Capturing and detection of MCF-7 breast cancer cells with a CMOS image sensor

Javid Musayev\(^a\), Caglar Altiner\(^b, c\), Yekbun Adiguzel\(^d\), Haluk Kulah\(^a, b, d, *\), Selim Eminoglu\(^c\), Tayfun Akin\(^a, b, c, d\)

\(^a\) Middle East Technical University, Electrical and Electronics Engineering Department, Ankara, Turkey
\(^b\) Middle East Technical University, Micro-Nanotechnology Department, Ankara, Turkey
\(^c\) Mikro-Tasarm Ltd, Ankara, Turkey
\(^d\) METU-MEMS Research and Application Center, Ankara, Turkey

**A B S T R A C T**

This paper presents a CMOS image sensor with a 32 × 32 pixel array for cell capture, detection, and quantification. Pixels measuring 15 μm × 15 μm have a modified structure, suitable for post-CMOS electroless gold plating, which enables surface activation for cell capture without the need for any intermediate layer. This structure also increases the detection probability of captured cells, even when cells are much smaller than the pixel, owing to a special light mask implemented on pixels. Cells as small as 3 μm in diameter can be detected with this pixel structure. The proof of concept for surface activation of the gold coated sensor pixels was demonstrated by capturing and imaging MCF-7 breast cancer cells on the modified sensor surface. Accordingly, electroless gold coating of the Al pixels was achieved and the gold coated surface of the CMOS image sensor was activated with thiol-modified antibodies that can capture MCF-7 cells. Cells were then optically detected under green LED illumination.

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1. **Introduction**

Ever growing population and increased health related costs forces the authorities to anticipate contribution from rising technologies, to the health care and maintenance. When managed, proper and early diagnosis of most diseases, including cancer, is crucial in the success of the following therapies, which will be resulting in the improved life qualities and health services, at lower costs [1]. However, especially in case of cancer, proper and early diagnosis requires the use of cell separation and detection technologies, which is definitely not a simple task, considering the tremendous biological variety of cells in morphology, size, function, electrical and chemical properties, inner cell components, viability requirements, and abundance in a medium of interest. Yet, probably the most straightforward approach is modifying a surface with specific cell detection antibodies that can capture the cell of interest and detection of the cell through the use of facility instruments, like a microscope, after capturing. However, an established facility, equipped with instruments, chemicals, and technicians or researchers, is not always available for service. Luckily, sensor-based applications are developing as imperative technologies to cell separation in the fields of health care and point-of-care diagnostics, thanks to their advantages over conventional separation techniques.

The potential of miniaturization and automation of the laboratory tests by sensor-based, portable devices is immense. This is sourced by plentiful advantages that are inherited in these devices, which can be summed up as higher reliabilities and sensitivities during testing and analysis, along with the reduction in the demands for large devices and bulky equipment, financial sources, time, effort, and energy and sample expenditure [2,3]. Micromachining technologies facilitate fabrication of sensors for devices that are realistic candidates to possess all the listed advantages. Application of microtechnologies for blood cell counting started in 1990s [4], which had improved in terms of electrode stability during measurements, in less than a decade [5]. In the meantime, this technology developed to the level sufficient to bring out commercial devices [6], despite existing drawbacks for cell counting, like the requirement of multiple wash steps, inconsistency in the samples from different patients, and low signal–to–noise levels [7]. Fluorescence-activated cell sorting is a conventional method of cell separation and its alternatives in Microsystems are termed as microtometers, which can make use of mechanical structures [8,9], optical forces [10], hydrodynamic forces [11], dielectrophoresis [12], electrokinetic transport [13] and ultrasound effect [14].
Automated imaging cytometry, which is of interest here as well, utilize image processing algorithms. This type of cytometry can take advantage of sensors and techniques such as CMOS-based sensors [15], ring resonators [16], immunomagnetic separation [17], and chemiluminescence-based detection [18]. Mass detection is an alternative for automated imaging or fluorescence detection, with the cantilever based detection and quartz crystal microbalance [19] as the most well-known representatives of this approach. Ultimately, no choice of the technique and device should be considered regardless of the target cell and the sample to be used, along with the conditions and requirements of the study to be undertaken. Yet, CMOS-based approaches are superior in the sense that multitasking can be achieved, for example, by performing dielectric manipulation and detection at the same time [20]. Furthermore, CMOS-based sensors can be optimal for separation of large numbers of cells [21].

