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Nanotechnology in Multimodal Theranostic Capsule Endoscopy

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***Abstract*— Video capsule endoscopy (VCE) has become a clinically accepted diagnostic modality in the last 20 years and has established a technological roadmap for other capsule endoscopy (CE) devices, incorporating microscale technology, a local power supply and wireless communication. However, VCE does not provide a therapeutic function and research in therapeutic capsule endoscopy (TCE) has been limited.**

This paper proposes a new route towards viable TCE based on multiple CE devices including essential nanoscale components. A first device is used for multimodal diagnosis, with quantitative microultrasound as a complement to video imaging. Ultrasound-enhanced fluorescent marking of sites of pathology allows follow-up with a second device for therapy. This is based on fluorescence imaging and ultrasound-mediated targeted drug delivery. Subsequent treatment verification and monitoring with a third device exploits the minimally invasive nature of CE.

Clinical implementation of a complete patient pathway remains the subject of research but several key components have been prepared in early prototype form. These are described, along with gaps that remain to be filled.

I. Introduction

Conventional endoscopy through oral and anal routes, respectively, provides routine access to the upper and lower parts of the gastrointestinal (GI) tract. Whilst these techniques are minimally invasive, subjects must attend hospital, require sedation, and have the procedure administered by highly skilled clinicians. Assessment of the full length of the GI tract with double-balloon enteroscopy is possible, but this is a non-routine procedure performed only in large healthcare centres.

Video capsule endoscopy (VCE) [1] has been developed, introduced and accepted as a routine clinical procedure in the past 20 years. It is based on three areas of innovation linked to work in other fields: miniaturization of cameras and related electronic circuitry; minimal power consumption from a local battery; and wireless communication with a data logger. A fourth innovation, automated information extraction and interpretation is still a topic of research. Additionally, localization with accuracy compatible with targeted therapy remains impossible.

Conventional optical endoscopy is now allied with multiple additional diagnostic modalities. Of these, ultrasound (US) has been argued to be most important [2] since it permits subsurface imaging of optically-opaque tissue. Its implementation is based on its nature as a safe, inexpensive, real-time technique deployed at the point of care. Resulting data have been shown to be amenable to quantitative analysis in some situations and it carries therapeutic potential through ultrasound-mediated targeted drug delivery (UmTDD).

II. Proposed Patient Pathway

Important components in a multimodal diagnostic CE device include sensing and actuation devices, a battery power supply, and wireless communication circuitry and an antenna. A therapeutic device must additionally include a reservoir and release mechanism for the nanotechnological therapeutic agent and a targeting mechanism is likely to be essential for non-systemic therapies. The form of a typical CE device is a cylinder with spherical ends, overall length 30 mm, diameter 10 mm [3]. Hence, a solution comprising two or more separate devices in a theranostic combination may be needed to accommodate the proposed functions. This has the additional advantage that clinical validation may be incorporated in the procedure at the diagnostic stage, prior to therapy.

The proposed patient pathway begins with a patient presenting with indications of a condition such as Crohn's disease. The patient is subject to conventional diagnosis and a diagnostic CE device is administered if the diagnostic outcome is positive. This device generates optical and microultrasound (μUS) data identifying disease sites within the GI tract through quantitative analysis working at the nanoscale. These sites are marked with fluorescent nanoparticles using an US-mediated process. By reviewing the results manually, a clinician validates the diagnosis then administers a therapeutic CE device. This device can detect fluorescent markers but does not require diagnostic or more than minimal communication capabilities. Instead, available volume is used for a reservoir of a nanotherapeutic agent, a release mechanism, and US components to drive the agent towards the target and permeabilize the tissue to enhance uptake.

Subsequently, a further CE device can be administered to verify disease response. The ability of CE devices to penetrate the full length of the gut in a minimally invasive manner thus allows closed loop diagnosis and therapy.

III. Relevant Results

Preliminary results have been obtained for some of the stages in the outline procedure and the prototype CE devices from which these results were obtained have demonstrated key components though the need for a local power supply and wireless communication was avoided with multimodal tethers.

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Nevertheless, the prototype CE devices themselves conform to the maximum dimensions set by current clinical practice.

