White Paper by Anitoa Systems, LLC

CMOS biosensor breakthrough enables portable diagnostics solution

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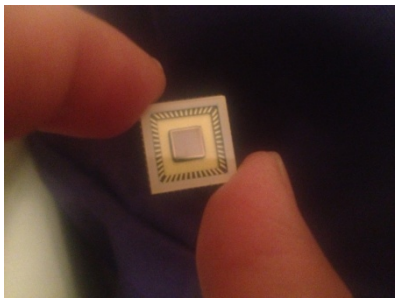
In the past 10 plus years we have seen vast advancement in molecular diagnostics technologies. Doctors can now use nucleic acid (DNA) or protein analysis to get very precise answers about the type of virus, bacteria or cancerous cells that cause our illness. This is great news as the world is facing new and re-emerging microbial threats. Precise diagnostics leads to effective, targeted drug and treatment to help counter these threats.

Still much of the world's population does not have access to these technologies. This is largely due to the cost and bulkiness of the instruments used. There is now a pressing need for low cost, small portable molecular diagnostics system solutions.

Ultra low-light CMOS imager for molecular sensing

Despite past efforts by the research community to develop novel technologies such as microfluidics to help lowing cost and achieve miniaturization, truly portable molecular diagnostics have largely eluded us. This is due to the lack of compact instrumentation. Engineers at Anitoa (Palo Alto, CA. www.anitoa.com) strive to solve this problem by introducing CMOS molecular sensors that are highly integrated and low power, yet have the sensitivity to enable portable molecular diagnostic instruments.

Most of today's molecular diagnostic systems use optical methods[1] to detect molecular events, based on principle of fluorescence and chemiluminescence signaling. To meet the high sensitivity requirement for molecular sensing, engineers have to resort to bulky and expensive devices such as photon multiplier tubes (PMT) or cooled CCDs.



Anitoa's ULS24 ultra-low light CMOS imager chip

Recent innovations of CMOS image sensors have made it possible to achieve far better sensitivity than what is possible before. But still more improvements are needed for CMOS to compete with PMT and cooled CCD. Engineers at Anitoa uses process optimization and novel circuit techniques to reduce the various noises of CMOS image sensor to achieve high signal-to-noise ratio. The excessive noise that cannot be eliminated in the chip, due to limitations of physics, is further computed and filtered through software algorithms that "understand" the statistical nature of different sources of noises and signals in the system.

With this approach, Anitoa has fabricated a CMOS molecular imager chip built on 0.18um CIS technology from a world-leader specialty foundry. This chip has shown to achieving 3e-6 lux detection sensitivity,

[1] Electrochemical molecular sensors have shown promise but require sophisticated surface chemistry and suffer from stability and specificity problems.

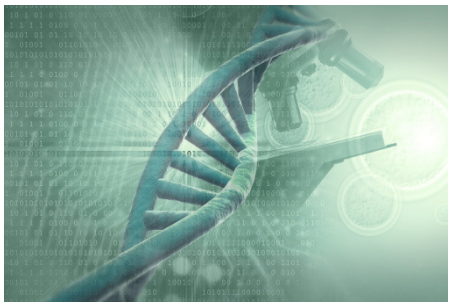
capable of detecting just a few molecules labeled with fluorescence reporter probes. Anitoa is creating a palm-sized qPCR (quantitative polymerase chain reaction) system with automatic sample preparation using its CMOS imager. The CMOS imager is paired with LEDs as the optical excitation source, to achieve fluorescence-based molecular sensing in a very compact platform.

Anitoa ULS24 Performance Parameters:

Imager configuration	24x24 (w/ 4–binning) active pixels at 150um x 150um
ADC resolution	12-bit
Signal Interface	Serial Peripheral Interface (SPI), 4 wires
Responsivity	132V/lux-sec
Dynamic range	>85dB
SnR	>13dB at detection threshold of 3e-6 lux narrow band light signal
Supply and power	3.3V (analog); 1.8V (digital), < 30mW active power
Operating temperature	-25 – 85 ºC (* up to 45 ºC to meet optical SnR spec).
Packaging	48-pin CLCC

qPCR for infectious disease diagnostics

When it comes to detecting very small amount of pathogenic molecules, such DNA molecules released from viruses or cancerous cells, it is important that the method is not only sensitive, but also specific.



DNA amplification and detection with qPCR

qPCR achieves sensitivity and specificity through combined amplification and detection. By amplification, qPCR can cause target DNA strands be selectively replicated millions of times, with the help of a special enzyme called polymerase. As the target DNA strands being replicated, they bind with specially design molecular probes that are labeled with fluorescence materials.

The high sensitivity and SnR in Anitoa's CMOS imager means the instrument is able to work with small reaction volumes confined in a microfluidic structure. Small reaction volume means faster reaction and faster time to results. Integration of CMOS sensor with microfluidic module also allows for other fluid automation features such as sample preparation.

Future trends

Anitoa envision in the near future, small and portable molecular diagnostics devices would be deployed at point-of-care, enabling rapid diagnostics of infectious disease on-the-site, so that doctors can respond quickly with life-saving drugs and treatment, and prevent the further spread of these diseases. The diagnostics device will be internet enabled, and the diagnostic results will be transmitted to a central database in the cloud, allowing doctors, drug companies and policy makers to make better-informed decisions on global epidemic control. (For more information, please contact Zhimin Ding at info@anitoa.com).