SepsPIC: Rapid, Simultaneous Detection of Sepsis Biomarkers in Patient Serum Using Serial Al_2O_3 Microring Resonators

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Biosensor research aims to create faster, more affordable, and sometimes more accurate alternatives to conventional diagnostic assays that often require costly materials, experienced operators, and lengthy protocols. A tool that detects multiple biomarkers within 30 minutes could transform treatment for sepsis. We propose SepsPIC which will be described in this article as a multiplexed biosensor system based on a photonic integrated circuit using aluminum oxide waveguide technology, developed at the University of Twente. This sensor leverages micro-ring resonators with parallelizing several micro-rings on the same bus waveguide to detect multiple biomarkers in less than 30 minutes. The system, integrated with AI-based analysis, is expected to enable rapid diagnostics and personalized treatment for sepsis patients. It also provides a tool for further Sepsis research.

Introduction

Every four seconds, someone in the world dies of sepsis. Two percent of hospital admissions are due to sepsis [1]. Next to the enormous societal impact, sepsis also has a huge economic impact, with intensive care (ICU) costs of ~170 M/year and indirect costs of ~3.4 B/year in the Netherlands alone. The risk of mortality due to sepsis increases by 7% per hour [2].

Sepsis is both widespread and associated with significant morbidity and mortality, yet defining it and its related conditions remains a complex challenge [3]. The latest agreement is to define it as “life-threatening organ dysfunction due to a dysregulated host response to infection” [4].

Effective treatment of acute diseases hinges on prompt recognition and informed clinical decision-making. However, current diagnostic tools fall short of this goal: biomarker assays are typically performed in centralized labs with costly equipment, which limits access to rapid testing and offers limited multiplexing capabilities. This gap is especially critical in acute conditions like sepsis, where diagnostic delays can be life-threatening. A simultaneous, comprehensive biomarker analysis could not only enable the swift and accurate diagnosis of sepsis but also predict responses to specific treatments. Moreover, the clinical questions that need to be addressed for patients with suspected sepsis are multiple, and include the question whether the patient has an infection, whether this is bacterial or viral and what the risk of deterioration is.

SepsPIC is a multiplexed biosensor using a photonic integrated circuit (PIC) with aluminium oxide waveguide technology from the University of Twente [5]. This sensor employs multiple micro-ring resonators on a single bus waveguide to detect multiple biomarkers from just a few drops of blood in under 30 minutes. Integrated with AI-based analysis, it enables rapid diagnosis and personalized treatment for sepsis patients. The prototype is supposed to be ready by summer 2026.

Transducer: serial microring resonators

At the core of sepsPIC is a photonic integrated circuit (PIC) sensor, based on the aluminum oxide technology developed at the Integrated Optical Systems (IOS) group, University of Twente. The sensor is based on individually addressable micro-ring resonators on a single bus waveguide. This chip provides the demand for sensitivity, multiplexing, and speed of the device.

Microring resonators (MRRs) operate by sensing changes in the resonance frequency of a ring structure. When the surfaces of MRRs are functionalized with capture probes, and biomarkers bind to these probes, the refractive index of the medium on the surface of waveguide changes. This changes lead to a measurable shifts in the MRR resonance frequency, which is proportional to the biomarker concentration [6].

To enable parallel sensing, a common approach has been to split the input laser across separate waveguides, each coupled to its own MRR, allowing data to be extracted in parallel. This setup, however, requires higher laser power and increases data acquisition complexity. Our previous work demonstrate a method arranges multiple MMRs of varying radii along a single bus waveguide (Figure 1), resulting in combined resonances from all rings in a shared output [6]. An algorithm was developed to distinguish the data from individual MRR and achieve parallel sensing. The key concept is shown with a reproduced figure from reference [6]. For even greater resolution, it is possible to study the phase shift in the separate ring data using FFT again. [7].

Recognition layer

The label-free immunoassay will be developed based on the achievements of the Molecular Nano-Fabrication (MNF) group, University of Twente for ten selected protein-based biomarkers guided by sepsis experts Dr. Bouma and Dr. Krabbe, giving insight to the origin of infection, likely pathways and level of severity, all relevant for sepsis diagnosis and treatment. To limit the influence of patient-to-patient variation in plasma samples and non-specific binding, an antifouling coating will be used and select rings will be functionalized with inactivated capture probes to monitor background changes. Systems explored for the anti-fouling coating include the use of supported lipid bilayers and betaine-based polymer brushes. Different anti-body or aptamer-based capture probes will be used in the assay, including Nanofitins® developed by the company Affilogic and already proven as effective for protein detection [8]. Localized delivery of capture probes will be reached using for example inkjet printing.

