A Packaged Ingestible Bio-pill with 15-pixel Multiplexed Fluorescence Nucleic-acid Sensor and Bi-directional Wireless Interface for In-vivo Bio-molecular Sensing

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Abstract: This paper presents the first wireless multiplexed fluorescence-based bio-molecular sensing system in a pill form for GI-track health monitoring application. This application is geared towards quasi-real time analysis of microbiome distribution through nucleic acid detection. A silicon chip integrates both the sensor and the wireless system, including a 124 μW ULP wireless receiver with -59 dBm sensitivity, a dual mode FSK/OOK transmitter, and a fluorescent sensor array with 1.6 attomoles and 100 pM of target DNA detection limit per pixel. The complete package includes a CMOS fluorescent sensor chip with integrated filter, a prototyped UV LED and optical waveguide, functionalized bioslip, off-chip power management and Tx/Rx antenna that fits in a standard FDA approved capsule size 000.

Introduction: Ingestible bio-electronic sensors with robust wireless communication capability and multiplexed bio-molecular sensing can enable real-time monitoring of human health in an in-vivo setting. Recent discoveries shows linkages between microbiome population in GI-track and a wide range of health conditions [1]. Traditional methods to analyze gut microbiome balance is lab-based DNA/RNA sequencing of bacteria in fecal samples. Therefore, a wireless ingestible pill with integrated bio-marker sensor that can map the microbiome distribution in-vivo can revolutionize existing health care system. While prior work has shown ingestible electronics capable of sensing pressure, pH, temperature, performing ultrasound endoscopy [2], and extracting microbiome samples from gut fluid in-vivo [3], enabling a multiplexed nucleic acid sensor in a compact bio-pill with a complete RF transceiver is extremely challenging due to the level of sensitivity required in such a low power and compact form factor. By eliminating external bulky optics, this paper presents a packaged prototype bio-pill system including a 15-pixel fluorescence CMOS nucleic acid sensor array with on-chip optics, signal processing and bi-directional communication capability.

System Overview: Fig. 1 shows the packaged system that is powered by a 1.55 V, 12.5 mAh battery. The chip architecture is shown in Fig. 2. The sensor array is integrated using metal-based, angle-and-scattering-insensitive, nano-optic excitation filters (M1-M4), eliminating bulky and expensive optics [4]. To enhance sensitivity, each pixel employs a differential measurement scheme with a sensing and shielded reference photodiode (150×170μm) that are laid out in an interlaced pattern to suppress common mode dark current. The fluorescence read-out circuitry contains a capacitive-TIA (CTIA) that is digitized with an on-chip 10-bit SAR ADC. In the SAR ADC, a MOM capacitor with minimum value of 27 fF is used as unit cell. A preamplifier with auto-zeroing technique is implemented to reduce input-referred offset and suppress 1/f noise (Fig. 6). Then, the ADC output is transmitted via a dual-mode OOK/FSK transmitter realized with a current-starving ring oscillator and a switching PA at 915 MHz (ISM).

The entire system operation goes as follows (Fig. 3): after the system startup, it will be forced into receiving mode, waiting for a 16-bit hardware verification ID. The purpose of the verification is to guard against false trigger due to RF scattering effects in tissue [5]. Concatenated with the 16-bit verification ID, a 32-bit instruction ID that includes pixel selection, transmitter timing controls and 12-bit dynamic range control (~30 dB) for the pixel. Finally, upon reception of the 32 bits, the system moves to the wireless transmitter mode.

ULP Wireless Front-end: To minimize power consumption of the receiver, envelope detector (ED) based architecture along with pulse-pause encoded (PPE) data is chosen (Fig. 7). This eliminates high-power PLL-based CDR circuity. In this encoding scheme, bit "0" is defined as a short pulse followed by a short null, while bit "1" is defined as a longer pulse. The input LNA is designed with an inverter with a resistor feedback, followed by an open loop inverter (~33 dB voltage gain). The amplified signal passes through a sub-Vt active ED. Then, an oversampling comparator is used to decode the clock signal. Such implementation allows all digital programmability, eliminating any external analog voltage control. Then, the Tx/Rx path share a single antenna in TDD operation. The inverted-F antenna with an off-chip tapped capacitor matching network at 915 MHz is designed for both PA and LNA (Fig. 4). The total power consumption of the chip in the Rx and Tx mode is 860 μW and 1.4 mW respectively (Fig. 11).