CMOS technology enables facile manufacturing of the miniature lab-on-a-chip microsystems with integrated microelectronic sensors, which have the sensing elements together with the circuitry, compulsory for signal amplification, filtering, multiplexing, and analog-to-digital conversion [22]. Photonic cell detection by using CMOS image sensors was proposed for cluster of differentiation 4 (CD4) T lymphocyte counts of human immunodeficiency virus (HIV) infected patients, from whole blood [7]. It is of immense value, considering that point-of-care CD4 cell-count testing of the newly diagnosed HIV infection revealed great reduction (from 57% to 21%) in the loss to follow-up before completing staging [23].

A significant progress in CMOS imaging of cells for point-of-care diagnostics is termed 'lens-free imaging' [15,24]. The need for fluorescent tagging and microscope imaging [25] has been eliminated by 'lens-free imaging' of cells on CMOS sensors [15,24]. Cell enumeration can be realized with this approach, but sensor surface is required to be activated by specific capture elements for studies involving rare cell detection. To address this problem and validate specific cell capture, an intermediate layer like a glass film with gold array was attached to a commercial image sensor, in a study [7]. However, such intermediate layers introduce extra separation between the cells and detection elements, thereby reducing the detection sensitivity [26].

In this paper, a CMOS image sensor with a modified pixel structure [27] is presented. MCF-7 breast cancer cells were captured on the sensor surface and imaging was performed. Pixel active areas were coated with gold, by using electrolec gold plating technique [28], and modified with antibodies that bind to the drug resistant MCF-7 cells. Then, MCF-7 cells were bound and imaged, while the surface was illuminated with green LED light. In addition, the output image was processed by applying a threshold to improve the contrast of the sensor output image.

2. Pixel structure

An unconventional pixel structure was formed with a standard 0.35 μm CMOS process. Fig. 1 shows the pixel structure and close-up SEM photographs of a pixel. There is a 3 μm x 3 μm active area of exposed Al, suitable for electrolec gold plating, which can facilitate cell capturing right above the pixel, by chemical modification. The active area is formed by the top metal of the CMOS process, and is located at the center of each 15 μm x 15 μm pixel. The p-type silicon substrate of the pixel has a 6 μm x 6 μm n+ diffusion region, located right below the active area. Due to the reverse biased junction at the p–n+ boundary, a photosensitive area (sense node) is formed. The rest of the substrate is used to build the readout circuitry, for measuring the amount of photo-generated electrons. The circuitry is routed with the first and the second metals of the process (M1 and M2). The third metal of the process (M3) is used to implement a light mask between the active area and the photosensitive region. There are four holes on the mask, each having a width of 2.5 μm, which overlap with the corners of the active area. Cells captured on the active area affect almost all of the photons which penetrate through the mask and reach the photosensitive area. Therefore, even when the cells are much smaller than the pixel (3 μm compared to 15 μm), they affect the significant percentage of the sensed light, and the sensitivity does not drop drastically with decreasing cell size. So, the minimum detectable cell size is 3 μm, which is the size of the active area, and the maximum countable cell size is 15 μm, which is the size of the pixel. The latter constraint is due to the fact that larger cells can affect more than one pixel.

![Pixel structure](image_url)
3. Sensor electronics

Fig. 2 shows the distribution of the main circuitry blocks on the layout of the sensor, and electronics of a single pixel on a representative 2 × 2 array. The sensing part of the sensor is composed of 1024 such pixels forming a 32 × 32 array. Pixels consist of the reset, buffer and row switch transistors. The reset transistor periodically restores the voltage of the sense node (photosensitive area), which is discharged by photo-generated carriers. The buffer transistor isolates the sense node capacitance from the load of the column bus and output buffer. Finally, the row switch transistor enables row multiplexing. For column multiplexing, transistors connected to each column bus outside of the pixel area are used. Multiplexing is realized with the digital circuitry, comprised of vertical and horizontal scanners, and the control unit. The voltage of the sense node of the selected pixel is transferred to the analog output buffer, which drives the output pad of the sensor. Another analog block is the bias circuitry, which provides current biasing of pixels.

