AN ANGLE-SELECTIVE CMOS IMAGER WITH ON-CHIP MICRO-COLLIMATORS FOR BLUR REDUCTION IN NEAR-FIELD CELL IMAGING

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ABSTRACT

Development of microfabricated imagers placed within the resection bed intraoperatively can significantly improve image-guided surgery. One application is identifying microscopic disease during cancer removal. This class of imagers requires robustness against variations in fluid, blood, and tissue surface profile which vary the distance of the tissue from the imager, causing light from the sample to be incident on the imager at a wide range of angles, thereby blurring the image. This paper addresses this problem by demonstrating an angle-selective imager fabricated in a 0.18\textmu m CMOS process, capable of reducing light incident at angles >25° from the perpendicular by >50%.

INTRODUCTION

Resection of all tumor cells is essential in treating early stage cancer, yet one quarter of all women who undergo surgery (also called a lumpectomy) for breast cancer require additional operations. Leaving tumor cells behind doubles the risk that cancer cells return, from 15 to 30% over 10-15 years, and reduces survival rates [1]. Ensuring that no breast cancer cells are left behind equates to a prevention of 2000 deaths every year. In order to remove all cancer cells in a single operation, while maintaining the highest cure rates, all cancer tissue must be labeled and identified. While there has been work done in recent years on the in vivo labeling of cancer cells [2], little work has been done on how to image these molecularly labeled cells during a resection, when cancer tissue can be easily removed (without incurring any further cost or hardship for the patient).

Current intraoperative imagers, consisting of large working-distance microscopes and fiber optics [3], are bulky and inflexible, respectively, limiting their ability to view the entirety of small, complex resection cavities, such as in breast and prostate cancer surgeries. Devices capable of manipulation and imaging within the resection cavity are needed, necessitating near-field imaging, which is defined here as imaging within microns of the surface. Microscope-quality optical elements are impossible to fabricate at the sub-mm scale, and thus typical near-field imagers for biological applications suffer from low resolution [4]. In addition to making individual cells difficult to resolve, blur leads to a large amount of background light entering pixels that ideally should only collect light from a single cell, increasing dynamic range requirements of the sensor as well as noise.

One strategy to reduce blur utilizes the angle of the incident light, in addition to intensity, to resolve images, as demonstrated in commercial cameras [5]. While CMOS-only angle-sensitive imagers have been demonstrated using the Talbot effect [6, 7], this technique is wavelength dependent and requires several angle-sensitive elements per pixel, reducing fill-factor and resolution. Therefore a chip-scale strategy for leveraging the directionality of light to mitigate the need for optics, while being robust to changes in wavelength and retaining fill factor is still needed for near-field cell imagers.

Further adding to the complexity required for cancer imaging, tumor cells and their normal tissue counterparts have many of the same physical characteristics, including size and shape. Therefore, definitive identification of tumor cells often relies on molecular markers, such as fluorescently labeled antibodies. In addition to resolving tumors cells, a cancer imager must be capable of fluorescence imaging, whereby the bound fluorophore absorbs light and re-emits at a slightly lower energy, resulting in a photon shifted by 15-30 nm in wavelength. This subtle shift in wavelength (the Stokes Shift) is only identifiable with a precision optical filter. This optical filter further increases the distance between the sample and the imager surface. To eliminate the need for an optical filter, time-resolved fluorescence imagers have been designed to distinguish fluorescent particles based on their fluorescence lifetime [8]. The autofluorescence of human tissue has lifetimes on the same order as most molecularly bound fluorescent particles making this approach unsuitable in vivo [9].

To achieve blur reduction, we eliminate divergent light using an array of microfabricated angle-selective collimators over the surface of a photodiode. Each aperture in the grid measures 2.4\textmu m wide by 6.8\textmu m tall and is made from the metal interconnect in CMOS processes. We demonstrate an angle-selective fluorescence imager fabricated in a 0.18\textmu m CMOS process, capable of reducing light incident at angles >25° from the image sensor normal vector by >50%. The
imaging array is hexagonally packed and consists of 32x32 pixels with each pixel containing a 45x45µm n-well/p-substrate photodiode as shown in Figure 1 (a). A close-up of the collimating grids can be seen in Figure 1 (b). The micro-collimators block off-axis light and effectively couple each pixel to the portion of the sample directly opposite it, reducing blur. A custom optical filter is integrated onto the surface of the device, enabling fluorescence imaging.

