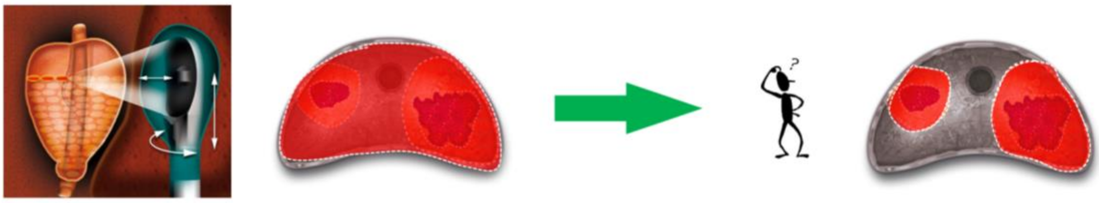
Post-Doctoral position – 1 year (renewable)
Development of a dual-mode CMUT medical device for ultrasound-guided HIFU ablations in the context of endocavitary focal therapy of localized prostate cancer (PCa)



Context of the study

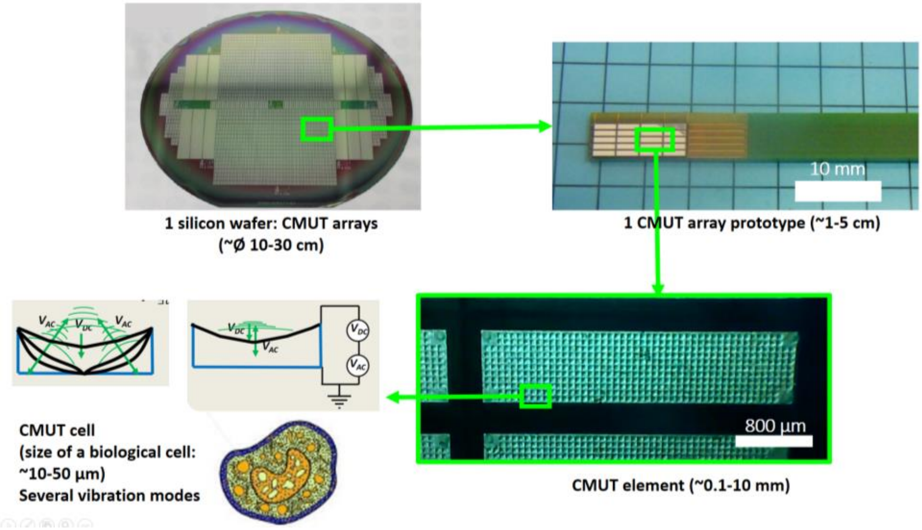
Image-guided High Intensity Focused Ultrasound (HIFU) therapies have showed promise to treat localized diseases such as localized tumors. The most established application of HIFU at the clinical level is certainly the treatment of localized prostate cancer (PCa) using an endocavitary approach guided with ultrasound imaging [**1,2**]. In order to treat localized PCa, it is essential to generate ablation volumes in depth while ensuring a particularly high level of treatment precision to preserve native interleaving structures (e.g. rectal wall) and safe regions in the prostate surrounding (e.g. neurovascular bundles). The most common HIFU strategy to treat localized PCa is to perform the thermal ablation of the entire prostate gland. However, a more desirable treatment, and the current trend, is towards a **focal** HIFU treatment where only a portion of the prostate is treated (e.g. hemi-ablation) or even just the tumor regions ((multi-)focal treatment) [**3,4**]. There is evidence that focal HIFU therapy can be a safe alternative to the treatment of the entire prostate in cases where the tumors are localized [**5-7**]. This evidence showcases a need for improved focal therapy devices which have the ability to accurately localize treatments under real-time image guidance. Any modifications to current tools that improve upon the accuracy of HIFU targeting or imaging, will help to advance future generations of focal treatments. In order to accomplish this goal improved imaging of the tumor environment (prostate tumor are not visible on B-mode US images, which requires using fusion imaging techniques) is needed along with accurate, finely tunable, generation of thermal lesions.

