Monolithically integrated semiconductor fluorescence sensor for microfluidic applications

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Abstract

This article presents a monolithically-integrated semiconductor sensor for fluorescence detection on a microfluidic platform. Vertical-cavity surface-emitting lasers (VCSELs) for 773 nm excitation, PIN photodetectors and optical emission filters have been integrated on one GaAs substrate. These optoelectronic components are optically coupled to a glass microfluidic channel (100 μm width and 45 μm depth) through the use of a discrete micro-lens to form a complete sensor. The experimental limit of detection was 250 nM of IRDye 800 Phosphoramidite. Based on an S/N = 3, the theoretical limit of detection was determined to be 40 nM. Laser background levels currently limit the sensor sensitivity. Large gains in sensitivity are possible through the systematic reduction of laser background by increasing spectral and spatial filtration. The low-cost, compact and parallel architecture makes this sensor a candidate for fluorescence-based sensing applications.

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1. Introduction

Microfabrication technologies have had a tremendous impact on the development of analytical systems for biology and chemistry. The integration of microfluidic systems (e.g., channels, mixers, pumps, particulate filters, etc.) with chemical processing and analysis (e.g., polymerase chain reaction (PCR) amplification, fluorescence-based DNA hybridization assays, capillary electrophoresis, etc.) enables the realization of miniaturized and total analysis systems (μTAS) [1–7]. For research applications, μTAS promise reduced costs through less reagent and sample consumption and increased speed and parallelism for high throughput analysis [1]. In medical diagnostics, μTAS can provide immediate point-of-care services that could facilitate detection of common diseases, pathogens, and early-stage cancer [2].

One technical challenge facing the practical application of μTAS is the size and expense of conventional fluorescence detection systems. Fluorescence detection remains one of the most widely used techniques in μTAS due to its superior specificity and sensitivity. Unfortunately, traditional fluorescence-sensing systems use bulky and discrete elements which are expensive and non-portable. The deployment of such optical systems coupled to μTAS has been cost-prohibitive and impractical. Integrated fluorescence sensing systems are needed to reduce manufacturing cost and increase portability, allowing for the mass production and implementation of μTAS.

There has been much research to develop more integrated fluorescence detection systems [8–17]. The use of integrated waveguides and optical gratings to excite fluorescent molecules has been proposed [8,9]. The integration of waveguides adds additional complexity to biochip fabrication and may be difficult to implement with a large number of channels. In addition, these waveguide-based sensors
typically use discrete light sources, filters and photodetectors, complicating packaging and alignment. Several groups have proposed the integration of photodetectors directly onto the biochip [10–12] but have not shown an integrated excitation source. The integration of optoelectronics devices such as photodetectors directly onto the biochip may be cost-prohibitive to disposable applications. Other integrated optical solutions have been proposed [13,14] but these systems use non-integrated and discrete optical components. Some progress towards a compact integrated sensor has been made by the clever packaging of discrete optical components (semiconductor lasers and LEDs, photodetectors, optics and emission filters) to facilitate on-chip detection [15–17].

Our approach is to integrate lasers, photodetectors and emission filters monolithically on the same substrate for reduced cost and size. The cost-effectiveness of this approach could enable the development of applications with disposable fluorescence sensors that may be cost prohibitive with systems that use discrete optical components. Also, the proposed optoelectronic sensor is ideal for non-disposable applications because the optoelectronic sensing is decoupled from the biochip, allowing for a removable sensing unit. Monolithic integration allows sensor units to be fabricated in parallel using conventional semiconductor fabrication techniques and used as building blocks for highly parallel detection systems, such as with flow channel arrays. Also, the extremely small size of the proposed technology will enable robust bonding to microfluidic platforms and could reduce noise from optical alignment variance and mechanical vibrations.

