Highly sensitive lab-on-chip for rapid diagnosis

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Accurate extraction of optical signals and multiple sensors on a single optical chip enable low-cost detection of specific proteins at the doctor’s desk.

Sometimes life depends on rapid diagnostic tests. However, even in more everyday cases, time and money can be saved by getting the diagnosis right at the first consultation, rather than requiring the patient to come back a second time when tests have been analyzed. Often, these tests use optical sensors based on antibody reactions to detect specific proteins associated with different illnesses. To move this kind of powerful analysis from central hospital laboratories with their expensive instruments to the desk of the single medical practitioner at the point of care, lab-on-chip solutions must be developed.

In such a device, an optical detection chip is combined with a microfluidic sample-distribution network in a disposable cartridge that can be read by a multi-use tabletop reader. In the cartridge, the sample-distribution network is a microscale plumbing layer with channels to transport sample, reagents, and wash solutions. Optical-waveguide-based ring resonators are emerging as one of the main candidate detection devices. These are rings, typically up to 100µm in diameter, of micrometer-wide waveguide tracks that allow very accurate monitoring of the wavelength of the light propagating through the ring. Such chips can be mass produced at reasonable cost and the resonators’ small size allows several simultaneous bio-assays on the same chip. In the European collaborative project SABIO (ultrahigh-sensitivity slot-waveguide biosensor on a highly integrated chip for simultaneous diagnosis of multiple diseases), we recently demonstrated the first optical ring-resonator sensor array fully packaged and integrated with an on-chip microfluidic network.1 We achieved extremely high sensitivity, which can be expressed as a refractive-index detection limit of $5 \times 10^{-6}$ refractive-index units or as a surface-protein-layer mass-detection limit of 0.9pg/mm². We believe that this is the best value published so far for planar ring sensors.

Figure 1. The bound biosubstance increases the refractive index (blue curve) close to the surface, where the evanescent field (red curve) will be affected. Si₃N₄: Silicon nitride. SiO₂: Silicon dioxide. n: Refractive index. E: Amplitude of the electric field of the light wave.

So, how does the device work and why can the sensitivity be expressed in refractive-index units as well as in pg/mm²? When light propagates in a thin, single-mode, waveguide-on-a-chip substrate, part of the propagating wave is actually outside the waveguide core. The evanescent field extends a fraction of a wavelength outside the core (see Figure 1). This means that changes in the refractive index in a thin layer of the surrounding medium will influence the wavelength in the waveguide. The ring resonator has resonances for wavelengths that fit an integer number of times in the ring circumference. By monitoring the resonance wavelengths, we can see how the wavelength in the waveguide ring changes and, thus, understand what happens in the evanescent field. We can thus give the detection limit in terms of refractive-index changes in the sample. This change might be caused by a protein binding to receptors on the waveguide surface. Proteins are both approximately the right size (a few nanometers) to fit in the sensitive layer where the evanescent field is, and also have a higher refractive index than water-based solvent. As a result, we can give our detection limit in terms of how dense a layer of protein is needed for a detectable signal.

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We used slot waveguides (see Figure 2). They have a narrow open slot in the middle of the core, causing a larger fraction of the light power to propagate outside the core and, thus, giving higher sensitivity for changes there. Combined with an accurate method to find and track the resonance wavelengths, this gave us good detection limits. To fully exploit the good sensitivity, we also had to limit the influence of temperature changes. By referencing the sensors to an identical sensor without bioreaction on the same chip, we could increase the tolerable temperature change during measurement from 0.1 to 7°C (without and with referencing, respectively). Finally, the device was packaged with an on-chip poly(dimethylsiloxane) microfluidic layer and a hard plastic shell into a complete, replaceable cartridge (see Figure 3).

To allow easy replacement of the compete cartridge, light is coupled into the chip using a grating coupler designed for high alignment tolerance and coupled out through the edge of the chip in eight waveguides, one for each channel. This means that passive alignment of the precision-cut chip is good enough to guarantee at least some coupling, allowing automatic fine-adjustment in the reader.

In summary, we have developed a complete device with several multiplexed sensors, on-chip microfluidic integration, and competitive performance. However, no good method for large-scale production of the integrated fluidic network and packaging exists. In fact, development of a method for wafer-scale optofluidic system integration and packing is a priority for future work.

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Hans Sohlström was born in Stockholm in 1952. In 1993, he received his PhD from KTH for work on fiber-optical magnetic-field sensors using yttrium iron garnet thin films. He is an associate professor and coordinated KTH’s involvement in SABIO.

References