SPECIFICATIONS

Near-field cell imaging requires that the imager be placed as close to the tissue or sample to be imaged as possible. However, in applications such as fluorescence imaging, there are two constraints on the distance of the imager from the surface. The first is that the sample must be illuminated in order for the fluorescent particles to emit light, and this requires a path with which to guide light to the sample. The second is that an optical filter is necessary to prevent the excitation light and the bulk of tissue autofluorescence from reaching the image sensor. Highly selective optical wavelength filters are typically patterned on discrete wafers that are generally 500µm thick or larger (~5 mm) to be used in a macro-scale imaging systems such as fluorescence microscopes. Clearly a 500µm distance is significant when trying to image cells that are on the order of 10µm large without the help of quality optical elements.

If the pixels in an imaging array were angularly-selective for only light that is incident perpendicular to the normal vector of the array, then a perfect image could be constructed. However, this scenario is not practical as when the subset of angles of incident light allowed to hit the photodiode is limited to a very small dθ, the received power in the photodiode also approaches 0. A method for evaluating the performance improvements achieved by angle-selectivity must be devised in order to design for a specific application. It can be shown that a small pixel of area Apix across from an infinite plane emitting light of intensity I0 (power per area) collects a power of

\[ P = \frac{1}{2} I_0 A_{pix} \int_{\theta_{max}}^{\theta_{min}} \tan(\theta) f(\theta) \, d\theta, \]

from light incident at angles between \( \theta_{max} \) and \( \theta_{min} \). \( f(\theta) \) is the angle-selectivity function and the product of \( A_{pix} \) and \( f(\theta) \) can also be understood as the effective pixel area when looking at the pixel from an angle \( \theta \). For a normal photodiode with no angle-selective grids, \( f(\theta) = \cos(\theta) \).

If a pixel is directly opposite a circular area of interest of radius \( r \) on the infinite plane, then a signal-to-background ratio (SBR) and signal-to-noise ratio (SNR) can be found using (1). Light incident on the pixel that originated from within this circular region will be contained in the subset of angles from \( \theta \) to \( \theta_{sig} \), where \( \theta_{sig} = \tan^{-1}(r/h) \), and \( h \) is the distance from the surface of the imager to the object. The background light originates outside the circle of interest, at angles greater than \( \theta_{sig} \).

If no angle selectivity is present, then imaging a cell (an approximately 10µm circle) at a distance of 500µm will give an SBR of -66dB and an SNR of only 12dB, equivalent to an error rate, the probability a cancer cell is not detected, of 2.3%, considering a 45x45µm photodiode as the detector and a 100ms integration time. The intensity of the molecularly tagged cells is typically approximately ten times higher than the autofluorescence of surrounding tissue. If no angle-selectivity is used, the sensor requires a usable dynamic range of 88dB, extremely high for an image sensor, and has an excessively high error rate considering there can be as many as 10 million cells or more in the typical tumor bed after gross tissue is removed. 1%, 100,000, or more of the remaining cells may be cancerous and even 200 cancer cells left behind greatly increases recurrence chances.

A brick-wall angle filter cutting off all light that does not originate from the circle of interest would be ideal. This filter would allow an infinite SBR and SNR of 38dB to be attained, but would require a cutoff angle of 0.57º, impossible to attain using the metal grids of a CMOS process. This would be the best possible performance achievable under the constraints of the application.

DESIGN

A model of the metal grids that compose the angle-selective collimators that we have designed is shown in Figure 2. The grids are fabricated in metal layers one through five of a standard 0.18µm CMOS process. The process has an additional metal six layer that was not used for angle-selectivity as no planarization occurs after metal six is deposited. Using metal six would lead to an uneven imager surface and degrade the photodiode angle-selectivity. This pattern is repeated above each 45x45µm photodiode in the 32x32 pixel array.

![Figure 2: A 3D model of angle-selective grids shown with dimensions. The grids are identical in each metal layer M1-M5 with 2.4µm holes. The total height is 6.8µm.](image)

The imager circuit schematic as well as illustration of the operation of the angle-selective grids can be seen in Figure 3. Each angle-selective photodiode in the array is read out sequentially through a PMOS source-follower, M1, and two switches, SW1 and SW2. The source-follower was chosen to be PMOS for a higher dynamic range. This four-transistor structure allows a single bias current to be used for the entire pixel array, as opposed to one bias current for each column as in the conventional column-readout method for CMOS image sensors. Since the integration time in low-light fluorescence imaging applications is quite long, on the order of 100s of milliseconds, the slower readout speed of this method compared to a column-parallel design is not a concern.
The holes in the metal grids are limited to the minimum size as determined by the technology we are using. In principle, the holes could be made smaller in a more modern technology, however care should be taken such that they do not become comparable to the wavelength and significant attenuation of the input signal occurs. If the aperture had a smaller diameter however, greater angle-selectivity could be achieved. Higher angle-selectivity could also be achieved using a process with a taller metal stack and the same aperture size.