For reduced cost and fabrication simplicity, we capitalize on the well-developed optoelectronic devices available in the deep-red to near-infrared (NIR) spectrum [18]. Fortunately, fluorescence sensing in the deep red to NIR spectral region has proven to be a viable and advantageous spectral range for a variety of applications [19–24]. The lower background fluorescence, absorption and scattering ($\mu_{\text{abs}} \approx 0.02 \text{ cm}^{-1}$, $\mu_{\text{scattering}} \approx 8 \text{ cm}^{-1}$) at longer wavelengths offer key advantages over working with visible fluorescence. For example, it was found that in point-of-care rapid diagnostic assays (Biosite Inc., San Diego, CA) that NIR dyes (Ex. at 670 nm) can be used as fluorescent markers attached to antibodies to increase sensitivity and overcome background fluorescence problems involved with using visible dyes in blood samples [22]. In addition, many researchers and companies are beginning to capitalize on the inherent spectral advantages of the NIR and develop novel markers [25,26].

We report the use of a monolithically integrated semiconductor sensor for fluorescence detection in a microfluidic channel. The first part of this paper details the optical design and experimental setup for optically coupling the sensor to the microfluidic channel using a micro-lens. Then, the sensor sensitivity is characterized by detecting continuous free-flowing fluorescent dye molecules. Finally, design modifications are proposed to increase sensor sensitivity through reduction of the laser background.

2. Experimental

2.1. General sensor design

The integrated sensor elements are a vertical-cavity surface-emitting laser (VCSEL), PIN photodetector, emission filter, lens and microfluidic channel (see Fig. 1A and B). The 773 nm AlGaAs VCSEL is surrounded by an annular GaAs photodetector. An emission filter is integrated directly on top of the photodetector. The lens is used to both focus the laser beam into the microfluidic channel and collimate the emitted fluorescence into the photodetector.

2.2. Optoelectronic design

There are many possible optoelectronic designs that could be utilized in the configuration shown in Fig. 1. However, achieving lasing, photo-detection and filtration by a monolithically integrated device fabricated using one GaAs substrate in a practical and inexpensive way is a design challenge. We designed and fabricated a device that capitalizes on current VCSEL technology [27]. Through one simple modification to a typical VCSEL structure used for telecommunication, we obtain the components (VCSEL, PIN photodetector...
Table 1

<table>
<thead>
<tr>
<th>Absorptivity (ε cm⁻¹ M⁻¹) at λ = 773 nm</th>
<th>QE of dye (%)</th>
<th>QE of detector (%)</th>
<th>Filter transmission (%)</th>
<th>Lens collector (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>161,000</td>
<td>15</td>
<td>100</td>
<td>40</td>
<td>2.5</td>
</tr>
</tbody>
</table>

and emission filter) needed for a high performance fluorescence sensor. This will result in reduced costs and higher yield as compared to other integration schemes. This technology holds much promise for fluorescence sensing spanning the spectral range from 0.6 to 1.5 μm, fluorescence lifetime detection, and simple incorporation of a host of other capabilities such as signal processing, low noise amplification and avalanche photodiode (APD) technology.

Although this device’s optoelectronic fabrication and characterization has already been reported in the literature [27,28], the optoelectronic characterization of the structure used in this paper (Fig. 1B) will be listed here briefly for completeness. The AlGaAs intra-cavity-contacted VCSEL (oxide aperture diameter = 20 μm) emits light in multiple transverse modes at a wavelength of 773 nm and has a maximum output power of 4 mW [27]. The output power used in the microfluidic experiment is 1.9 mW. The far-field intensity profile of the laser is toroidal and diverges at approximately 14° full width at half maximum (FWHM). It is important to note that VCSEL technology can give more ideal beam characteristics such as low divergence (less than 2.5° FWHM) and the generation of fundamental TEM modes [29].