The sensor allows pixel multiplexing rates up to 400 kHz, corresponding to 391 frames per second (FPS), which is fast enough for many practical cell imaging applications. The output rms noise level of the sensor measured at 100 FPS rate is 160.4 electrons (e−) rms. The noise was measured with an 18-bit analog-to-digital converter (ADC) having a resolution of 3e− and 100 kSPS sampling rate, considering that 1 frame contains 1024 pixels. The noise of external electronics comprising ADC was measured to be 4.8 e− rms, which is much below the sensor noise level. The most of the sensor noise is due to the low frequency noises, such as reset noise of the 30 fF sense node capacitance (70 e− rms) and flicker noise of the pixel buffer transistor, which is hard to predict theoretically or by simulation because of poor flicker noise modeling. To reduce the effect of these noises, correlated double sampling (CDS) was applied, by reading every frame twice after reset, and taking the difference of correlated readings in the processing software. This reduced the noise down to 28.3 e− rms proving that the major noise contribution is indeed the low frequency noises. This low noise level leads to a very high sensitivity, considering the measured output swing of 60.3 × 10^2 e−, which is the maximum amount of light that can be absorbed by a pixel within one frame without saturation. Note that the variation of only 0.047% in the incident light can be detected with the signal-to-noise ratio (SNR) of 1, when the sensor is illuminated to the full swing. All quantities presented here were measured in volts and converted to e−, considering 5.3 μV/e− pixel conversion gain, resulting from 30 fF sense node capacitance.

4. Packaging and test set-up

4.1. Sensor packaging

Fig. 3 shows the cross-section and top-view of the developed sensor package. The sensor chip was wire bonded to a dual inline package. The wire bonds were preserved with non-conductive white epoxy. Epoxy was used also to build a reservoir over the sensor surface, for containing cell solutions. Four green LEDs, each in series with a 100 Ω resistor, were immersed in the epoxy walls at four sides of the sensor array, to provide a constant and controllable illumination. Controllable voltage was applied to the LEDs through two output ports. The surface of the sensor was easily accessible for cell addition and/or removal by washing. Moreover, it was possible to examine the surface under the microscope, in order to verify validity of the output image.

4.2. Electronic test set-up

The test setup consisted of the packaged sensor, ADC and field-programmable gate array (FPGA) boards, and a PC. An 18-bit ADC with a resolution of 3e− was used to convert the analog output of the sensor to digital data. A custom ADC board was designed and fabricated for this purpose. The board was compatible with a commercial BRK3010 FPGA board. FPGA was used for generating digital signals required for the sensor chip and the ADC, storing the output data, and transferring it to a PC. An output image was generated on the PC screen, in 8-bit grayscale format, while the ADC data was 18-bits. Therefore, 10 least significant bits (LSB) of the output data had to be truncated. To avoid the data loss due to truncation, the ADC output was multiplied by the gain of 200 in the processing software. Therefore, the least significant bit in the displayed image corresponded to 15.4 e− (≈ 3 e− × 2^{10}/200), instead of 3072 e− × 2^{10} as in the original output. This value is lower than the 28.3 e− rms noise value; hence the sensor output...
data could be imaged accurately without significant loss of LSB information. About 8 of the most significant bits (MSB) would be lost by applying this software gain of 200 (since log_2 200 ≈ 7.6), however, this is not important, because these bits are set to zero with the fixed pattern noise correction in most cases as explained further in this section. Some additional software processing was applied to the sensor output data to improve the final image. First of all, CDS was performed to eliminate the reset noise and reduce the effect of the flicker noise and drifts. CDS was done by resetting pixels every second frame and taking the difference of the data of consecutive frames. Then, to eliminate the fixed pattern noise, the background image was stored without cells on the surface, and was subtracted from the actual image after addition of cells to the surface. Assuming that cells modify the LSB’s of the output data up to Nth bit, (18–N) MSB bits become zero after subtraction. Therefore, multiplication by the software gain does not result in the data loss, if gain is adjusted properly. Finally, pixel gain correction was applied to correct the non-uniform output image, resulting from pixel gain variation throughout the array, owing to process and readout mismatch. Gain correction was implemented by measuring the pixel data under constant illumination and normalizing the output with a multiplier coefficient, calculated for each pixel. Illumination was provided by four LEDs on the sensor package. To obtain higher SNR, intensity of the LEDs was increased up to 50 × 10^{3} e^{-}, closer to the full swing level. Frame rate was reduced down to 0.1 FPS, to decrease the noise of the illumination down to the sensor noise level. The test set-up was enclosed in a Faraday cage, to prevent any electro-magnetic interference and external light input other than the LED illumination.

