Extended Abstracts of the 2015 International Conference on Solid State Devices and Materials, Sapporo, 2015, pp618-619

Si and SiN Biophotonic Technology Platform, Applied to Biosensing, Spectroscopy, and Lens-Free Imaging

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Abstract

Si and SiN based photonic technologies have the capability to play a game-changing role in many biomedical and other application areas. This presentation reviews our recent efforts on developing a 200 mm wafer-scale SiN biophotonic platform compatible with embedded CMOS logic and imagers and with waferscale on-chip fluidics. Biomedical application cases to be highlighted include label-free and label-based biosensing as well as ultracompact lens-free holographic microscopy, both suitable for point-of-care settings.

1. Introduction

Optical techniques are extensively used in a wide range of biomedical applications, varying from fluorescent and bright field imaging, over spectroscopy, fluorescence and refractive index based molecular sensing, to fluorescence-activated cell sorting (FACS), and more. The setups are often bulky and expensive, may require specialized skills to set up and align properly, and the degree of parallelization is often limited by the physical size of traditional optical components. Hence there is a growing interest in integrated optical solutions, where the optical functionality is integrated in a photonic chip. It is particularly beneficial if the photonics can be directly integrated on top of a CMOS chip, and/or if it can be combined with on-chip microfluidics, resulting in very compact, cheaper, and easy-to-operate lab-on-chip systems that can help to move healthcare from centralized laboratories to the point of care (PoC), such as the doctor's office or the patient home.

In this presentation we will give a brief overview of the SiN platform we are developing, and highlight two specific examples focusing on biomolecular sensing and imaging.

2. Technology platform

In the past we have worked on Si waveguides based on SOI wafers, building on the experience gained in optical interconnect technology, and using infrared wavelengths (1.3 to 1.5 μm range). SOI-based Si waveguides have many attractive properties including a very high index contrast, low losses, and CMOS compatibility, and refractive index based biosensing has been demonstrated. However, as they only operate in the IR regime, a different platform was needed for applications such as fluorescence or imaging.

The material of choice in the visible regime is SiN, which is compatible with CMOS production tools for low-cost mass fabrication, has a relatively high refractive index ($n \approx 1.9$) for tight confinement, doesn't suffer from two-photon absorption, and has a lower temperature coefficient than Si. Traditionally, low-loss SiN waveguides are fabricated using high-temperature LPCVD processes, which are not compatible with back-end-of-line processing on top of active CMOS circuitry. Therefore we have developed and optimized a low-temperature PECVD-based process that runs in a 200 mm pilot line [1] and created an extensive component library [2, 3].

Basic waveguide properties include low loss (< 1 dB/cm) for single-mode waveguides in the 532-900 nm wavelength regime for SiO_2-cladded waveguides, slightly higher losses for unclad single-mode waveguides (< 1 dB/cm only at λ = 900 nm, increasing to 1.3 dB/cm at λ = 780 nm and 2.3 dB/cm at λ = 532 nm), and autofluorescence levels below the detection limit. For biosensing applications where part of the waveguide needs to be exposed to the sample while the other parts remain covered, a selective cladopen process has been developed with waveguide losses equal to the original uncladded waveguides.

The component library includes multimode interference (MMI) splitters and fractal power distribution trees, evanescent couplers for asymmetric power distribution, arrayed waveguide (AWG) and echelon gratings, ring resonators, Mach-Zehnder and Fabry-Perot interferometers, Bragg filters, focusing grating couplers, TE/TM mode rotators, and more. The process and the devices can run on top of CMOS circuitry, e.g. CMOS imagers, can be combined with custom filters, e.g. to reject fluorescence excitation light or for hyperspectral applications, and can be combined with polymer-based microfluidics also fabricated using wafer-level processes.

3. Application examples

The biophotonic platform enables many different applications, including molecular biosensing, compact lens-free cell imaging, Raman and other spectroscopies, optical coherence tomography OCT, integrated zero-mode waveguide (ZMW)-based single-molecule fluorescence,

optogenetics, etc. In this presentation we will focus on the first two applications, in the framework of e.g. a blood test.