The GaAs PIN photodetector has a quantum efficiency (QE) of 100% and low dark current (500 fA/mm detector diameter) is possible with this technology [28]. It is difficult to measure the photodetector QE directly due to the integrated filter [28]. For simplicity, a photodetector QE of 100% is assumed; see Table 1. The inner and outer diameters of the photodetector/filter module are 200 μm and 1 mm, respectively. The emission filter is a distributed Bragg reflector (DBR) made of AlₓGa₁₋ₓAs alloys (x = 0.25 and x = 0.95). The high index of refraction, n, of these materials (n = 3.55 for x = 0.25, n = 3.06 for x = 0.95 at 773 nm) makes this filter relatively insensitive to changes in angle of incidence. Theoretically, an optical density (OD) of 5 can be maintained for external angles as high as 40° from the normal. Filter angular insensitivity is important in microscale sensing systems where collimated detection schemes may not be possible or where scattered or reflected light may illuminate the photodetector at a variety of angles. At normal incidence, the filter was measured to have OD 3 at the lasing wavelength of 773 nm, which deviates significantly from the theoretical performance of OD 5 [28]. Experiments are underway to understand why the filter deviates from theoretical performance and to fabricate better filters. The filter cutoff wavelength was measured to be about 795 nm and the typical oscillation (i.e. side lobes) of the DBR reflectivity spectrum was observed above this wavelength, which can be eliminated by simple filter design techniques. Due to the oscillating side lobes in the current design, the amount of transmitted fluorescence through the filter (T_filter) is calculated to be about 40% for IR-800 in methanol; see Table 1. This calculation was made by measuring the filter transmission spectrum and normalizing against the measured fluorescence spectrum [28].

2.3. Experimental setup

A black anodized aluminum chuck is the central building block in the experimental setup used to align the sensor’s components; see Fig. 2. There is a hole in the center of the chuck for screwing the lens mount into the chuck. The microfluidic chip is mounted on top of the chuck via vacuum. On top of the chuck, micrometers align the microfluidic channel relative to the lens. The lens is mounted in a black anodized aluminum housing which can be screwed into the chuck, and the height of the lens can be controlled with respect to the chuck by rotating the lens mount. The optoelectronic elements are packaged in a 32-dip package through wire bonding and subsequently inserted into a printed circuit board. The printed circuit board (PCB) is mounted on a XYZ stage underneath the chuck so that the optoelectronic elements can be aligned to the lens.

2.4. Optical system design

The microfluidic channel is placed at the focal plane of the aspheric lens (Geltech 370060, N.A. = 0.6, f = 0.682 mm). A non-sequential ray tracing program called ASAP (Breault
Research Organization, Tucson, AZ) was used to determine the focal plane location in the microfluidic chip. In the architecture shown in Fig. 1A, the collection efficiency of the lens ($C_{lens}$) simulated with ASAP is found to be about 2.5%; see Table 1. The microfluidic chip and lens are anti-reflective (AR) coated on both sides to reduce laser background. The microfluidic chip has a specialized AR coating at 773 nm, and the lens has a broadband coating. The lens is separated from the microfluidic chip by a space of approximately 20 μm. The optoelectronic sensor is placed 1.7 mm away from the lens. Due to the far-field toroidal profile of the laser beam, the excitation spot is a ring and has a diameter of about 90 μm within the flow channel. Smaller laser divergence angles and excitation spot sizes are possible through redesigning the laser to obtain more ideal beam divergence and mode behavior [29]. For example, Kamei et al. report a spot diameter of 30 μm in a similar optical architecture using an external laser source [12].

2.5. Micro-fluidic design and preparation

The microfluidic channel was made by standard wet-etching and bonding of two glass substrates (Schott D263), detailed elsewhere by Throckmorton et al. [30]. The glass substrate closest to the lens is thinned from an original thickness of 1.1 mm to 300 μm so the channel is at the focal point of the lens. The channel depth, $d$, and width are 45 and 100 μm, respectively. Inlet and outlet connectors (Upchurch Scientific) are mounted to the microfluidic chips. Standard tubing and syringes are used to interface with the microfluidic connectors. A syringe pump (Kd Scientific, Model #100) is used to inject the reagents to the channel at a continuous flow rate of 100 μL h⁻¹. The channels are cleaned with 200 mM NaOH and rinsed with deionized water rinse before use.

2.6. IR-800 dye preparation and characterization

IRDye™800 Phosphoramidite (LI-COR, Inc.) was dissolved in methanol, and dilutions were made to generate samples of various concentrations. The absorption and fluorescence characteristics of the dye solutions were measured with UV/VIS/NIR spectrometer (Perkin-Elmer Lambda 19) and fluorimeter (Instruments S.A.- FluoroMax-2). The molar absorption coefficient ($\varepsilon$) of IR-800 dye in methanol at 773 nm was measured to be 161,000 cm⁻¹ M⁻¹; see Table 1. For simplicity, we assume the IR-800 dye in methanol has a QE of 15%, which is the value reported by the manufacturer; see Table 1.