Measurement Results: The Rx performance is characterized in a wireless setup. Figure 7 shows the measured sensitivity of the Rx mode is -59 dBm with 10^{-3} BER at 1 Mb/s, demonstrating 124 pJ/bit with 124 μW of power with 128.1 FoM (Fig. 9). With a human body between the bio-pill and the external transmitter, ~6 dB of transmitting power increase is observed. The decoded signals from the Rx is also shown in Fig. 7, demonstrating the correct verification and the instruction set. In Tx mode, an output power of -15 dBm is measured (Fig. 7) that is received by the external receiver. The wireless specification is summarized in Fig. 9 demonstrating robust performance against other state-of-the-art implantable radios. In addition, a 10-bit differential SAR ADC is designed on-chip and achieves SFDR of 72 dB with 1 Hz input sine wave and ENOB of 9.5 bits. This is sufficient to sample CTIA output, from which the noise source is primarily dominated by the photon shot noise (~1.5 mV) [4].

The on-chip optical filter achieves ~39 dB extinction ratio. This removes complex and bulky optics and allows the limit of detection (L.O.D.) for Qdot 800 to reach ~40 dots/μm^2 or 1.6 attomoles (Fig.10) that is comparable to modern fluorescent scanners and readers [4]. Figure 8 shows the absolute responsivity at the output of the CTIA at varying target DNA concentrations, demonstrating a detection limit of ~100 pM with S.N.R. ≈ 1. The dynamic range and sensitivity of the sensor proves sufficient coverage to map gut microbiome distribution which is typically in the range of nM to μM. The system demonstrates, for the first time, a multiplexed fluorescence-based bio-molecular sensor with bi-directional communication capability in a FDA approved pill form.

References: [1] C. Steiger, *et al*., *Nat. Rev. Mater.*, 2018. [2] J. Wang, *et al*., *IEEE IUS*, 2017. [3] H. R. Nejad, *et al*., *Advanced Intelligent Systems*, vol. 1, no. 5, 2019. [4] L. Hong, *et al*., *ACS Photonics*, Dec. 2018. [5] C. Zhu, *et al*., *IEEE IMS*., 2019. [6] S. A. Mirbozorgi, *et al*., *IEEE TBioCAS*, vol. 10, no. 3, 2016. [7] M. Cai, *et al.*, *IEEE TMTT*, 2018. [8] M.-C. Lee, *et al*., *IEEE CICC*, 2018. [9] L. Hong, *et al.*, *IEEE JSSC*, 2017. [10] D. Ho, *et al.*, *IEEE TBioCAS*, vol. 7, no. 5, 2013.

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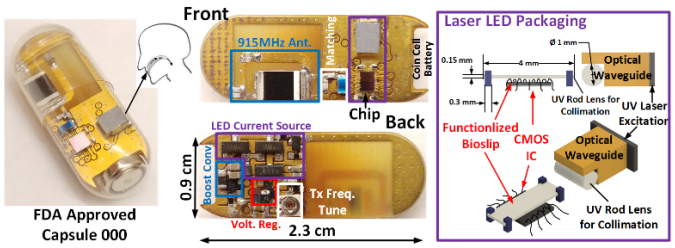

Fig. 1: The complete system is packaged in a bio-pill operating at 915 MHz, including UV LED, optical waveguide, functionalized bioslip, off-chip power management and Tx/Rx antenna that fits in a FDA approved capsule 000.