The **LabTAU** has been developing a partnership with the companies **Vermon** (Tour) and **Edap-TMS** (Vaulx-en-Velin) on a research project which aims at developing a new generation of dual-mode **ultrasound** (US) medical devices based on the **CMUT** technology (Capacitive Micromachined Ultrasonic Transducer), and allowing both US imaging and therapy (HIFU) for ultrasound-guided HIFU (USgHIFU) focal therapy of localized prostate cancers (PCa) [**8**].

CMUT transducers have several advantages that make them competitive with those of conventional piezoelectric transducers. These include ease of miniaturization (cell size: micron scale) enabled by MEMs-based fabrication processes and low fabrication costs at the industrial scale. They also have an inherently broad frequency bandwidth ($\Delta f/f > 100\%$) and a potential for high electro-acoustic efficiency ($\rho = P_{Ac}/P_{El}$). This is due to the mechanical impedance of the thin vibrating CMUT cells which confer to the CMUT elements a total radiation impedance much smaller than the acoustic impedance of water. The transmission to water of the ultrasound wave is then optimized in contrast to bare piezoceramic transducers. CMUT devices can also exhibit good MR compatibility if the associated electronics and packaging are chosen properly. Another interesting characteristic is that CMUTs can exhibit a significantly higher electromechanical coupling factor k_t when operating in "collapse" rather than in "conventional" regimes [**9,10**]. All of these characteristics suggest that CMUTs could be interesting for developing new generations of ultrasound devices for image-guided HIFU therapies. Until recently, only a few preliminary

Unité de recherche U1032
Cyril LAFON, Directeur
151 Cours Albert Thomas
69424 LYON Cedex 03
Tél. +33 (0)4 72 68 19 30
Fax. +33 (0)4 72 68 19 31
u1032@inserm.fr
http://labtau.univ-lyon1.fr

studies have investigated CMUTs for high intensity ultrasound applications [11-15]. The difficulty in adapting CMUTs to these applications is that it requires the development of specific cell structures and driving strategies [16-18]. High intensity ultrasound surgery involves continuous emission of acoustic energy in contrast to ultrasound imaging applications, which only require intermittent pulsing. These driving conditions thus require a CMUT architecture which is mechanically, electrically and thermally more robust than those developed for imaging applications.



The development of dual-mode US medical devices with high density phased-array CMUT transducers is expected to lead to significant enhancements in treatment quality and safety. Ultimately, a new generation of medical devices is expected to emerge (not only for prostate applications), which will allow with the same device precise focal **HIFU** therapy (dynamic focusing) and high-performance endocavitary imaging for guiding the treatment procedure.

[1] A. Gelet *et al.*, "Transrectal High-Intensity Focused Ultrasound: Minimally Invasive Therapy of Localized Prostate Cancer," *J. Endourol.*, vol. 14, no. 6, pp. 519–528, Aug. 2000.

[2] S. Crouzet, F. J. Murat, G. Pasticier, P. Cassier, J. Y. Chapelon, and A. Gelet, "High intensity focused ultrasound (HIFU) for prostate cancer: Current clinical status, outcomes and future perspectives," *Int. J. Hyperth.*, 2010.

[3] T. H. Kuru, J. Van Essen, D. Pfister, and D. Porres, "Role of Focal Therapy with High-Intensity Focused Ultrasound in the Management of Clinically Localized Prostate Cancer," *Oncol. Res. Treat.*, vol. 38, no. 12, pp. 634–638, 2015.

[4] J.-Y. Chapelon, O. Rouvière, S. Crouzet, and A. Gelet, "Prostate Focused Ultrasound Therapy," in *Therapeutic Ultrasound*, 2016, pp. 21–41.