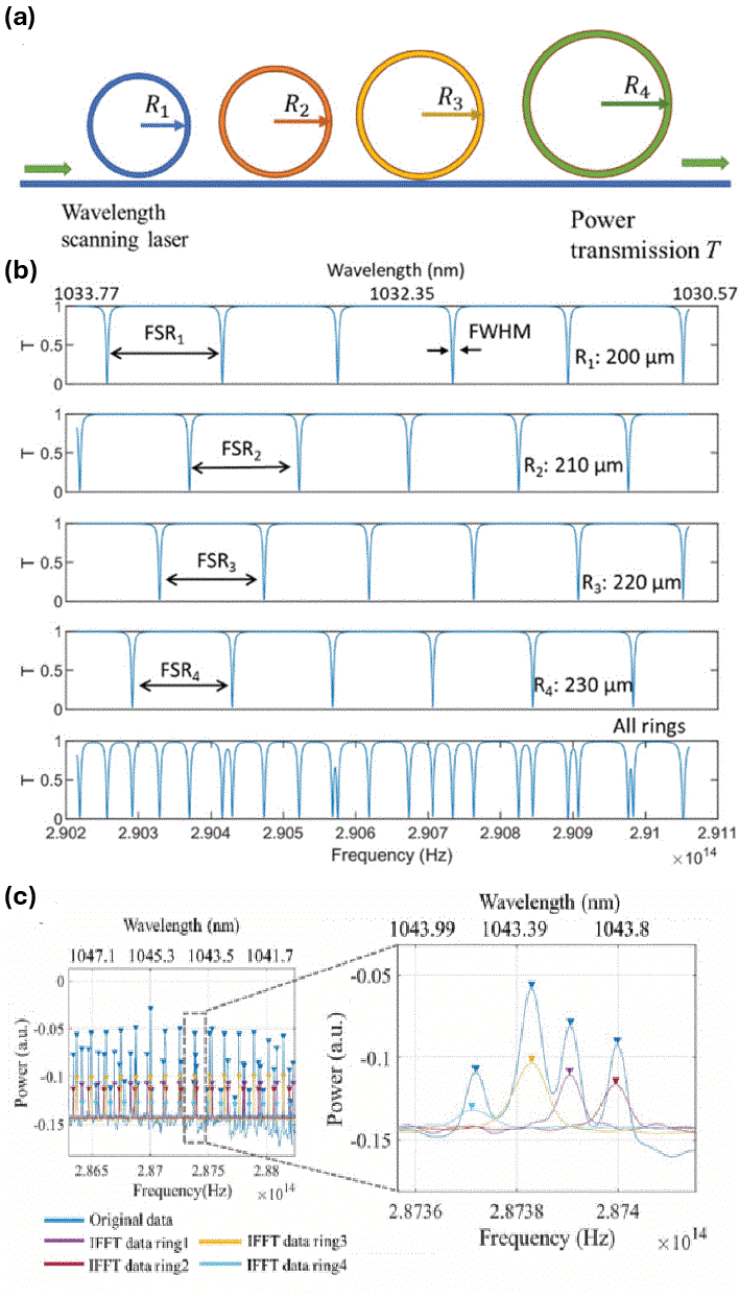

Figure 2. (a) Schematic of parallel MRRs coupled to a single waveguide bus. (b) Transmission spectrum showing a series of dips generated by each ring, determined by its diameter. The overall output is the multiplication of the individual transmission functions of the MMRs. (c) FFT of the total transmission spectrum, decomposed into individual FFT components corresponding to each ring. IFFT of these components isolates the response of each microring.

Device

The prototype device is designed as a tabletop machine with a usable interface. The process from collecting blood to receiving results should take less than 30 minutes. The chip will be housed in a disposable cartridge with a microfluidic pathway, where plasma, extracted from whole blood, flows across the sensor before being collected in a waste container. Given the use of patient blood, the cartridge is single-use. Once inserted, the machine automatically aligns the laser inlet with the chip's edge and initiates measurement in less than a minute. An onboard computer controls the tunable laser source, manages a pressure pump to handle flow in the microfluidic path, drives motors for laser alignment, and gathers data from a photodetector. The data will first be analyzed for biomarker concentrations and then transmitted to a database for AI-driven sepsis research analysis. We will use real-world samples collected by the Acutelines data-biobank [9] upon arrival to the ED from patients with suspected sepsis, before a diagnosis was made and prior to initiation of treatment, to validate the diagnostic accuracy of the device. After analytical validation in a laboratory environment, the device will be clinically validated at the ED.

Human factors and socio-technical considerations

For a sepsis diagnostic sensor and decision support tool to have a real impact on healthcare, it must be intuitive and seamlessly integrated into the workflows, sensemaking, responsibilities and decision-making processes of healthcare professionals, while maximizing resilience of the socio-technical system [10]. It should also be aligned with reimbursement policies and regulatory requirements. Furthermore, it should be usable in different healthcare settings and for diverse patient groups. To achieve this, we aim to generate requirements at an early stage in a formative way to embed key factors in the design considerations [11], such as the expected usefulness, acceptance, trustworthiness, and perceived usability of the device and its anticipated impact on clinical decisions and workflows. This will be accomplished by conducting semi-structured interviews, focus groups, and socio-technical scenario workshops, building on the Constructive Technology Assessment approach [12], and drawing on the consortium's expertise and involving additional stakeholders. This approach will generate design recommendations and guide the envisioned usage process, refining the value proposition based on anticipated clinical impact, usefulness, acceptance, and feasible application scenarios.

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