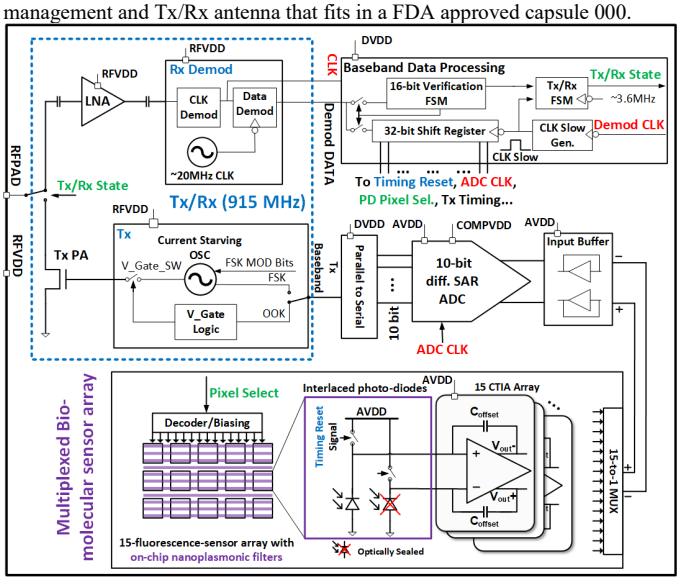

Fig. 2: Complete system schematic showing multiplexed fluorescence 15-pixel sensor array with integrated optics, data converters and integrated bidirectional wireless communication capability in a CMOS chip.

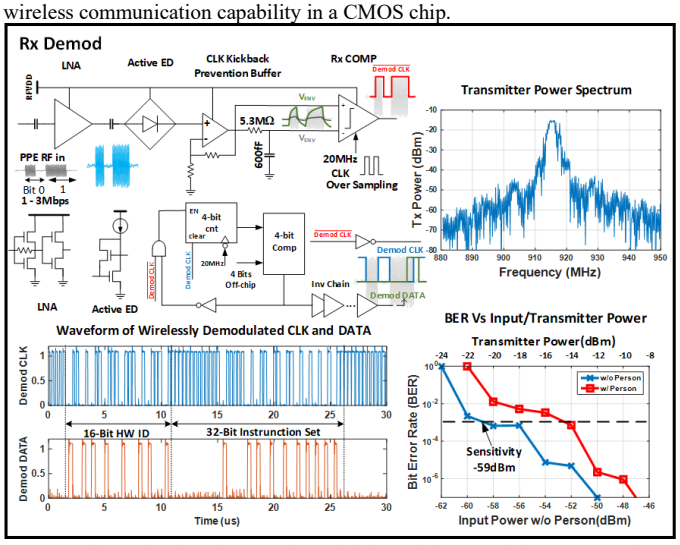

Fig. 7: Schematic showing Rx demodulation chain (top left). Measured Tx power of -15 dBm (top right). -59 dBm of Rx sensitivity @ 1 Mbps (bottom right) . Examples of demodulated CLK and DATA (bottom left).

	This Work	[6]	[7]	[8]
Process	65 nm	180 nm	130 nm	180 nm
Packaging Size	Capsule 000 0.9 × 2.4 cm	3 × 1 cm	44-QPF 1.4 × 1.4 cm	N.A.
Rx Ant. Size	3 × 5 mm Inverted IF	1x1 cm^2	N.A.	N.A.
Rx Carrier Freq	915 MHz	2.4 GHz	915 MHz	413 - 419 MHz
DC Power (P_{DC})	121 µW	5 mW	9.1 µW	92 µW
Rx Sens. (P_{SENS}) @ data rate (DR)	-59 dBm @ 1 Mbps	N.A.	-48 or -39 dBm @ 1 or 100 kbps	-79 or -74 dBm @ 1 or 10 kbps
Rx Energy per bit	40.4 pJ/b @ 3 Mbps	50 pJ/b @ 100 Mbps	91 pJ/b @ 100 kbps	9.2 nJ/b @ 10 kbps
FoM	128.1	N.A.	109.4	124.3
On-chip Bio-molecular Sensor	Yes	No	No	No

$$FoM = -(P_{sens} - 10log(DR)) - 10log(\frac{P_{DC}}{1mW})$$

Fig. 9: Comparisons with state-of-the-art wireless implantable receiver and FoM eq.

	This Work	[9]	[10]
Process	65nm	65 nm	0.35 µm
Optical Filter	Integrated nano-plasmonic	Integrated nano-plasmonic	Off-chip assembled thin film filter
Excitation Laser	405nm	405 nm	450 nm
Package	Packaged LED laser in capsule	External optics	External optics
Laser Power	1-5 µW	4 mW	10 mW
Circuit Power (Sensor Only)	14 µW	6 mW	N.A.
Photodiode Area	150 × 170 µm^2	91.4 × 123 µm^2	50 × 50 µm^2
Detection Limit	40 molecules/µm^2	70 molecules/µm^2	~10^5 molecules/µm^2 (estimated)

Fig. 10: Comparisons with recent works on fluorescent sensor.

