Towards a Fluoroscopic Cancer Screening Capsule for the Small Intestine

Panayiota Demosthenous* and Julius Georgiou*

Abstract

Efficient microcancer detection in the small intestine can be realised by infrared fluorescence endoscopy (IRFE). The affected areas can be visualised through that technique in conjunction with an infrared fluorescent-labeling contrast agent, which is selectively uptaken by cancerous cells. In this paper we present a screening capsule prototype that is able to measure IR fluorescence levels emitted by fluorophore indocyanine green (ICG) of different concentrations. The mixed-signal system presented has small area footprint, and very little power requirements. In-vitro experiments have shown that the system is able to detect and discriminate low concentrations of ICG in the micromolar region, which is required to detect early cancer in the small intestine.

1. INTRODUCTION

Early detection of cancer is crucial to the success of treatment and the survival of patients. One of the organs that present a diagnostic challenge, with respect to early cancer detection, is the small intestine because of its convoluted structure. Swallowable imaging capsules have been developed to address this issue [1] by offering visual access to parts of the small intestine. However, conventional white light imaging techniques rely on the examination of the physical appearance of the GI track for late diagnosis, like areas with abnormal morphological or color appearance, thus this is not always sufficient for detecting cancer at an early stage. It is expected that early detection of colorectal cancers, through an effective screening process, could cut the deaths in half, as stated in an American Cancer Society report [9].

A well known technique used for efficient microcancer detection is infrared fluorescence endoscopy (IRFE) in conjunction with an infrared fluorescent-labeling contrast agent. Specific antibodies tagged with Indocyanine Green (ICG) derivatives can label cancer cells by generating a strong enough infrared fluorescence (IRF) signal. However, this technique has, so far, been limited to use with an IRF endoscope [2].

A step in the right direction for early cancer diagnosis was the development of an endoscopic imaging system that offers additional imaging modes, i.e. autofluorescence (AFI), Narrow Band (NBI) and infrared (IRI) imaging, in addition to the conventional white light imaging [3]. Nevertheless, this is still an endoscopic system and cannot effectively access the small intestine. One capsule that targets early cancer diagnosis [4] attempts to do so with narrow band imaging. However, narrow band imaging is not sensitive to molecular probes and the sensitivity in IR fluorescence of individual pixels (5.6 um x 5.6 um) is reduced, since the photocurrent is not sufficient. Another autofluorescence-based diagnostic capsule [5] is currently too big to be practical (2.64 cm x 8.26 cm).

In this work we present a screening capsule prototype, designed specifically for IR fluorescence detection emitted from ICG fluorophore solutions of very low concentrations.

2. HARDWARE ARCHITECTURE AND IMPLEMENTATION

The presented hardware module is characterised by its small area size, low power requirements and IR fluorescence sensitivity in the range of micromolar to nanomolar ICG concentrations. Figure 1 shows both sides of the main printed circuit board (PCB). A flexible PCB is wrapped around the main PCB. Figure 1b shows the full four layer PCB, which was designed with Altium software. Standard mixed-signal design techniques were used with separated analog and digital parts, as well as different ground and power plane. The dimensions of the main body rigid PCB are 13 mm x 27 mm and the dimensions of the flexible PCB are 40 mm x 27 mm. The total diameter of the capsule system

*P. Demosthenous and J. Georgiou are with the Holistic Electronics Research Lab of the Department of Electrical and Computer Engineering and the KIOS Research Centre, University of Cyprus, 1678 Nicosia, Cyprus. (e-mail: demosthenous.panayiota@ucy.ac.cy).
Manuscript received March 17, 2014.

978-1-4244-7929-0/14/$26.00

is 13 mm.

