Sensors and Actuators A 245 (2016) 180–188

Contents lists available at ScienceDirect

Sensors and Actuators A: Physical

journal homepage: www.elsevier.com/locate/sna

Component based design of a drug delivery capsule robot☆

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ARTICLE INFO

Article history:
Received 30 December 2015
Received in revised form 4 April 2016
Accepted 13 April 2016
Available online 6 May 2016

Keywords:
Surgical robotics
Medical cyber-physical systems
Drug delivery
Medical Capsule Robots
Design environment
Embedded micro-systems

ABSTRACT

Since the introduction of Wireless Capsule Endoscopy (WCE) researchers have started exploring the design space of Medical Capsule Robots (MCRs): embedded micro-systems that can operate autonomously within the human body and can diagnose, prevent, monitor, and cure diseases. Although the research in the area of MCRs is an active topic and has grown exponentially, current devices provide only limited functionalities because their design process is expensive and time consuming. To open this research field to a wider community and, at the same time, create better designs through advanced tool support, in our previous works we presented a design environment for the rapid development of MCRs. In this paper, this environment was adopted to design a Drug Delivery Capsule (DDC) based on a coil-magnet-piston mechanism. The force of the coil acting on the magnetic piston and the drug release profile were modeled and assessed on bench-top with a maximum relative error below 5%. Then, *in vivo* trials were performed to validate the DDC functionality with a scheduled drug release profile for a 5 h and 24 min procedure. The resulting design environment template is available open source for further development of drug delivery applications as well as to serve as guideline in prototyping novel MCRs addressing other clinical needs.

1. Introduction

The introduction in year 2000 of the PillCam by Given Imaging [1] showed that embedded micro-systems can be used to reach the more remote regions of the human Gastrointestinal (GI) tract. Since then, millions of patients have swallowed this self-contained wireless camera to get a non-invasive diagnosis of diseases in the small intestine. Unfortunately, this approach is not effective for other districts of the GI tract, such as the colon and the stomach, where more deadly forms of cancer usually develop [2]. The main reason for this is related to the lack of advanced functionalities, such as active locomotion [3], advanced diagnosis and tissue manipulation [4], biopsy sampling [5], or drug delivery [6].

In recent years, the research community has addressed this issue by developing a number of robotic smart capsules, referred in this paper as Medical Capsule Robot (MCR). MCRs typically enter the human body through natural orifices or small incisions and can perform endoscopy and surgery by interacting with the surrounding environment with sensors and/or actuators.

The design process of MCRs however is challenging because it has to address severe cross-cutting constraints such as size (to gain non-invasive access, MCR diameter is limited to about 1 cm), power consumption (limited space for battery is available onboard), and fail safe operation (MCR operates deep inside the human body). Therefore, MCR design and development requires significant skills and efforts in embedded systems, miniaturized electronics, packaging, debugging, and mechanical miniaturization of the device. Custom circuit boards and mechanical enclosures have to be engineered, which makes MCR development an expensive and time consuming process that is only accessible to a limited number of groups in the research community [7].

Because many of the MCRs developed in the past share equivalent hardware and software components such as specific sensors, data processing, actuation, and wireless communication, we believe that it is indeed possible to systematize the design of MCRs. This would lower the barrier of entry to this field to research groups that do not have the resources to develop MCRs from the ground up.

In our previous works, we presented our contributions towards the creation of an environment for the rapid design and development of MCRs [7–9]. The basic elements of the integrated design

☆ Selected paper from EUROSENSORS 2015 conference, September 6–9, 2015, Freiburg, Germany.

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http://dx.doi.org/10.1016/j.sna.2016.04.035
0924-4247/

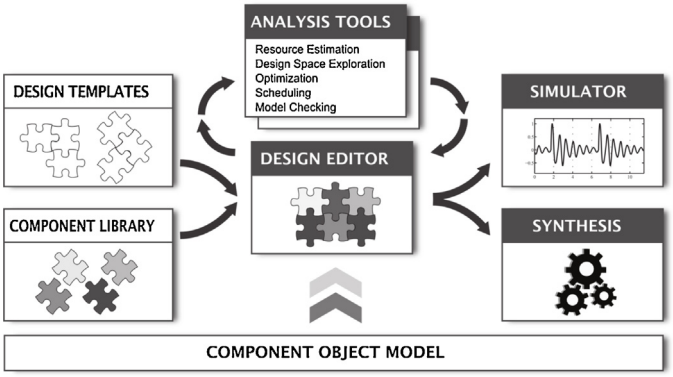

Fig. 1. The elements of the integrated design environment for MCR.

environment are shown in Fig. 1. At the time of writing, the design environment includes a library of hardware modules built up from our experience with existing capsule designs [10]. The hardware components include fundamental elements of MCR design such as sensors (inertial sensors, encoders, vital sign sensors), actuators (DC motors, coils, illumination, servo motors, stepper motors), batteries and voltage regulators, wireless transceivers working at different carrier frequencies, and microcontrollers (MCUs), which serve as building blocks for the system. A flexible backbone enables plug-n-play connectivity of up to six hardware modules. Each of the hardware modules is coupled with a software component and integrated in an open-source web environment available at `pill-forge.github.io` for the developer to implement specific MCR applications.