5. Materials and methods

5.1. Gold coating of pixels

Electroless gold plating of the pixel active areas eliminates the need for mask preparation and extra foundry process. Moreover, this technique allows die level coating. The procedure of the electroless gold plating was performed as in [29]. First, the Al top metal of the standard CMOS process was subjected to zinication process, which served as a seed layer for Ni coating. After coating the zinicated surface with Ni, gold was plated over nickel. The scanning electron microscope (SEM) pictures and the energy dispersive spectroscopy (EDS) results of both single Al pixel and successfully gold coated pixel are shown, respectively, in Fig. 4.

5.2. Chemicals for surface activation

The cross-linker sulfo succinimidyl 6-[3′(2-pyridyl)dithio)-propionamido] hexanoate (sulfo-LC-SPDP) was purchased from Pierce (Rockford, IL, USA). 20 mM sulfo-LC-SPDP was prepared in
deionized water (DI). TCEP·HCl was purchased from Sigma–Aldrich (St. Louis, MO, USA). 150 mM TCEP·HCl solution was prepared in DI and stored at room temperature. Anti-P-glycoprotein antibody (JSB-1) was purchased from abcam (London, UK) and stored at 4 °C. Phosphate-buffered saline (PBS) was purchased from Sigma–Aldrich (St. Louis, MO, USA) and 1× PBS was prepared by diluting the stock solution with DI.

5.3. Optimization of suspension medium type for cell imaging

In the previous study [27], test with the baker’s yeast cells was performed for the proof of concept. Resistance of yeast cells to desiccation, owing to their cell walls, enabled well suitability of these cells to our purpose. The cells were simply mixed with DI in desired amounts and 3 μL of this suspension was immediately pipetted on the sensor. Scattered cells over the sensor surface were imaged (Fig. 5) after evaporation of the water [27]. Working in pure water could not be selected as the straight working condition of the mammalian cell tests. Therefore, working in cell culture medium and PBS were tested comparatively, by preparing cell suspensions in cell culture medium, 10× PBS, 1× PBS, and 0.1× PBS. The outcome of the sensor imaging tests with these preparations revealed that the cell suspension in 1× PBS was proved to be the best, both for the cells and the sensor output image quality. Tests with the cells that were suspended in cell culture medium and 10× PBS were leaving reminiscent of the cell culture medium and/or salt. This was diminishing the sensor output image quality. Whereas, test with the cells suspended in 0.1× PBS was not leading to any loss in the image quality, but majority of the cells did not remain intact.