2.7. Data acquisition and instrumentation

A semiconductor parameter analyzer (HP 4156A) was used to drive the VCSEL and readout the photodetector signal. The intracavity contact of the VCSEL and the backside substrate contact are grounded. The laser was driven through the top mesa contact of the VCSEL at 10 mA current (1.9 mW) and at a drive voltage of 3 V. The photodetector readout voltage was set at 0 V and the detector current was measured through the top mesa contact of the photodetector. For the fluorescence measurement, data is collected for 20 s with an integration time of 16.7 ms and sampling rate of 100 ms.

3. Results and discussion

Dilute concentrations of the fluorescent dye (IR-800 in methanol) are flowed (100 μL h⁻¹) through the channel with methanol flushes between dilutions to remove any dye adhesion to the sidewalls. Background signals are closely monitored to make sure that the channels have been thoroughly flushed between dilutions, and no problems have been observed. For each concentration, the signal is measured to determine the sensor sensitivity (see Fig. 3). The sensor has a linear response of 1.62 nA μM⁻¹ or 1.62 pA nM⁻¹. The background signal from running methanol buffer is approximately 63.5 nA with an RMS fluctuation of approximately 20 pA. Therefore, one can subtract the DC value (63.5 nA) from the total laser background which yields the remaining rms noise of 20 pA (corresponds to 13 nM noise variation). Assuming a S/N = 3, our theoretical limit of detection is extrapolated to be 40 nM in a peak identification measurement such as capillary electrophoresis (CE). However, the average fluctuation of the background from run to run was approximately ±150 pA. This fluctuation over the timescale of a few minutes limits the detection sensitivity to 250 nM in continuous flow. In addition, the sensor response was measured at variety of flow rates (10, 100, and 600 μL h⁻¹). No change in fluorescence collection was observed, illustrating successful detection over a wide range of typical flow rates for microfluidic separations [5].

The detection limits reported above are comparable to or within an order of magnitude of other integrated optical sensors coupled to microfluidic channels seen in the literature [10,12,13,15,17]. In approaches with a similar optical detection architecture to one presented in this report, detection

Fig. 3. Sensitivity measurement of IR-800 phosphoramidite in methanol in continuous flow (100 μL h⁻¹). Laser output powers is 1.9 mW at a wavelength of 773 nm.
limits of 17 and 120 nM have been reported [12,17]. The advantage of our approach is a completely monolithically integrated sensor solution for drastically reduced cost and increased parallelism.

Unfortunately, as one moves to applications such as CE that employ aqueous buffers, the quantum efficiency of IR-800 dye in solution is likely to decrease, thereby reducing the sensitivity of this approach for certain biologically relevant applications. In preliminary experiments with a fluorimeter (Instruments S.A., FluoroMax-2), we found that the QE of IR-800 covalently attached to a DNA oligonucleotide in aqueous buffer (10 mM phosphate buffered saline, pH 8.0) dropped by a factor of about 2.5 when compared to dye in methanol.

The detection limits reported here will be sufficient for certain medical diagnostic applications such as immunoassays and clinical chemistry [7]. However, for many applications, the sensor sensitivity will not be sufficient. Preamplification methods such as PCR based detection and surface immobilization will be needed for successful detection in certain applications. On-chip PCR combined with integrated detection would be useful in overcoming sensitivity limitations [6]. As a comparison to typical detection limits seen in the laboratory, fluorescence detection limits using bulk-optic approaches are typically in the 0.1–1 nM range. As discussed below, we believe large increases in sensitivity will be possible in the future and enable more applications.