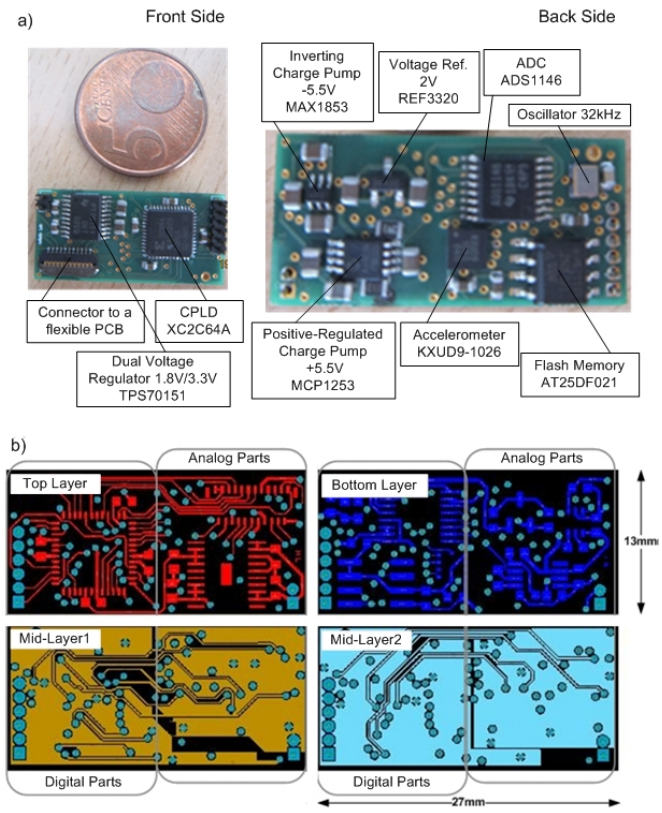

Figure 1. a) Hardware Implementation, b) Four Layer PCB.

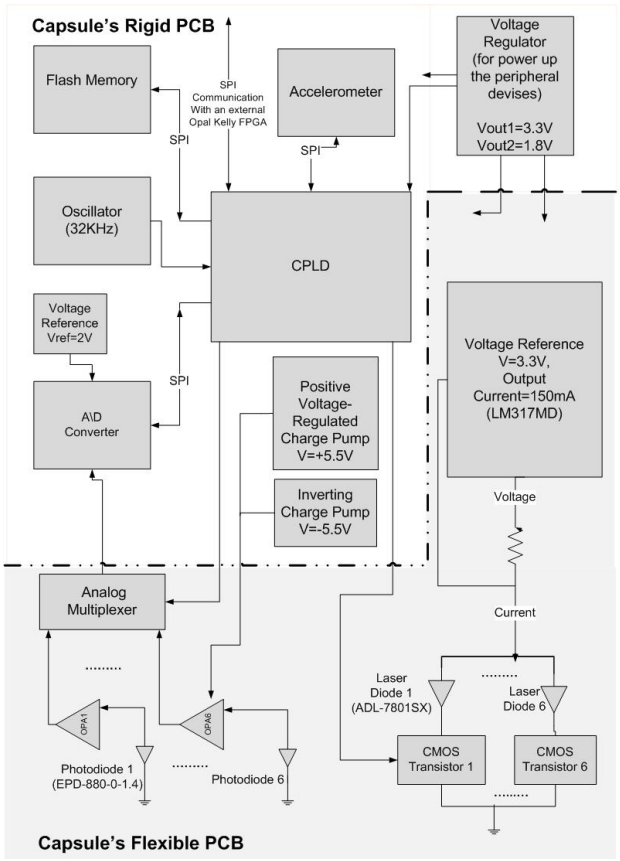

Figure 2. Hardware Architecture

Figure 2 shows the hardware architecture of the capsule, which is segmented in the flexible and the rigid PCB. The flexible PCB consists of: (1) six excitation laser diodes (LDs) with a constant current biasing module, (2) n-channel transistors for lighting up LDs one at a time, (3) detector photodiodes with their operational amplifiers and (4) an analog multiplexer. The rigid PCB consists of: (1) a sixteen bit analog to digital converter (ADC) with 2 V voltage reference, (2) a non-volatile memory module, (3) an accelerometer, (4) a complex programmable logic device (CPLD), (5) an oscillator of 32 kHz, (6) a dual voltage reference 1.8/3.3V and (7) charge pumps supplying $\pm$5.5 V for biasing the operational amplifiers required to detect the tiny photocurrent.

Indocyanine green was chosen as the IR fluorescent-labeling agent, since it has convenient optical properties. Its excitation maximum at 780 nm allows deeper penetration of the light into the tissue, providing a more thorough screening. Its emission spectrum is around 790 nm to 860 nm with an emission maximum at 810 nm. For that reason the capsule system is equipped with laser diodes with excitation wavelength at 785 nm, biased with current at 90 mA. For each LD there is a corresponding photodiode with a large active area (1.2 mm^2) for the detection of ICG fluorescence. The large active area gives high sensitivity and high signal-to-noise ratio. Furthermore, each photodiode has an integrated optical long-pass filter with a cut-off frequency of 800 nm, to prevent the high-intensity excitation light from reaching the detector. Thus the resulting photocurrent is mainly produced by fluorescent light.

Figure 3 shows the timing diagram of the system. Laser diodes flash in sequence every one second with a pulse duration of 1 ms. A corresponding photodiode senses the fluorescence and produce a photocurrent which is amplified and multiplexed to an ADC. Each time that a LD is lit up, an analog to digital conversion takes place and the binary data are extracted from ADC through an Serial Peripheral Interface (SPI) Bus. Next, the digitalized data are stored to a flash memory. SPI Master modules are included in the CPLD code, in addition to a clock divider and a system controller. One of the task of the controller is to regulate the sampling rate of the capsule, which moves slow the most of the time (average velocity of intestine peristalsis is 0,5 mm/s). During rapid movement, acceleration infor-

mation is used to increase the sampling up to 0.1 s and thus, ensure a thorough scan of the gastrointestinal tract, whilst consuming less power than the fixed sampling rate used in existing capsules [6]. When the screening procedure is accomplished, the data are extracted from the capsule system to an external Opal Kelly FPGA board through SPI interface, and further are recovered to a .bin file through USB interface.

