Near-field dielectric imager using field-modulated standing-wave oscillators for intraoperative tissue imaging

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I. INTRODUCTION

Tumor margin assessment is a critical step in breast tumor surgery to ensure complete removal. Such a procedure is routinely performed by post-surgical pathological examinations on the excised specimen. A re-excision surgery is often needed if a positive margin is identified (Fig. 1), bringing significant discomfort to the patients. Thus, *intra-operative imaging* that can perform rapid margin assessment (< 5 minutes) at real-time feedback is highly desirable. Among all different approaches [1]–[4], RF spectroscopy has been one of the most promising techniques. It performs diagnosis based on tissue permittivity without the need for any labeling. Remarkably, this technique has been applied in clinics using an FDA-approved MarginProbe[4]. Its studies have demonstrated a reduction from 61.7% to 23.1% in re-excision rate in breast conservation surgeries (BCS) of ductal carcinoma in situ (DCIS). This is achieved using a 7-mm diameter resonator measuring the average in the coupling area[5].

To detect sub-mm tumor-cell clusters for improved diagnostic accuracy, a scalable near-field imager with a small pixel size (< 100μm × 100μm) and high filling factor is needed. As RF circuits occupy a large area, these requirements are hardly achieved with conventional impedance and LC-oscillator sensing circuits[6]–[8]. We address these challenges by implementing a field-programmable differential trans-mission line (t-line) configured as a standing-wave oscillator (SWO) at 13 GHz (selected for largest permittivity differences [9]). The presented RF imager features a pixel size of 51.2μm × 50μm at 64% filling factor and an 0.54-ppm sensitivity limit

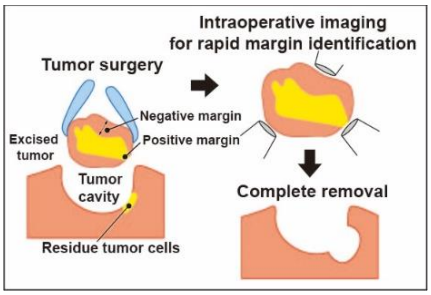

Fig. 1. Intraoperative imaging.

II. SENSOR ARCHITECTURE

A. *Pixelated Coplanar Strip line*

Fig. 2 presents the proposed pixelated near-field "imaging" technique using a $\lambda/2$ differential transmission line (t-line). The idea is to control the fringing E-fields (in z-direction) using MOS switches to enable *localized* sensing. We start with a differential t-line at Metal-1 and Metal-2 and distribute multiple 21 μm × 50 μm Metal-6 strips at a pitch of 25 μm orthogonally to the direction of wave propagation. These strips serve as shielding metals that prevent the fields from fringing outside the chip surface. Each Metal-6 strip is further split into half, with each covering one signal line, and connected by a bridge switch SW_1. As shown in Fig. 3, the local E-fields are *shielded* by the Metal-6 strip when SW_1 is enabled. On the other hand, the E-fields are allowed to fringe out of the CMOS surface when SW_1 is off. Imaging is thus performed through individual control of the switches distributed on a millimeter-long t-line. This approach enables a high filling factor (the ratio between the sample-sensitive area versus the physical area) and 2D-imaging is readily achieved with multiple t-line placed in parallel. To maximize the coupling between Metal-2 and the floated Metal-6 during the sensing operation, $SW_{2\text{-}3}$ and MIMcaps are included (Fig. 3). This boosts the sensitivity by 58.7× from simulations.

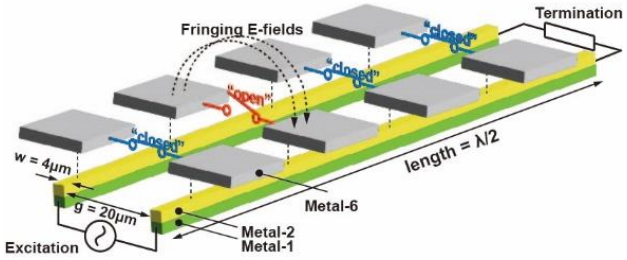

Fig. 2. Pixelated t-line concept.

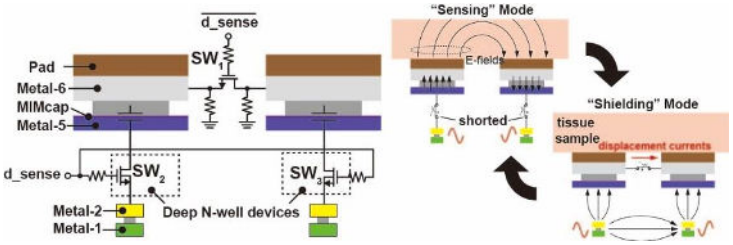

Fig. 3. Pixel schematic and its operation modes.

B. *Field-Modulate SWO system operation*

In this work, we will configure each λ/2 (= 1.1mm, 22 pixels) pixelated coplanar strip line into a standing-wave oscillator (SWO), and will place 22 SWOs to be an array. Each SWO will measure the tissue permittivity through shifts in its free-running frequency, and we easily see this shift on the output. About the readout, the output of each SWO is AC-coupled to a frequency divider (N = 64) and a shared 32b-counter is used for frequency detection. Through this architecture, we can simply detect all the shift on each SWO and can easily know which pixel at the SWO array can be corresponded to the shift and finally transfer the output to an image by data processing. We implemented a 22x22 imaging array in 180-nm CMOS using three SWOs to validate the concept (Fig. 4). and achieve a 64% (= 51.2μm/80μm) filling factor, mainly limited by the need for divider and logic power rails[10].