A. Microultrasound Diagnosis and Quantitative Analysis

μUS uses frequencies above the conventional diagnostic upper limit of 20 MHz. Through its reduced wavelength, it has been demonstrated that such high frequencies provide direct access to ultrasonic effects resulting from scattering from nanoscale acoustically-contrasting features. Following early results [4], an exploratory program based on μUS scanning of porcine tissue *ex vivo* with a typical frequency of 47 MHz is under way and has shown that the distinct layers within the GI tract can be imaged. The highly specialized single-element transducers for this work used 1-3 connectivity piezoceramic - polymer composite material made with micromoulding and casting processes. To avoid US artefacts whilst maintaining the sensitivity inherent in piezocomposites, these materials were designed with pseudo-random ceramic phase patterns [5]. These allow higher than usual frequencies to be achieved with viable ceramic dimensions. Additionally, successful *in vivo* testing has begun, with simpler piezopolymer transducers.

To progress towards automated diagnosis, quantitative analysis of the scan data has been explored [6], focusing on measurement of acoustic impedance, attenuation and backscattering, with promising results presented in this paper.

B. Fluorescence Marking and Imaging

To explore the marking process [7], experiments were performed on *ex vivo* murine and porcine tissue using fluorescent CdSeS/ZnS quantum dots (QDs) (Sigma-Aldrich, USA). These were directed towards the focal zone of a miniature high intensity focused US (HIFU) transducer operating at 4 MHz. The results presented in this paper show preferential concentration where the US was applied.

In the work outlined here, fluorescence imaging was based on the configuration of single-photon avalanche diode (SPAD) arrays with bespoke application-specific integrated circuits (ASICs) in miniaturized configurations for capsule deployment [8]. Successful demonstrations of both imaging and miniaturization are demonstrated.

C. Therapeutic CE Device Feasibility

To determine if the HIFU components for UmTDD can be incorporated in CE, and the extent of their capabilities, a prototype device was constructed. This included a confocal arrangement of: a HIFU source (Meggitt Sensing Systems, Kvistgaard, Denmark), diameter 4 mm, focal distance 6 mm, frequency 4 MHz; a miniature white light camera (Micro ScoutCam 1.2, Medigus, Omer, Israel), length 5 mm, diameter 1.2 mm; and a delivery channel for agents mimicking drugs and drug-delivery vehicles [9].

The prototype demonstrated that a stream of microbubbles could be directed towards a target based on US radiation force from the HIFU transducer, with an excitation level of 8 V_{pp}, compatible with the voltage amplitude that may be available in a CE device. Measuring transepithelial resistance in a model of the wall of the GI tract using Caco-2 cell monolayers showed that the same transducer with similar excitation levels could influence uptake *in vitro* [9].

D. Ultrasound-mediated Targeted Drug Delivery

A typical use for the clinical procedure outlined above is to deliver drugs to treat localized disease within the GI tract in a targeted manner. With UmTDD, this involves three mechanisms [10]: packaging of the drug to passivate it so that systemic effects will be reduced; physical direction of the packaged drug towards the treatment site; and reduction in the permeability of the target to enhance uptake. Additionally, it may be necessary to disrupt the drug - package complex so that the drug may be released and taken up by cells.

An approach explored by the authors is to combine a drug with a nanoscale, chemically-engineered package. This is demonstrated through work on the creation of a chemical complex comprising the chemotherapeutic drug doxorubicin (Dox) and γ-cyclodextrin. With Dox on its own as a control, it is shown that the chemical complex has a reduced effect on cells *in vitro* whereas mildly hyperthermic and cavitational effects of US compatible with use in the GI tract enhanced the effect of the drug when applied as a nanoscale complex [11].

IV. CONCLUSIONS

A potential theranostic strategy for treatment of diseases of the GI tract based on the use of nanotechnology combined with CE has been outlined. This relies on US analysis of targets at the nanoscale, marking with nanoscale agents and delivery of nanoscale drug complexes for treatment. The clinical procedure involves multiple steps with development relying on multidisciplinary research. Progress in several directions is presented in this paper and further work is under way to demonstrate the viability of the procedure.

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