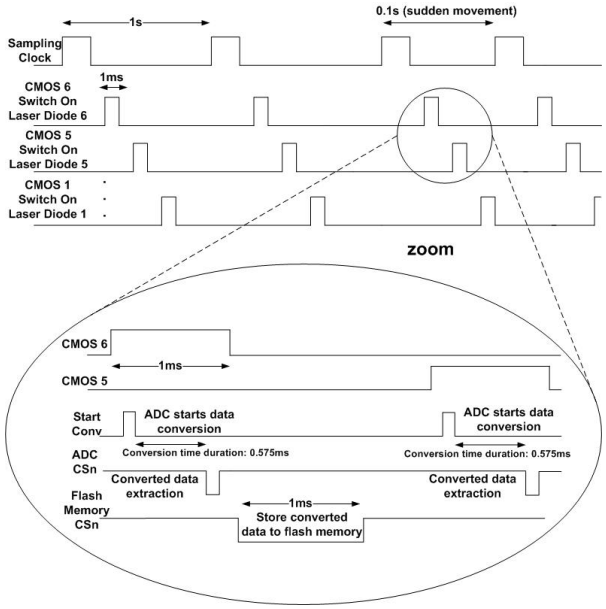

Figure 3. Timing Flow Diagram

3. EXPERIMENTAL RESULTS

The main and the most important functionality of the presented system is the ability to detect increased levels of fluorescence. That functionality will provide a system able to detect and discriminate future-developed molecular ICG contrast agents which are selectively absorbed by cancerous cells. Inayama et al. [7] present the development of an indocyanine green derivative used as an infrared fluorescent labelling substance for the detection of microlesions by an IR fluorescence endoscopy. They show that human gastric cancer tissues stained with different concentrations of ICG in the range of 125nM (0.1ug/ml) to 12.5uM (10ug/ml) can provide sufficient fluorescence intensity.

In-vitro experimental results are shown in Figure 4. The presented system is able to detect the range of concentrations of ICG that are required to detect early cancer in the small intestine. Furthermore, the measurements made with the capsule agree with previous literature on the fluorescence of low concentrations of ICG [8].

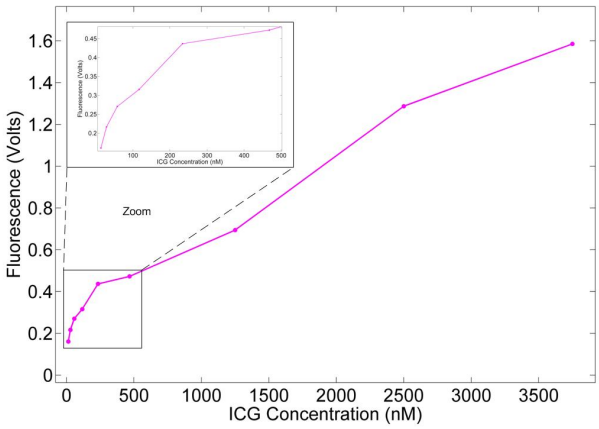

Figure 4. Fluorescence Vs. ICG Concentration

4. SYSTEM POWER CONSUMPTION ANALYSIS

For a complete small intestine screening system, six laser diodes are required to be placed in a ring structure with beam divergence of 60 degrees. During fast movements an increased sampling rate of 10 circular scans per second (csps) is used. If we assume that this rate is only required 1/8-th of the time, 1 circular scan per second would be sufficient for the remaining time, as the average velocity of intestine peristaltic movement is around 0.5 mm/s. Then, the equivalent sampling rate for this capsule is $(1/8)10csps + (7/8)1csps = 2csps$. Thus, the sampling rate of 2 circular scans per second corresponds to 12 fluorescence data per second.

The power consumption analysis of a complete system is shown in Table 1. Some of the procedures do not need continuous operation to be executed, allowing less power consumption for the system. Analog to digital conversion requires approximately 0.7 ms to complete, thus conversion of 12 fluorescence data requires 8.4/1000 of a second, corresponding to 3.53 uA of current consumption. For the remainder of the time, the ADC (ADS1146) operates on sleep mode with lower current consumption at 0.3 uA. Similary, the flash memory (AT25DF021) requires approximately 12/1000 of a second to store twelve data of sixteen bits with current consumption at 12 mA. However, in sleep mode it consumes 51 uA. In addition, fluorescence amplification runs simultaneously with the excitation that lasts approximately 1 ms, thus the voltage regulators (MAX1853 and MCP1253) that power up the amplifiers (OPA129UE4) are in operation mode for a period of 12/1000 of a second, consuming a current of 2.7 uA. While the amplifiers are in operating mode, they consume a current of 14.4 uA. Higher current consump-

Table 1. Capsule System Power Consumption Analysis.