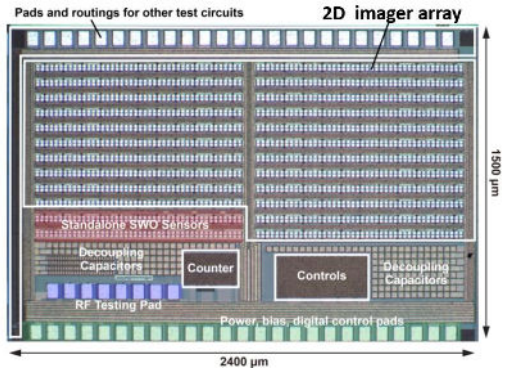

Fig. 4. Die photo

III. PRELIMINARY RESULTS

We detected the frequency difference between the sense & shield mode at each pixel in different material such as Air, de-ionized water and isopropyl alcohol (IPA) to observe its resolution and use these results for calibration, and then verify the imaging capability by using meander microfluidics channel immersed in inked water (Fig. 5(a)). Next, we use tumor tissues excised from mice and immersed in formalin for imaging demonstration (Fig. 5(b)).

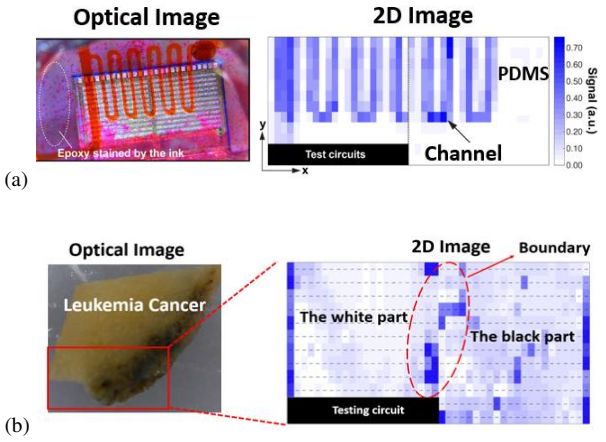

Fig. 5. (a) Meander Microfluidics and (b) Tumor tissue imaging.

IV. CONCLUSION

In this work, we successfully demonstrate a 13-GHz RF near-field imager for rapid intraoperative imaging. By employing near-field modulation on the standing waves from a half-wavelength transmission line using CMOS switches, a compact and scalable implementation of a 2D imaging array at a 50μm×50μm pixel size and 64% filling-factor is achieved. We implement a 484-pixel 2D imager in 180-nm CMOS technology, and validate the new imaging concept using tumor tissues. To avoid electrode corrosion, the CMOS surface is protected with 5-nm thick SiO2 through the plasma-enhanced chemical vapor deposition (PECVD). Wirebonds are encapsulated in a biocompatible epoxy (Epo-Tek 302-3M). A calibration flow using reference liquid measurements will be developed to convert the measured values to the absolute permittivity values. The image is acquired using a custom-built data acquisition module with automation at 5 sec per frame. Such a throughput enables rapid tumor margin identification for intraoperative applications. We are collaborating with Professor Liang-In Lin's research group at Department of Clinical Laboratory Sciences and Medical Biotechnology at College of Medicine, National Taiwan University. Table I summarizes our comparison table.

Table I. Comparisons.

	This work	[6] JSSC'16	[7] JSSC'16	[8] JSSC'18
Applications	Intraoperative Imaging	Bacteria Detection	Flow Cytometry	General purpose
Tech.	180 nm CMOS	65 nm CMOS	65 nm CMOS	130 nm SiGe
Frequency	13 GHz	60/120 GHz	6.5/11/17.5/30 GHz	550 GHz
Sensing Element	Differential t-line	Spiral inductors	Coplanar capacitor	Split-ring resonator
Sensing area	50μm×50μm	80μm×90μm*	30μm×50μm	12μm×12μm
Filling factor	64%	< 50%**	0.7%	0.55%***
Pixel numbers	22×22	12×16 @120GHz	4	64×2
Scalability	2D	2D	1D only	1D only****
Detection	Standing-wave oscillator + counter	LC oscillator + counter	Injection-locking + phase detection	Non-coherent detection
Chopping	Yes, 100 Hz	No	Yes, 50 MHz	Yes, 100 kHz
Sensitivity	0.54 ppm (40msec gate time)	2.87 ppm (6msec gate time)	1.25 ppm (100-kHz filtering)	-
Dynamic Range	78.7 dB @ center 52.7 dB @ edge (air to water)	75.8 dB (air to water)	45.1 dB (readout circuit)	63.8 dB @ 125-Hz filtering (readout circuit)
Power	107.8 mW (4.9 mW/pixel)	34.8mW/element	65 mW (16mW/ch.)	37 ~ 104 mW

*Estimated from the paper figure. **Peripheral around each element is not provided in the paper.
***Estimated based on the following calculation: (12μm×12μm×4ch)/(550μm×190μm) = 0.55%
****Limited by the area of power splitters. Paper achieve 2D image through mechanical scanning.

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