5.4. MCF-7 breast cancer cells for sensor imaging

Applicability of the chip for mammalian cell detection was tested with drug resistant MCF-7 breast cancer cells, bearing over-expressed P-glycoprotein molecules on their surfaces [30]. Drug resistant MCF-7 breast cancer cells were received from Biological Sciences Department of the Middle East Technical University, with courtesy. Trypsin enzyme was not used for the separation of the MCF-7 cells from the culture flasks. Instead, cells were detached by a gentle, mechanical intervention. Then, 1× PBS was exchanged with the cell culture medium and MCF-7 cells were transferred to
Fig. 5. Yeast cell test results: (a) microscope photograph of yeast cells in water, when the water completely evaporated; (b) output image of the sensor when the sensor surface is dry. Green markers indicate cells attached to active areas, resulting in white spots, and red markers indicate cells standing elsewhere on pixels, resulting in dark spots. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Fig. 6. Microscope and sensor images of the MCF-7 cells: (a) microscope photograph of MCF-7 cells in 1× PBS, when the sensor surface is about to dry; (b) microscope photograph of burst cells, when the solution is completely evaporated; (c) output image of the sensor when the sensor surface is about to dry; (d) output image of the sensor when threshold processing is applied. False positives are shown with red dots and false negatives are shown with green dots. Correlation of the threshold processed output image with the microscope photograph is high, since only 6 of 78 detected spots are false. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)
the sensor surface in a similar manner as performed in case of the yeast cell tests [27].

5.5. Surface activation with antibodies

The protocol for activation of the gold coated pixels of the CMOS sensor for MCF-7 capturing was modified from a specific cell detection procedure [31]. Accordingly, 12.6 μL of 67 μg/mL anti-P-glycoprotein antibody solution was taken from the stock and mixed with 3 μL of freshly prepared 20 mM sulfo-LC-SPDP cross-linker solution. It was incubated for 1 h. Then, 7 μL of freshly prepared 150 mM TCEP-HCl was added to this solution and incubated for 30 min more. Afterwards, whole content was added onto the sensor surface and left in a rough, home-made humidity chamber for 1 h, in order to achieve the binding of antibodies to the gold surface, through the free thiol ends of the linker molecules. The sensor surface was rinsed with 1× PBS and gently dried to eliminate the remaining bulk water, after 1 h.

5.6. Capturing and detection of MCF-7 cells on the sensor surface

Following activation of the sensor surface with antibodies, MCF-7 breast cancer cells in 1× PBS were added on the sensor surface. The surface was washed with 1× PBS, after 1 h. MCF-7 cells were bound to the antibodies on the sensor. The second and third washing processes were also done by using 1× PBS and light microscope imaging was performed after each washing step.

Sensor images were obtained when the solution on the surface was close to evaporate completely. Vertical thickness of the liquid was monitored manually, by optical means. Acquired sensor images (Figs. 6c and 8b) were processed by applying a threshold to extract the cell position data in an easier manner (Figs. 6d and 8d). Cell detection performances were evaluated visually, through the outcome of the image processing results.

6. Results and discussion

6.1. Imaging of MCF-7 breast cancer cells

Fig. 6 shows the test results obtained with MCF-7 cells that were suspended in 1× PBS. It was not practical to obtain the images when the reservoir was filled with PBS solution or after its thorough evaporation, because in the former case, light scattering severely diminishes the image quality, and in the latter case, cells burst (Fig. 6b). Mammalian cells have cellular membranes, which are much thinner and fragile in comparison to the yeast cell wall, and osmotic pressure is necessary. Thus, as already mentioned, mammalian cell tests could not be performed in water alone. Conversely, sensor surface needs to be dried before the measurement, because the LED light randomly scatters in the bulk solution, which destabilizes the amount of light reaching each pixel. This drawback can be eliminated with the implementation of micro-fluidic channel over the sensor, which would be limiting the thickness of cell suspending solution to the channel height, and minimizing the light scattering. Nevertheless, the micro-fluidic channel is not implemented yet.

Considering all the constraints described above, MCF-7 cells were decided to be transferred to the sensor surface as a suspension in 1× PBS and imaged only after bulk water content of the suspension medium was evaporated. The proper time for imaging was the moment close to complete evaporation (Fig. 6a), when the remaining hydration layer still allowed the cellular viability but did not lead to any deterioration in the sensor output image, due to light scattering, or so. A very high correlation was attained between the microscope (Fig. 6a) and the threshold processed sensor (Fig. 6d) images, considering the location and number of cells. Only three false positives (detection in locations absent of cells) and three false negatives (undetected cells) were present within detected 78 cells. These false detections are the result of uneven buffer solution profile due to evaporation on the surface, which leads to uneven light scattering and refraction. With the
accommodation of a micro-fluidic channel, this problem is expected to be resolved. Consequently, applicability of the sensor for mammalian cell detection was verified.