[5] S. Muto, T. Yoshii, K. Saito, Y. Kamiyama, H. Ide, and S. Horie, "Focal therapy with high-intensity-focused ultrasound in the treatment of localized prostate cancer," *Jpn. J. Clin. Oncol.*, vol. 38, no. 3, pp. 192–199, Feb. 2008.

[6] G. Hou, F. Marquet, S. Wang, and E. Konofagou, "Optimization of Real-Time Acoustical and Mechanical Monitoring of High Intensity Focused Ultrasound (HIFU) Treatment Using Harmonic Motion Imaging for High Focused Ultrasound," 2013.

[7] S. Crouzet *et al.*, "Salvage high-intensity focused ultrasound (HIFU) for locally recurrent prostate cancer after failed radiation therapy: Multi-institutional analysis of 418 patients."

[8] Bawiec CR, N'Djin WA, Bouchoux G, Sénégond N, Guillen N, Chapelon JY. Preliminary investigation of dual mode CMUT probe for ultrasound image guided HIFU therapy. *Ultrasonics Symposium (IUS) Proceedings;* 2017 IEEE International : 1-4. **DOI:** 10.1109/ULTSYM.2017.8092212

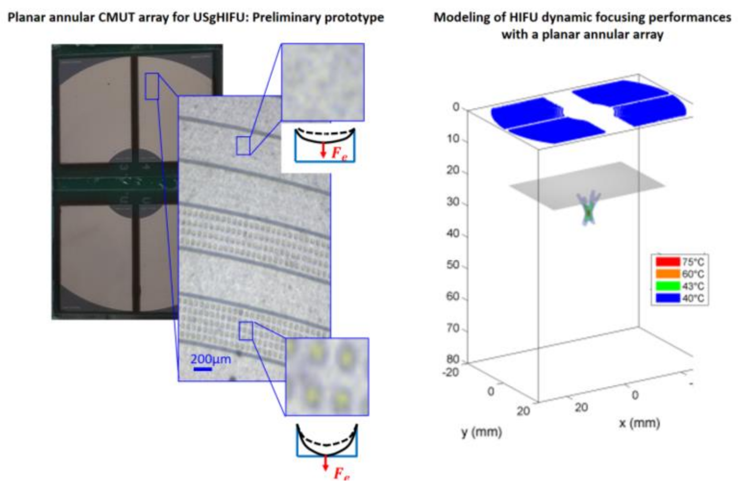
[9] B. Bayram, E. Hæggström, G. G. Yaralioglu, and B. T. Khuri-Yakub, "A new regime for operating capacitive micromachined ultrasonic transducers," *IEEE Trans Ultrason Ferroelect Freq Contr*, vol. 50, no. 9, pp. 1184–1190, 2003.