Component	Operating Mode	Sleep/Shutdown Mode	Consumption
AT25DF021	(12*1ms/1000ms)*12mA=144uA	(988ms/1000ms)*51uA= 50.39uA	194.39uA
ADS1146	(12*0.7ms/1000ms)*420uA=3.53uA	(991.8ms/1000ms)*0.3uA= 0.29uA	3.83uA
MAX1853	(12*1ms/1000ms)*165uA=1.98uA	(988ms/1000ms)*0.5uA= 0.49uA	2.47uA
MCP1253	(12*1ms/1000ms)*60uA=0.72uA	(988ms/1000ms)*0.1uA= 0.09uA	0.81uA
OPA129UE4	(12*1ms/1000ms)*1.2mA=14.4uA	-	14.4uA
Laser Diodes	(12*1ms/1000ms)*90mA=1080uA	-	1080uA
CPLD	50uA(at 32kHz)	-	50uA
REF3320	3.9uA	-	3.9uA
KXUD9	220uA	-	220uA
Oscillator	1.5uA	-	1.5uA
LM317MD	50uA	-	50uA
SN74LV4051AT	20uA	-	20uA
TPS70151	230uA	-	230uA
Total Current			1871.3uA

tion occurs when the laser diodes switch on with a bias constant current at 90 mA. The total current consumption of six LDs with pulse duration of 1 ms and average sampling rate 2 csps is approximately 1 mA. The rest of the devices (CPLD, REF3320, KXUD9, oscillator, LM317MD, SN74LV4051AT, TPS70151) are in continuous operation with current consumption at approximately 575 uA. Therefore, the total current consumption is estimated at 1.9 mA, allowing the system to run for almost 32 hours with silver-oxide SR45 batteries of 60 mAh capacity (mean value screening duration is around 8 hours).

5. CONCLUSION

In this paper a fluoroscopic cancer screening capsule prototype is proposed for the detection of ICG based contrast agents for microcancers in the small intestine. The presented endoscopic capsule is unique in that it is not constrained to the extremities of the intestine, like endoscopes. Furthermore, by using the near infra-red spectrum, this capsule can detect early stage cancers as opposed to existing white light endoscopic capsules. The variable sampling rate methodology reduces current consumption to 1.9 mA and allows the system to function continuously, for almost 32 hours, which is adequate for screening the entire small intestine. Moreover, by storing only pertinent data locally, there is no need for an external belt to collect data intensive images. Actual measurements show that the proposed system is able to distinguish low concentrations of ICG with higher resolution at micromolar concentrations.

References

[1] C. O'Loughlin and J.S. Barkin, "Wireless capsule endoscopy: summary.", Gastrointest Endosc Clin North Am., 14: 229-237, 2004.

[2] M. Tadatsu, S. Ito, N. Muguruma, Y. Kusaka, K. Inayama, T. Bando, Y. Tadatsu, K. Okamoto, K. Ii, Y. Nagao, S. Sano and H. Taue, "A New Infrared Fluorescent-Labeling Agent and Labeled Antibody for Diagnosing Microcancers. ", Bioorganic and Medicinal Chemistry 11: 3289-3294, 2003.

[3] K.Gono and Olympus Medical System Corp., "Novel Multifunctional Endoscopic Imaging System for Support of Early Cancer Diagnosis. ", IEEE, 2007.

[4] D. Lan-Rong and W. Yin-Yi , "A Wireless Narrow-Band Imaging Chip for Capsule. ", IEEE, 2009.

[5] M. Kfouri, O. Marinov, P. Quevedo and N. Faramarzpour, "Toward a Miniaturized Wireless Fluorescence-Based Diagnostic Imaging System. ", IEEE Journal of Selected Topics in Quantum Electronics 14: 1, 2008.

[6] P. Demosthenous and J. Georgiou, "Acceleration-dependent Sampling for Ingestible Endoscopic Imaging Capsule. ", BioCAS, Biomedical Circuits and Systems Conference, IEEE, 2012.

[7] K. Inayama, S. Ito, N. Muguruma, and Q. Zhu, "Basic study of an agent for reinforcement of near-infrared fluorescence on tumor tissue,", Digestive and Liver Disease, vol. 35, pp. 88?93, 2003.

[8] B. Yuan, N.G. Chen and Q. Zhu "Emission and absorption of indocyanine green in intralipid solution. ", J. Biomed. Opt. 9(3):497-503,2004.

[9] American Cancer Society. Cancer Prevention and Early Detection Facts and Figures 2013. Atlanta: American Cancer Society; 2013.