6.2. Capturing and detection of MCF-7 cells

Fig. 7a shows the sensor surface after the first and the second washing steps, following the sensor surface modification and immobilization of the MCF-7 cells. Cells on the surface remained the same even after the third washing step and no further cells were detached, indicating that they were firmly attached. As a control test, cells were incubated for the same duration on the unmodified sensor surface, followed by the same washing processes (Fig. 7b). In that case, no cells were left on the surface after the second washing step. Captured MCF-7 cells were imaged both with the sensor and the light microscope (Fig. 8).

Cells were not counted for quantifying the detected and missed cells since a crowded cell cluster remained on the sensor surface. This cell cluster was impeding a proper correlation among the number of cells within the cluster and the underlying pixels. However, as revealed by the processed image, there were only one false negative and two false positives (Fig. 8c vs Fig. 8d). One of the false positives was due to a residual particle which was not removed after washing. This kind of undesired effects can be eliminated with the utilization of a microfluidic channel and hence clean test environment. Yet, the test set-up was eventually an open system and the particulates other than cells remained on the sensor surface. The cells were quiet distinguishable with their characteristic round appearance, especially before the drying process was ended. Visual characterization of cells may also be feasible with the cellular staining approach. However, cellular staining was not preferred; mainly due to the possible loss in the detection performance. Besides, it is an extra step that would be prolonging the detection time, increasing the complexity, and elevating the costs.

7. Conclusion

The goal of the presented work was to demonstrate a method for rare cell capture on the CIS, as a robust CMOS-based system, which can be developed for point-of-care testing studies. The intention of the initial tests was to demonstrate the applicability of cell imaging through the proposed system. This was achieved with baker's
yeast cells. In case of those tests, bright or dark appearance of the pixels in the sensor output images were heavily depending on the interaction manner of the cells with the sensor surface and with each other.

The two major achievements following the above-mentioned early test with the yeast cells were (1) proving the applicability of the chip for mammalian cell imaging, and then, (2) showing cell capturing and detection by a modified sensor surface. The latter is imperative to specific cell detection. Pursuing this aim, pixels of the CMOS sensor were coated with gold. Then, a chemical protocol was successfully employed for the sensor surface modification and capturing of drug resistant MCF-7 cells, prior to the imaging of the cells with the CMOS sensor.

Eventually, cell capturing and detection with the proposed CMOS chip were demonstrated here, and testing selectivity is left for the future efforts. Also, the performance of the system will improve when the built-in micro-fluidic channels are realized, together with the use of illumination having minimized scattering.

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References


Biographies

Javid Musayev received BSc and MSc degrees from the Middle East Technical University, Electrical and Electronics Engineering Department in 2009 and 2011, respectively. From 2012 to 2013 he worked in Mikrosens Company, Turkey as an IC design engineer. He is currently a PhD student in the University of Toronto, Department of Electrical and Computer Engineering.

Caglar Altiner was born in Ankara, Turkey in 1985. He received his B.S. degree in Electrical and Electronics Engineering and M.S. degree in Micro and Nanotechnology Department from Middle East Technical University (METU), Ankara, in 2009 and 2012, respectively. His master studies focused on designing and testing an image sensor for rare cell detection applications. From 2009 to 2012, he has worked as a VLSI design engineer in Mikro-Tasarim Ltd. Sti., Turkey. Currently, he is working on ToF cameras at 3DTIM Electronics A.S. which he has co-founded.

Dr. Yekbun Adiguzel completed her master of science studies at the Pediatric Molec- ular Genetics Department of Ankara University Medical Faculty, Turkey, following her undergraduate studies at the Molecular Biology and Genetics Department of Middle East Technical University, Turkey. Afterward, she fulfilled her doctor of philosophy studies at the Biophysics Department of the Ruhr-University of Bochum, Germany, and involved in postdoctoral studies at the Neurobiochemistry Department of the same university. She is now a faculty member at the Istanbul Kemal University Medical Faculty, Turkey, and was studying as a postdoc- toral scientist at the BioMEMS Division of the METU-MEMS Research and Application Center, during this work.