In this work, we present how the design environment can be adopted to develop a Drug Delivery Capsule (DDC) based on a coil-magnet-piston mechanism for controlled deployment of drug doses over time. As a result of this work, we have created a design template for the DDC. This template aims to provide MCR researchers a solution that shortens the development time of new DDCs based on the same or a similar actuation principle. Template parameters such as the drug viscosity and deployment schedules can be adjusted according the specifics of the application. The force exerted by the coil-magnet-piston mechanism and the drug release profile over time have been modeled and characterized experimentally. Beyond the specific application of controlled drug delivery, this work also illustrates how the open-source design environment we have developed can be used to rapidly design an MCR.

This paper is organized as follows: Section 2 briefly presents the state of the art for drug delivery MCRs, Section 3 illustrates the mechanical, electrical, and embedded firmware and software design considerations for the developed MCR. This section also describes the design environment and the design template that have been created for the MCR. Section 4 presents the experimental assessment on bench and *in vivo* results. Sections 5 and 6 include respectively a discussion and conclusions.

2. Clinical motivation for drug delivery systems

The formulation of drugs that allow for reproducible absorption profiles for targeting specific areas of the GI tract represents a major bottleneck in current development of orally administered medications [11]. This is mainly due to unpredictable gastric transit time and physiochemical characteristics of the GI tract that differ from patient to patient [12].

The availability of a controllable drug delivery systems (DDS) may reduce toxicity associated with systemic administration and prevent the formation of antibodies to drugs, particularly in the case of colon cancer or inflammatory bowel disease therapies [13]. These are two extremely common diseases, with colorectal cancer being the second leading cause of cancer-related deaths in USA [14], while Crohn's disease and ulcerative colitis – both inflammatory bowel diseases – being diagnosed in 201 and 238 per 100,000 people in the USA, respectively.

Controllable MCRs targeting drug release have been developed for therapeutic treatment of diseases in the GI tract [6,15] as well as for drug absorption studies [16]. Although some devices are already commercially available, such as the IntelliCap [17], the InteliSite [18], or the Enterion capsule [19], they cannot implement an intelligent release algorithm due to the lack of real-time localization and active position control. Several MCRs have been proposed to address these limitations. Yim et al. [20] developed a magnetic locomotion system that can collapse under magnetic guidance and is able to deploy a liquid drug. Kim et al. [21] proposed a three-axis Helmholtz coil capsule which moves with a rotational motion and deploys a drug. Woods et al. [22] integrated a holding mechanism inside the capsule to resist to peristalsis and a needle for local drug deployment. The MAARS capsule, presented in [23], is composed of magnetic semi-hard modules and deploys a single shot of drug upon a demagnetization process. Yo et al. [24] recently proposed an MCR where the drug release can be triggered through a reed switch. Finally, Hafezi et al. [25] developed an ingestible sensor that allows patients, families, and physicians to monitor prescription compliance and drug-adherence patterns in real time.

While each of these capsules taken alone solves a specific problem, none of them offers a complete solution to achieve an intelligent release of a drug on a specific target. In order to do that, multiple functionalities need to be combined and several design iterations need to be tested. Thanks to the modular approach adopted in this work, we have done a first step in that direction by implementing a controllable mechanism for drug release and an intelligent scheduler. These components take only part of the available slots on the flexible circuit backbone, leaving space for adding other functional modules, such as localization and/or active position control.

3. Design consideration

3.1. Principle of operation – mechanism consideration

Referring to Fig. 2, where the principle of operation of the MCR is presented, the DDC mechanism consists of a drug chamber, two coils, and the magnetic piston. The drug chamber (d = 7.94 mm, l = 6.35 mm, volume = 314.42 mm^3) is hosted in a cylindrical enclosure together with an axially magnetized cylindrical permanent magnet acting as a piston (D54-N52, K&J Magnetics, USA). The DDC shell and the drug chamber were prototyped with an Objet30 3D printer (Stratasys, USA) with Vero white material. The clearance between the outer diameter of the magnetic piston and inner diameter of the chamber was 0.4 mm. This value guaranteed a low friction with the magnet, resulting in no leakage of the drug and the actuating mechanism. The distal collar edge of the chamber has twelve circular holes (each with a radius of r_h = 0.8 mm) from where the drug is released into the environment. The number of holes and their radius has been chosen such that the drug is deployed uniformly without being affected by capillarity. In case the application requires a drug with a different viscosity, the number of holes as well as their dimension can be adjusted. The combination of proper drug viscosity and aperture size prevents the drug from leaking for any possible orientation of the capsule. Bench trials showed that the proposed design is able to deploy solutions with a viscosity up to 1000 cP, which is higher than water (0.89 cP), blood (between 3 and 4 cP) and air (0.018 cP).