

Development of a swallowable diagnostic capsule to monitor gastrointestinal health

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Introduction

Biomolecular mapping within the gastrointestinal tract may offer advantages for the detection and management of disease but is hindered by access. Here we present a swallowable diagnostic capsule for in situ biomolecular detection based on a localization technology, a miniaturized fluorometric reader, wireless communications and physician medical application (PMA). As a proof of concept, we have developed a smart capsule bacterial detection system (SCBDS) designed to act in the aid of the diagnosis of small intestinal bacterial overgrowth (SIBO).

SIBO is a clinical condition associated with abnormally high bacterial counts in the small intestine and clinical features such as diarrhea, constipation, abdominal pain, distension and bloating. It is estimated that SIBO may be as prevalent as up to 20% in healthy populations, up to 67% in celiac disease, up to 88% in Crohn's disease, and up to 44% in diabetics. SIBO is

under-diagnosed and significant limitations exist with currently available diagnostic testing methods. Current diagnostics include aspiration and culture of proximal jejunal contents (which is invasive, costly and has low reproducibility due to the nature of sampling culture techniques), and the potential use of breath testing techniques as an indirect, non-invasive, commonly used alternative to direct aspirate culture endoscopy.

There is currently no suitable gold standard for the evaluation of SIBO, but a systematic review suggests that $\geq 10^5$ Colony Forming Units (CFU) bacteria per mL by aspirate and culture of proximal jejunal contents is a generally accepted reference standard. Given the invasive nature of endoscopy and aspiration of the jejunum, problems with sample contamination, difficulty culturing bacteria, lack of reproducibility, lack of appropriate training, and cost, there is consensus that novel tools are needed.

Smart capsule bacterial detection system (SCBDS)

- The SCBDS system consists of three main components: a capsule, wearable receiver (WR), and PMA. The three components have no physical connections between them, but instead communicate wirelessly (Figure 1).
- The capsule is a single use device swallowed by a patient with symptoms supportive of suspected SIBO. The capsule is approximately the size of a capsule endoscopy device with domed radii for ease of swallowing (Figure 2).
- The capsule contains an integrated assay which measures live bacteria in the sample. The kinetic fluorescent signal measured within the capsule is transmitted to the WR on the patient.
- The capsule can determine its location within the gastrointestinal tract and takes a sample when the capsule localization mechanism determines it is in the jejunum. The fluid in the jejunum is sampled through the opening of a valve on the surface of the capsule, exposing a sample wick to saturate the internal assay sponge.
- The WR contains a call algorithm which converts the signal to a bacterial concentration and positive or negative SIBO indication. The results of the assay are communicated wirelessly from the receiver to the PMA on a smart phone or computer for review by the treating physician.

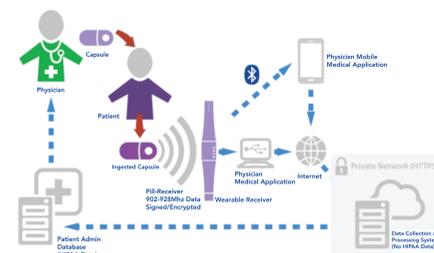


Figure 1: High-level overview: Smart Capsule Bacteria Detection System (SCBDS)



Figure 2: Exterior view of the capsule with key subsystems (left) and early prototype capsule (right)

Autonomous Capsule Localization

- The sensor array and algorithm for determining capsule location is composed of radial light emitting diodes (LEDs)/photodiodes pairs that function as reflectance sensors, as well as a temperature sensor and oscillator for keeping time.
- The device software keeps track of all measurements and events, storing each within device memory and applying an onboard algorithm to determine the device's location.
- The emission angles of the LEDs as well as their physical placement within the capsule allow for sensing large changes in reflectance around the capsule.
- The reflectance data from the radial reflectance sensors are used by the onboard microprocessor and algorithm to identify the capsule's location in the GI system by accurately identifying key anatomical landmarks (Figure 3).

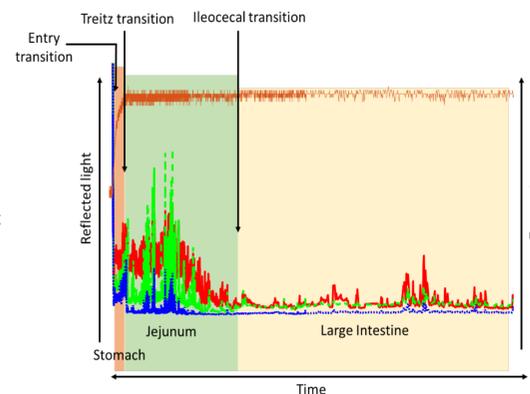


Figure 3: Plot of average radial LED response (red, green, and blue lines) and temperature (orange line). Algorithmic detection of transition through anatomical structures (Entry Transition, Treitz Transition and Ileocecal Transition) provides current anatomical location of the capsule (esophagus/stomach, jejunum and caecum) within the gastrointestinal tract. A description of algorithm states and function is detailed on the right.