[10] Y. Huang, E. Haeggstrom, B. Bayram, X. Zhuang, A. S. Ergun, C. H. Cheng, and B. T. Khuri-Yakub, "Comparison of conventional and collapsed region operation of capacitive micromachined ultrasonic transducers," *IEEE Trans Ultrason Ferroelectr Freq Control*, vol. 53, no. 10, pp. 1918-33, Oct, 2006.
[11] S. H. Wong, M. Kupnik, R. D. Watkins, K. Butts-Pauly, and B. T. Khuri-Yakub, "Capacitive micromachined ultrasonic transducers for therapeutic ultrasound applications," *IEEE Trans Biomed Eng*, vol. 57, no. 1, pp. 114-23, Jan, 2010.
[12] S. Wong, R. Watkins, M. Kupnik, K. Pauly, and B. Khuri-Yakub, "Feasibility of MR-temperature mapping of ultrasonic heating from a CMUT," *IEEE Trans Ultrason Ferroelectr Freq Control*, vol. 55, no. 4, pp. 811-8, Apr, 2008.
[13] H.-S. Yoon, C. Chang, J. H. Jang, A. Bhuyan, J. W. Choe, A. Nikoozadeh, R. D. Watkins, D. N. Stephens, K. Butts Pauly, and B. T. Khuri-Yakub, "Ex Vivo HIFU Experiments Using a 32x32 -Element CMUT Array,"IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control, vol. 63, no. 12, pp. 2150–2158, dec 2016.
[14] W. A. N'Djin, B. Gerold, J. Vion-Bailly, M. S. Canney, A. Nguyen-Dinh, A. Carpentier, J.Y. Chapelon, "Capacitive Micromachined Ultrasound Transducers for Interstitial High-Intensity Ultrasound Therapies," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*, vol. 64, no. 8, pp. 1245–1260, Aug. 2017. **DOI:** 10.1109/TUFFC.2017.2707663
[15] Farhanieh, O., Sahafi, A., Roy, R. B., Ergun, A. S., & Bozkurt, A. (2017). Integrated HIFU drive system on a chip for CMUT-based catheter ablation system. *IEEE Transactions on Biomedical Circuits and Systems*, *11*(3), 534-546.
[16] O. Oralkan, B. Bayram, G. G. Yaralioglu, A. S. Ergun, M. Kupnik, D. T. Yeh, I. O. Wygant, and B. T. Khuri-Yakub, "Experimental characterization of collapse-mode CMUT operation," *IEEE Trans Ultrason Ferroelectr Freq Control*, vol. 53, no. 8, pp. 1513-23, Aug, 2006.
[17] S. H. Wong, M. Kupnik, X. Zhuang, D.-S. Lin, K. Butts-Pauly, B. T. Khuri-Yakub, "Evaluation of wafer bonded CMUTs with rectangular membranes featuring high fill factor," *IEEE Trans. Ultrason., Ferroelectr., Freq. Control*, vol. 55, no. 9, pp. 2053–2065, Sep. 2008.
[18] Gross D, Boulmé A, Sénégond N, Bawiec C, N'Djin WA, Certon D. Analysis of CMUT power efficiency for optimized therapeutic operation. *Ultrasonics Symposium (IUS) Proceedings;* 2017 IEEE International : 1-4. **DOI:** 10.1109/ULTSYM.2017.8091708

Project objectives

The post-doctoral researcher will be working at LabTAU and will benefit from a multidisciplinary environment (expertise in biomedical ultrasound, acoustic physic, engineering, image-guided therapies). This research project as part of the PERFUSE programme (ANR RHU 2017) will be carried out in close collaboration with two industrial partner, Vermon (Tours, France) and Edap-TMS (*Vaulx-en-Velin, France).*

The main objective of the post-doctoral researcher will be to study new focal HIFU strategies up to the preclinical level by developing HIFU therapies with an existing phased-array CMUT prototype and ultrasound imaging with an embedded US imaging CMUT transducer, in the context of endocavitary HIFU interventions guided by intraoperative real-time ultrasound imaging and image fusion (preoperative MRI).



The first objective will be to investigate the feasibility of using a CMUT phased-array for generating high intensity focused ultrasound robustly and compatible with the thermal ablation of a prostate volume. Various CMUT vibration modes will be investigated in modeling (COMSOL) and in experiment (laser vibrometry, hydrophone, acoustic balance) to optimize the acoustic power output by the CMUT for HIFU. Different CMUTs structures may also be evaluated in-sillico to improve the performances of CMUTs in high power mode (breakdown voltage, resonance frequency and electromecanical efficiency …). The capability of dynamic focusing (displacement of the HIFU focus electronically without device motion) will be evaluated to further study various treatment planning strategies: 1st step - simple planning (e.g. 7 x 7 lesions at specific tissues depth), 2nd step - conformal hemi-ablation of realistic prostate geometries (tissue mimicking gel phantom, virtual human prostate geometries defined in a liver tissue model), last step – focal ablation of realistic prostate tumor geometries (tissue mimicking gel phantom, virtual human prostate tumor geometries defined in a liver tissue model). The feasibility of using efficiently predetermined segmented target regions for defining a complex treatment planning including the description of target regions in 3D, the setting of suitable HIFU sequences (Dynamic HIFU focusing, ultrasound power, exposure duration) and prototype movement (rotations, translations) for achieving conformal and ultimately focal treatments will be studied both in modeling and in experiments.
The researcher will be working on open research platforms:

- HIFU modeling: a custom HIFU modeling software based on the Rayleigh Integral and Bio-Heat Transfer Equation (LabTAU plug-in of CIVA medical)
- USgHIFU experiments: an open ultrasound imaging scanner with full research access (Verasonics Vantage) which also includes a HIFU option for dual mode ultrasound generation (HIFU/US imaging). This system will have to communicate with the current treatment planning platform of the clinical device Focal One (Edap-TMS, transducer technology: piezo) for achieving full treatments. Direct comparison of the HIFU ablations performances will be performed between the Focal One probe and the new CMUT prototype.

The second objective will be to investigate, in parallel with the first objective, the performance of the new CMUT US guidance in pulse-echo mode, by developing advanced imaging sequences (mixed imaging sequences between "phased linear" and "linear phased" array strategies) to optimize the visualization of the target tissues. The inherent characteristics of CMUTs (e.g. broad frequency bandwidth, high density) may be utilized to improve US imaging strategies used to guide and monitor endorectal HIFU treatments: 1) the strategies currently used in clinics (e.g. B-mode imaging, Doppler-imaging, Contrast imaging), 2) the emergent strategies not currently used at the clinical level for monitoring prostate ablation (e.g. Ultrafast imaging for Compound Harmonic Imaging, Thermometry or Elastography).

Post-doctoral experience and project tasks

- Bibliographic studies, training, disseminations and valorizations of the research results
- Co-leading of the team (students, engineers) on the project tasks dealing with the CMUT modeling, characterization, preclinical validation
  Investigations on CMUT dual-modality
- Investigation on focal therapy in modeling and experimentally with an existing V1 prototype (a 64-annular array CMUT HIFU transducer embedding a 256-element CMUT imaging linear-array): conformal hemi-ablation, focal ablation of the tumor volume only

- Exploration of HIFU parameters: electro-acoustic characterization, electronic focusing in therapy mode: Vantage 256 platform (Verasonics) for HIFU
    - Exploration of US imaging parameters: mixed imaging sequences (“linear phased” VS “phased linear” (B-mode), communication with the Focal One platform for Fusion Imaging (Preoperative MRI + CMUT US imaging) and motorization of the CMUT device
- Preclinical studies: preliminary *in-vivo* validation of USgHIFU treatment using the studied V1 CMUT prototype
- Evaluation of several new designs of **CMUT** phased-array transducers for endocavitary ultrasound ablation of the prostate: simulation and optimization of the performances achievable in therapy mode (high power signals), in imaging mode (pulse signals) for developing a new V2 CMUT prototype (CMUT vibration modeling with COMSOL, HIFU modeling with CIVA)

Skills

The candidate must hold a PhD degree preferentially in the following field: Biomedical Engineering. With excellent skills: 1) to develop and characterize electrical and ultrasound instrumentation; 2) to apprehend the use of commercial and no-commercial expert softwares (HIFU modeling, management and processing of digital data), data analysis (interpretation and discussions of results, writing technical and scientific reports and papers), and programming (development of new tools)

- Programming skills: C++ (ideally ITK, VTK), Matlab, Labview
- Modeling tools: COMSOL, CIVA medical, Field II
- Signal and image processing
- Biomedical ultrasound: HIFU instrumentation, Ultrasound Scanners

Contacts

Send a CV and a motivation letter to:

- W. Apoutou N’DJIN apoutou.ndjin@inserm.fr
- Jean-Yves CHAPELON jean-yves.chapelon@inserm.fr