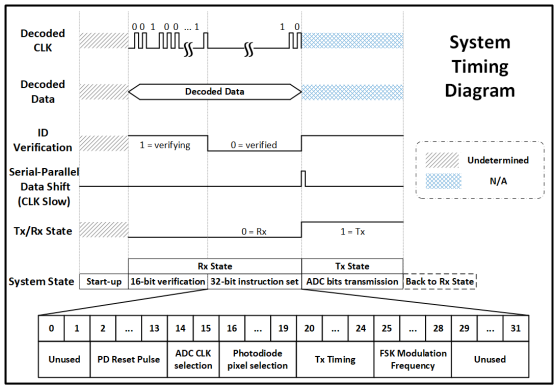

Fig. 3: Timing diagram showing system operation procedure, 32-bit instruction set definition and data transmission.

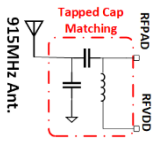

Fig. 4: Off-chip tapped capacitor mat. network.

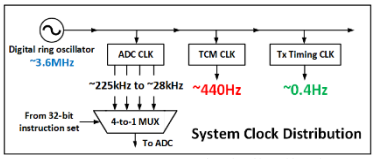

Fig. 5: System clock distribution

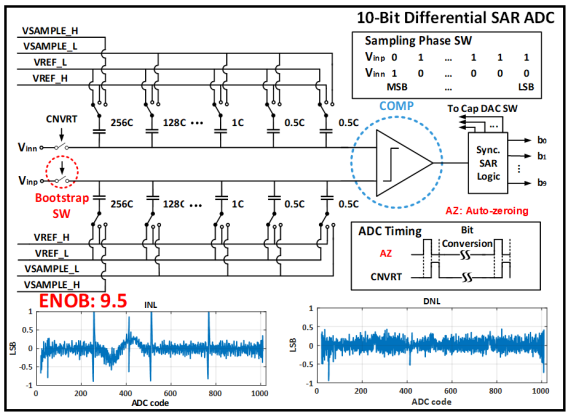

Fig. 6: 10-bit differential SAR ADC schematic and measured INL & DNL.

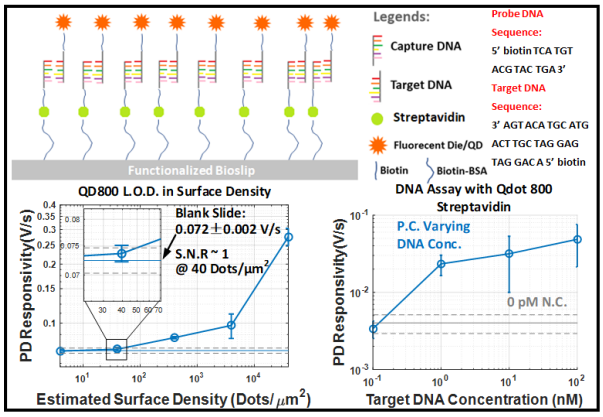

Fig. 8: DNA measurement protocol and sequences used for target and probe DNA (top). LOD measurement using QD800 and DNA assay results in positive (P.C.) and negative controls (N.C.) (bottom).

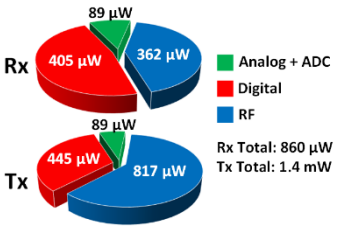

Fig. 11: Power summary in Rx and Tx Mode.

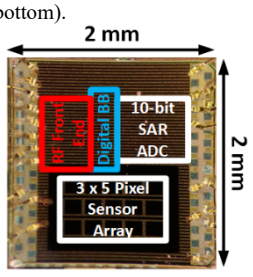

Fig. 12: Chip micrograph.