Sampling and Mucosal Fluid

- Once the localization algorithm determines that the capsule is in the jejunum, sample collection starts by opening a valve and exposing a wick.
- The valve is located on the radial surface along the axial length of the capsule to allow for the sample to be taken as close to the mucosa as possible. The sample moves along the wick into the assay chamber.
- The assay chamber is built into the polycarbonate structure of the device and contains an assay matrix on which a bacterial load assay is performed.

Total Bacterial Count Assay

- The capsule contains an integrated fluorescence-based assay to measure live bacteria. This data is subsequently interpreted by the electronics subsystem, specifically, the SIBO +/- call algorithm, to make a positive or negative call based on the signal.
- The capsule transmits the acquired data in an encrypted format via a radio frequency communication channel to the WR.

SIBO Call Algorithm

- The gold standard for the diagnosis of SIBO is generally agreed to be $\geq 10^5$ CFU/mL of total bacteria in jejunal fluid (Khoshini, 2008). Bacterial counts $\geq 10^5$ CFU/mL indicate positive SIBO and counts $< 10^5$ CFU/mL indicate negative SIBO.
- Figure 4 shows examples of the measured Relative Fluorescence Unit (RFU) responses for three bacteria commonly found in the GI tract. Different colors in the figure correspond to different input amounts of microbes (CFU) in replicate.
- To classify the bacterial count, we developed a machine-learning SIBO call algorithm based on key features of the RFU kinetics.
- All features are pre-calculated and then fed into the automatic call algorithm to judge whether each sample was SIBO positive or negative.

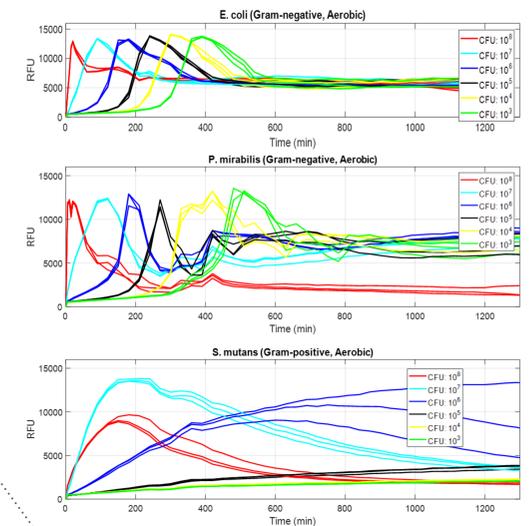


Figure 4: RFU response from various bacteria at different CFU levels

Wearable Receiver

- The WR is an external receiving and recording unit that receives and stores the acquired data from the capsule and uploads it to the PMA.
- The WR is paired with a capsule prior to ingestion of the capsule in a clinical setting. The WR also contains a transceiver and antenna for communications with the capsule, and a transceiver and antenna for communications with the PMA.
- The WR is intended to be worn continuously by a patient from the time the capsule is ingested until the SIBO assay is complete. Once ingested, the capsule periodically communicates wirelessly with the WR to report on status and other operational data.
- The WR uses the SIBO call algorithm to determine the bacterial concentration. The WR prototype is approximately the size of a small pager, and may be worn discreetly on a belt, in a pocket, or on a lanyard (Figure 5).
- The WR is powered by a rechargeable lithium-polymer battery, with integrated wireless power transfer antenna and battery charge.



Figure 5: Wearable receiver used in early clinical trials

Summary and Conclusion

SIBO is under-diagnosed and significant limitations exist with currently available diagnostic testing methods. The effectiveness of breath testing in evaluating SIBO is limited as there is no consensus on methodology, there are confounding factors to accurate measurement, sensitivity and specificity are limited, and the technique is not FDA approved for evaluation of SIBO. As a result, patients with SIBO are poorly served.

We developed the SCBDS to serve this unmet need by providing an aid to the diagnosis of SIBO that would offer the sensitivity and reproducibility of the aspirate and culture method but delivered with the comparable turnaround time, cost and non-invasive nature as the breath test. Currently the SCBDS system has undergone a series of validation and verification tests of the various subsystems including full Clinical Laboratory Standards Institute (CLSI) verification of the assay and a clinical evaluation of the localization algorithm.

Finally, the assay and call algorithm have been evaluated ex vivo in an ongoing prospective human clinical trial. The SCBDS system represents a powerful new tool to aid in the diagnosis of SIBO. As well, we believe this is the first autonomous swallowable diagnostic capsule capable of targeted sampling, biomolecular analysis and real-time external communications representing a potential breakthrough in the ability for clinicians to diagnosis, treat and monitor digestive diseases.

References

Khoshini et al. A systematic review of diagnostic tests for small intestinal bacterial overgrowth. Dig Dis Sci. 2008 Jun;53(6):1443-54.

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