algorithms (spectral system noise, wavelength optimization, frame averaging) will enhance the clinical sensitivity and specificity

- Future works
  - Multi-functional (theranostics), multi-modal (PA/US + MRI or PET) imaging capability will be developed.
  - Multi-institutional team for animal model and clinical testing is in preparation (NIH, Hopkins).
Remarks

Transformable TRUS/PA imaging

Motor and lead screw transmission for transducer extension

Motor and gear transmission for rotation

Piezoelectric array transducer + optical fiber

TRUS/PA diagnostics & interventional guidance

• Expanded role in PCa diagnostics
• Microtumor detection (3-5 mm → 1-2 mm)
• High-accuracy biopsy guidance, targeting PSMA expression

Piezoelectric transducer

Waterbag

PSMA-targeted imaging

Signal processing algorithm

\[
\arg \min_{x \geq 0} \left( \frac{1}{2} x^T Q x - y^T Q x \right)
\]

Complication of radical prostatectomy

• **Erectile dysfunction** is a post-operative complication of radical prostatectomy

• Current nerve-sparing techniques only consider neurovascular bundle (NVB), excluding cavernous nerve branches

• Only 60-85% of PCa patients recover erectile function, and early recovery is uncommon (up to 2 years) †

‡ https://www.virginiamason.org/radical-prostatectomy
**Current state-of-the-art**

**Fluorophore-based fluorescence imaging †**
- Concern on tissue toxicity
- Long staining time (2hr – 14 days)

**Coherent anti-Strokes Raman spectroscopy**
- Slow imaging
- Limited imaging depth

**Confocal and Multiphoton microscopy**
- Not optimized for intra-operative use
- Limited imaging depth

**Optical coherence tomography (OCT) ‡**
- Lack of nerve-specific contrast
- Limited contrast resolution due to speckle artifacts

**Prostate MRI §**
- Slow speed
- Not portable

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**Near-infrared VSD mechanism**

- **Transmembrane redistribution mechanism ††**

  - **Cyanine VSD (IR780 perchlorate)**
  - Non-fluorescent aggregates
  - PA signal

  - **Polarized cell state**
    - $\Phi_a \uparrow$, $\Phi_F \downarrow$

  - **Depolarized cell state**
    - $\Phi_f \uparrow$, $\Phi_A \downarrow$

  - **Polarized cell state**
    - Cyanine dye positively charged is attracted into cell membrane
    - The aggregation of VSD leads to fluorescence (FL) quenching, which increases PA efficiency

  - **Depolarized cell state**
    - Dispersion of VSD gives high FL efficiency

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Near-infrared VSD characterization

- Artificial membrane diffusion potential model

\[ \text{Polarized state} \quad \text{Depolarized state} \]

IR780 perchlorate
Valinomycin (K-specific ionophore)
Soybean lipid vesicle membrane
Potassium gradient
Free Na+
Gramicidin (nonspecific monovalent cation ionophore)
Na+
K+
K+ - specific ionophore

\[ \text{Absorbance and fluorescence emission spectrum of near-infrared VSD. (A) Absorbance and fluorescence emission spectrum of near-infrared VSD. (B) Photoacoustic spectrum and intensity change at the 790 nm peak absorbance.} \]

In vitro VSD characterization (6µM).

Preliminary evidence of neural sensing

Non-invasive epileptic seizure detection

Non-invasive characterization of excitatory neurotransmittance at rat hippocampus

\[ \text{Fractional change in VSD response [%]} \]

Motor cortex (0.3 mM NMDA)
Hippocampus (0.3 mM NMDA)
Hippocampus (3 mM NMDA)

\[ \text{extracellular glutamate concentration (% basal)} \]
**Proposed image-guided nerve-sparing laparoscopic radical prostatectomy**

- **Objective:** Image-guided nerve guidance with:
  1. **Real-time functional nerve localization** with high specificity,
  2. **Short VSD staining duration** (~10 min)
  3. **Wide field-of-view** familiar with surgeons, and
  4. **Near-infrared imaging** for better transfascial nerve localization

![Image-guided nerve-sparing laparoscopic radical prostatectomy](image)

Step 1: Robotic tool approach through the ports on the abdominal incisions,
Step 2: Direct transfascial VSD staining within a time limit up to 10 min,
Step 3: Flushing out of the VSD on the prostate surface which is not bound at tissue membrane,
Step 4: Nerve stimulation for nerve-selective VSD contrast, and
Step 5: Nerve-sparing prostatectomy with the augmented nerve map using intra-operative FL imaging solution

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**In vivo experimental setup:**

**Imaging system and animal preparation**

![In vivo experimental setup](image)

- **FL imaging module:**
  - Customized coherent fiber bundle-based endoscopic probe (50K cores at 0.1mm, 70°FOV, 2.5cm DOF)
  - sCMOS camera

- **Stimulation module:**
  - Electrical stimulator

- **ICP validation module:**
  - ICP measurement system

**Pr:** prostate; **Pn:** penis; **CN:** cavernous nerve; **RCC:** right corpus cavernosum; **ICP:** Intracavernosal pressure

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**In vivo experimental setup:**
Imaging and stimulation protocol

- **Experimental protocol**

<table>
<thead>
<tr>
<th>Pre-stimulation</th>
<th>Electrical Stimulation</th>
<th>Post-stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 min</td>
<td>1 min</td>
<td>3 min</td>
</tr>
</tbody>
</table>

**Validation of erectile stimulation**

- 4V Electrical pulses
- 5 ms
- 62.5 ms (16Hz)

**Intracavernosal pressure [mmHg]**

![Graph](image)

**Real-time trans-fascial functional prostate nerve mapping in vivo**

- **Time-averaged F/F₀ trace**
- **Fractional change in fluorescence intensity [%]**
- **Fluorescence intensity**

![Image of nerve mapping](image)

**References**

Histological validation of direct VSD delivery

- Successful direct VSD staining on nerve layer below prostatic fascia

![Image of histological staining]


Discussion

- We presented the preliminary results of real-time nerve guidance using dual-modal VSD and near-infrared FL imaging

- Our further works will be focused on
  - Collecting more data for statistical rigor
  - Toxicity study and efficiency evaluation with various VSD concentrations
  - Advance experimental setup to induce selective cavernous nerve blocking
  - Developing pulsed laser-based dual-modal intra-operative guidance system
  - *In vivo* large-scale animal study for evaluating clinical outcome (post-operative erectile dysfunction with functional guidance vs. no imaging guidance)
Defining the right form of “the sixth sense”

Knowledge in anatomy & surgery

PSMA-targeting agents

Voltage-sensitive dye

Transformable TRUS/PA x signal processing

Motor control

Vision: a dynamic input

Aggressive tumor

Erectogenic nerve

Anatomical context

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