Assoc. Prof. Dr. Haluk Kulah received the BSc and MSc degrees in electrical engineering with high honors from METU, Ankara, Turkey, in 1996 and 1998, respect- ively, and the PhD degree in electrical engineering from the University of Michigan, Ann Arbor, in 2003. From 2003 to 2004, he was employed as a research fellow at the Department of Electrical Engineering and Computer Science, University of Michigan. In August 2004, he joined the Electrical and Electronics Engineering Department of METU as a faculty member. His research interests include MEMS sensors, micro- signal interface electronics design for MEMS sensors, BioMEMS, and MEMS-based energy scavenging. He is also working as the deputy director of METU-MEMS Center.
Selim Eminoglu was born in Ankara, Turkey, in 1973. He received the B.S., M.S., and Ph.D. degrees in electrical engineering from the Middle East Technical University (METU), Ankara, in 1996, 1998, and 2003, respectively. His Ph.D. thesis on uncooled infrared focal plane arrays in standard CMOS technology received the "METU Thesis of the Year Award" in 2003, given by the Prof. Dr. Mustafa N. Parlar Education and Research Foundation. From 1995 to 1998, he was a part-time Researcher with the VLSI Design Center, Information Technologies and Electronics Research Institute (BILTEM), Scientific and Technological Research Council of Turkey (TUBITAK). From 1996 to 2003, he was a teaching and research assistant with the Electrical and Electronics Engineering Department, METU. From 2003 to 2008 he worked as a research scientist at Teledyne Scientific and Imaging, LLC (formerly Rockwell Scientific), Thousand Oaks, CA. From 2008 to 2011 he worked as an assistant professor at the Micro and Nanotechnology Department of Graduate School of Natural and Applied Sciences of METU, where he taught courses and co-supervised graduate studies in the area of imaging sensors and integrated circuits. He is the co-founder and CTO of Mikro-Tasarım Ltd, a fabless semiconductor company developing high performance imaging sensors for scientific and industrial applications. Dr. Eminoglu has authored and co-authored 3 journal papers, 12 conference papers, and holds 3 US patents.

Tayfun Akin was born in Van, Turkey, in 1966. He received the B.S. degree in electrical engineering with high honors from Middle East Technical University, Ankara, in 1987 and went to the USA in 1987 for his graduate studies with a graduate fellowship provided by NATO Science Scholarship Program through the Scientific and Technical Research Council of Turkey (TUBITAK). He received the M.S. degree in 1989 and the Ph.D. degree in 1994 in electrical engineering, both from the University of Michigan, Ann Arbor. Since 1995, 1998, and 2004, he has been employed as an Assistant Professor, Associate Professor, and Professor, respectively, in the Department of Electrical and Electronics Engineering at Middle East Technical University, Ankara, Turkey. He is also the director of METU-MEMS Center, which has a 1300 m² cleanroom area for 4”, 6”, and 8” MEMS process and testing. His research interests include MEMS (Micro-Electro-Mechanical Systems), Microsystems Technologies, infrared detectors and readout circuits, silicon-based integrated sensors and transducers, and analog and digital integrated circuit design.

He has served in various MEMS, EUROSENSORS, and TRANSUDCERS conferences as a Technical Program Committee Member. He was the co-chair of The 19th IEEE International Conference of Micro Electro Mechanical Systems (MEMS 2006) held in Istanbul, and he was the co-chair of the Steering Committee of the IEEE MEMS Conference in 2007. He is the winner of the First Prize in Experienced Analog/Digital Mixed-Signal Design Category at the 1994 Student VLSI Circuit Design Contest organized and sponsored by Mentor Graphics, Texas Instruments, Hewlett-Packard, Sun Microsystems, and Electronic Design Magazine. He is the co-author of the symmetric decoupled gyroscope project which won the first prize award in the operational designs category of the international design contest organized by DATE Conference and CMP in March 2003. He is also the co-author of the gyroscope project which won the third prize award of 3-D MEMS Design Challenge organized by MEMGen Corporation (currently, Microfabrica).