Biomolecular sensing

One part of every blood test is determining the presence and concentration of various biomarkers (proteins and other molecules) in the blood. The most common assays in clinical settings are label-based. In a typical sandwich ELISA (enzyme-linked immunosorbent assay), a first antibody immobilized on the sensor surface captures the targets, after which a second (or detection) antibody binds to the immobilized targets. Attached to the detection antibody is a label (e.g. an enzyme or a fluorophore) that will ultimately be detected. Several incubation and wash steps are required, resulting in a typical assay time of 1 hour or more. In addition, only the endpoint of the assay can be measured, as the presence of free labels during the incubation interferes with the detection of the immobilized labels. By contrast, label-free techniques that directly measure the immobilized target molecules allow real-time measurements, resulting in much simpler assays and much faster time-to-result.

In the past we have developed evanescent field-based refractive index sensors based on Si ring resonators operating in the infrared and are now moving to the SiN platform. Whereas the Si version used ring resonators and relied on high resolution external tunable lasers and infrared detectors, and was thus limited to lab settings, the SiN platform is much more compact with a broadband light source and an on-chip spectrometer [4], making it much more suitable for PoC applications. The example of a urine-based test platform that is currently under development for TBC testing in developing countries will be discussed [5].

A drawback of label-free biosensors is their vulnerability to parasitics and drift, in particular to the non-specific binding of background proteins present in plasma or serum samples. This can be circumvented by switching back to a label-based approach where the evanescent field is no longer used to directly sense the refractive index change associated with the target molecule (as well as all the non-specific binding events), but by using it to excite fluorophores attached to a detection antibody (and being blind to the target itself as well as to the non-specifically bound molecules) [6, 7]. We will discuss our recent progress towards an evanescent field fluorescence based biosensor platform compatible with integrated photodetection.

Lens-free imaging

Another major part in a blood test is the cell count (red and white blood cells, platelets, detection of rare cells such as circulating tumor cells CTCs, etc.). Also here the traditional equipment based on optical microscopy and flow cytometry is rather bulky, and miniaturization is desirable. Imec has various programs in this area, including lens-free microscopy and on-chip cell counting and sorting using fluorescent and/or lens-free imaging. In this presentation we will highlight the first application.

In lens-free holographic microscopy (LHM) the imaging optics of a conventional microscope is replaced by computer reconstruction based on the interference pattern (or hologram) between a reference beam and the light scattered by the sample. This results in compact and robust hardware with a high resolution and large field of view (FOV), and advantages such as software focusing after the image has been recorded [8] that can be applied in e.g. white blood cell differentiation [9]. However, in traditional LHM only the detection optics is miniaturized, while the excitation optics still requires an illumination source at a significant distance (e.g. 10-15 cm) from the sample.

Also here waveguide-based optics provides a means for aggressive further downscaling, of which we will show two examples [10]. High-resolution LHM uses a point illumination very close to the sample, to project an enlarged hologram on the detector, at the cost of a limited field of view. By using embedded SiN waveguides with a custom-designed focusing output grating, we succeeded to create a virtual point source at a predefined position in space. The complete imaging system (illumination, sample cavity, and imager, but excluding laser source and signal processing unit) fits in a volume of only 0.5 mm^3. The prototype reaches an imaging resolution of 550 nm and is capable of capturing 1000 images per second.

Large FOV LHM requires a planar incoming wavefront. Traditionally this is obtained by placing the source far away from the object, limiting system miniaturization. Using the possibilities of SiN waveguide technology for optical power distribution and wavefront shaping [11], we are working on plane wave illumination such that the FOV is only limited by the available imager sizes. Our prototype system was able to reach submicron resolution over the full FOV of 3.5 x 4.7 mm^2.

4. Conclusions

We have demonstrated the versatility of a CMOS compatible SiN-based photonic platform with the potential for aggressive miniaturization thanks to system integration with embedded fluidics and signal processing. This provides path to a wide variety of applications including very compact point-of-care biomedical applications.

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