3.1 Comparison to theory

Simple theoretical calculations agree reasonably well with the sensor response reported above. Table 1 lists some relevant parameters needed to theoretically calculate the sensor response. The following simple equation, based on the Beer–Lambert law, can be used to calculate the theoretical sensor response for detector current, \( I_{\text{Det}} \),

\[
I_{\text{Det}} = \frac{h\nu}{4\pi} \frac{P_{\text{Det}}}{T_{\text{Det}}} \eta \eta_{\text{Det}} \left( 1 - 10^{-\Delta M} \right)
\]

where \( q \) is Coulomb’s constant, \( h \) is Planck’s constant, \( c \) is the speed of light, \( \lambda_{\text{em}} \) is the wavelength of the fluorescent light, \( \epsilon \) is the molar absorption coefficient, \( d \) is the channel depth, and \( M \) is the dye concentration. For simplicity, we assume a constant \( \lambda_{\text{em}} \) of 805 nm, which is at the fluorescence maximum. Plugging in the parameters found in Table 1, \( d = 45 \mu\text{m}, P_{\text{Det}} = 1.9 \text{ mW}, \) and \( M = 1 \mu\text{M}, \) the detector response is calculated to be about 3.0 nA for IR-800 dye. Experimentally, the detector response was found to be 1.6 nA for 1 \mu\text{M} concentration.

The discrepancy between the calculation and experiment is likely due to some clipping of the laser power by the channel edges and misalignment. Also, the above equation assumes a uniform channel depth over the channel profile; whereas, as shown in Fig. 1a, the channel varies and effectively reduces the channel depth.

3.2 Increasing sensitivity

The primary source of background is caused by detected laser emission, i.e. laser background. Due to placing the laser in close proximity to the photodetector (100 \mu\text{m}), large laser background is caused by specular reflections of laser radiation, specular reflection of spontaneous emission and direct incidence of spontaneous emission into the photodetector [28]. In these experiments, all three sources make a significant contribution to laser background. With no optical interfaces above the sensor, the laser background is measured to be 29 nA for laser drive current, \( I_{\text{Det}} \), of 10 mA. This background results from direct incidence of spontaneous emission either through or around the metal optical blocking layer placed between the sensor and photodetector. With only the lens in place above the sensor, the background increases to 56 nA, which results from scattering and specular reflections that come from both the laser beam and spontaneous emission off the lens and black anodized lens mount. Finally, the addition of the microfluidic channel with running buffer results in a total laser background of 63.5 nA as reported above.

The emission filter limits the transmission of the fluorescent signal to ≈40% due to the reflectivity side lobes above 795 nm. These reflectivity side lobes can be eliminated by changing the DBR design slightly [31], allowing for an increase in fluorescence collection efficiency. Also, utilizing a higher numerical aperture lens would increase the fluorescence collection efficiency. Through these simple modifications, it is believed that the sensitivity of the current sensor can be improved by a factor of 2–3 to be in the range of a 20 nM detection limit.

We believe that order of magnitude improvements in sensor sensitivity are possible through the systematic reduction of laser background. Preliminary experiments show a dramatic reduction in laser background caused by direct spontaneous emission. With improved optical blocking structures, the 29 nA background was reduced to 430 pA, thereby achieving good internal isolation of the photodetector from the laser. The large increase in laser background from reflections from elements (lens and microfluidics) above the sensor can be reduced by increasing the spectral filtration of the emission filter above OD 3. Experiments are being conducted to determine why the filter deviates from the theoretically predicted performance of OD 5 and to design more effective spectral filters. We have measured OD 4 in filters based on an optoelectronic design similar to that of the sensor, which is promising. Additional depositions of standard dielectric filter technology onto our semiconductor filter is another promising approach. In addition to spectral filtration, spatial filtration can be used to reduce laser background. Significant reduction has been shown possible by increasing the distance between the sensor and any surface above the sensor and the use of anti-reflection coatings [28]. With improved spectral and spatial filtration, we expect at least an order of magnitude increase in sensor sensitivity.
4. Conclusions

In this paper, successful integration of a monolithically integrated semiconductor fluorescence sensor with a microfluidic channel is demonstrated. A theoretical limit of detection of 40 nM is determined, demonstrating the feasibility of attaining clinically relevant detection limits. Large increases in sensitivity are possible through a variety of methods such as increasing fluorescence collection efficiency and reducing laser background. By monolithically integrating all optoelectronic components onto one GaAs substrate and capitalizing on existing telecommunications technologies, tremendous cost reductions can be gained. This monolithically integrated sensor promises to be an inexpensive, parallel and portable alternative to conventional fluorescence detection systems, which will prove important for emerging uTAS technology.

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References

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