If the metal layers in the CMOS were perfectly absorptive, then no light at angles greater than approximately 30º would enter the pixel. However, the metal layers are shiny, leading to reflections off the surface of the grids, allowing light incident at steeper angles to reach the photodiode. In addition, there will be scattering in the oxide above the photodiode that will further degrade the angle selectivity. It is very difficult to simulate this exact response, as the roughness of the metal layers and the accuracy of the alignment between the metal layers is not known.

**EXPERIMENTAL RESULTS**

Figure 4 shows the output response of a typical pixel in the array to input light, showing the sub-picowatt sensitivity that is often required in fluorescence imaging applications. The output is in amperes per farad of photodiode capacitance (approximately 1pF), equivalent to the derivative of the output voltage of the photodiode source-follower.

Figure 5 shows the response of the array when a laser is shined on it at several incident angles with the array in imaging mode. In this mode, each pixel is allowed to integrate light and a final image is reconstructed. We use correlated double sampling, flat-field gain correction, and dark current correction. There is some attenuation at 15º, but the laser light is clearly significantly attenuated at a 30º angle to the normal vector. If an imager with no angle-selectivity were used, the attenuation would only be approximately 14% at the same angle. The laser light is almost completely attenuated by 45º by the angle-selective collimators.

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**Figure 3:** Diagram of the system operation and a circuit schematic of the ith pixel in the array.

**Figure 4:** The output current per photodiode capacitance (~1pF) of a single photodiode in the array versus the incident light power on the photodiode.

**Figure 5:** Normalized image of a laser source using custom imager at various angles of incidence to normal vector.

**Figure 6:** The angle-selectivity of a photodiode with micro-collimators and a bare photodiode. The full-width half-maximum is reduced from 120º to 50º when using the collimators. The response is normalized in all cases.
The normalized angle-selectivity is more clearly shown in Figure 6. The measured angle-selectivity for a bare photodiode is also shown, with the expected cosine response. The metal grids block off half of the angle-selective pixel’s photodiode area and the unnormalized peak response is 50% of that obtained when using the non-selective photodiode. The angle-selective pixel shows steeper roll-off compared to the bare photodiode. There is still some response at incident angles larger than 30° for the reasons mentioned above.

Using this response curve and equation (1) we can calculate the expected SBR, SNR, and error rate using the same method as did we did for a standard image sensor with no angle-selective grids. The SBR and SNR are calculated as -47dB and 18.5dB, respectively. With this SNR, the error rate is only 13ppm, a three order of magnitude improvement over the image sensor without any angle-selective grids. In addition, this sensor only requires a dynamic range of 66dB, 20dB less than a bare CMOS image sensor, significantly relaxing the in-pixel and readout circuitry requirements.

To illustrate the improved resolution obtainable with this image sensor, we imaged an aperture in front of a sheet of fluorescent quantum dots using our sensor and a sensor with no angle-selectivity. The normalized intensity versus edge roll-off, defined as the distance from the projection of the edge of the aperture on the image surface plane, is shown in Figure 7 (a). A diagram of the setup is shown in Figure 7 (b). The quantum dots emit uniformly in all directions when input light is applied and the aperture serves as a model of a large spot of stained cancer cells. The aperture is placed a distance of 1mm above the imager surface. The received light power drops to 50% of the maximum value at a distance of 320μm away from the edge for the angle-selective imager and 560μm for the sensor without angle-selectivity.

CONCLUSION

The angle-selective CMOS imager we have presented rejects greater than 50% of light incident at angles greater than 25°. This selectivity allows detection of a single cancer cell with an error rate of only 13ppm. The error rate if a non-selective image sensor is used is 2.3%. If only one percent of the surrounding tissue in a tumor bed containing approximately 10 million cells remains cancerous, then over 2,300 tumor cells will be missed using a generic imager, greatly increasing the chance of recurrence. Only 1.3 cells will be missed using our angle-selective imager, reducing the risk of cancer recurrence significantly and saving lives.

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