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Editorial

# Lab-on-a-Chip Technology for Near Patient Diagnosis

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Over the years bio electronic tools have proven to be a boon by establishing a synergy between biology and electronics. Exploitation of biology in conjunction with electronics provides a beneficial interface between biological material and micro and nano electronics. The developments of innovative devices for diagnosis of several diseases are the keystones of bio electronic research and development. During the last decade bio electronic industry has gained momentum with intensive research being carried out on mini portable devices capable of rapid detection and monitoring of lab scale processes with precision. Therefore invention of tiny laboratory devices, preferably in a chip form (only millimetres to a few square centimetres in size) having the ability to perform laboratory operations on a small scale are referred as "Lab-on-a-chip" (LOC). LOC refers to downscaling of single or multiple lab processes onto a chip format to perform biological or chemical analysis. Although the application of LOCs is still novel and modern, several companies and research groups have shown growing interest in their application in different analytical fields viz. chemical analysis, environmental monitoring and medical diagnostics. Such miniaturized systems promisingly offer shorter reaction times, reduced use of materials and solvents along with higher product yields, adeptly taking diagnostics to the point of care.

## Point of Care Testing (POCT)

LOCs have yielded an attention-grabbing magnitude as they enable the paramedics to perform on the spot diagnostic tests directly at the site of patient care. The technique employed is not only simple, rapid, automated and user friendly but also holds greater advantage by utilizing reduced amounts of sample volumes (micro fluidics) with high specificity, high performance and accurate results. As opposed to the conventional diagnostic techniques that involve time consuming and tedious laboratory procedures, LOCs provide rapid detection and diagnosis without the expertise of a skilled trained laboratory technician. Thus the Lab on a chip technology with its compact and portable features eliminates the roundabout trips of patients from doctors to diagnostic labs and back to the doctors, by bringing the lab itself at the site of patient care.

## Loc - State of the Art Technology

Lab-on-a-chip device is precisely a semiconductor fabrication technology utilizing micro fabrication to fabricate channels, chambers, reactors and active components on the size scale of the width of the human hair or even smaller. It integrates many cumbersome laboratory procedures into a single device with the help of micro and nano electronics. Therefore LOC is a miniaturized biomedical laboratory built on a thin glass or plastic chip with a network of micro channels, electrodes, sensors and electronic circuits. It is interesting to note that the micro fluidic technology involved in the LOC implements the use of only microlitre volumes of sample, (e.g. saliva, blood, urine, DNA, RNA) buffers and reagents in synergism for the rapid detection of test results. Thus it also proves its efficiency in detecting multiple analyses simultaneously called multiplexing. The LOCs also have a temperature control system, optics and can carry out multiple functions simultaneously. In LOCs due to its geometrical constrains, it has high surface to volume ratio with surface tension being a dominant parameter. The heat transfer between analyses is faster due to small distance and gravity holds minor importance thereby allowing precise control over the fluids and subsequently on the results of the diagnostic tests. Thus LOCs are wonder chips assimilating various facets of science like Diagnostics, Biotechnology, Bioinformatics, Pharmacy, Physics, Electronics, Chemistry and Research with the ultimate aim to improve global health by providing point of care testing devices.

## Gene Chips

With their portability, high efficiency and precision, LOCs have already found use in diagnostic tests involving blood, saliva and urine for detection of certain infectious diseases, blood glucose and other components in patient's body fluids. Intensive research is still being carried out on the use of DNA (Deoxyribose nucleic acid) samples in LOCs to carry out gene expression studies, cancer and diagnosis of other chronic and infectious diseases with precision. Such LOCs that use DNA (or RNA) as their test samples for diagnosis are commonly referred to as 'gene chips' or 'DNA chips'.

A DNA microarray chip is a small bio electronic chip that helps in screening the entire human genome (roughly 30,000 genes). Few microlitre of DNA/c DNA sample when loaded onto the applicator, hybridizes with complementary fluorescent labeled DNA probes on the chip. Subsequently, the detector shows varying levels of fluorescence indicating varying levels of gene activity. This biosensor-bio electronic technology distinguishes the active genes from the inactive genes of the patient involved, depending on the degree of florescence. It also holds significance by showing the relationship between specific genes and specific diseases.

A further sophisticated modification of DNA chip technology is the chip based PCR (Polymerase Chain Reaction). Chip based PCR is a plastic disposable Lab-on-a-chip for detection of pathogens samples. It consists of a micro fluidic plastic chip with integrated porous polymer monoliths and silica particles for cell lysis and nucleic acid isolation. It also involves use of a compact and portable PCR instrument that functions as a PCR thermal cycler. Here the samples are shuttled between oscillating temperature flow inside a micro fluidic chip to three different temperature zones required for DNA amplification. Together, the unit carries out bacterial lysis, nucleic acid isolation and concentration along with polymerase chain reaction and endpoint fluorescent detection. PCR chips manufactured




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and marketed by Genome Era CDX™ for rapid identification of Methicillin resistant *Staphylococcus aureus* (MRSA). In this system, a single colony of the test organism is picked up and cells are shaken in the sample buffer tube. Subsequent to this the mixture is pippeted onto PCR chips which are then inserted in an analyzer to carry out PCR assay and analysis. A furthermore modified technique based on this principle is the Vera MTB LOC kit by Veredus Laboratories that carries out rapid and accurate detection of *Mycobacterium tuberculosis* complex (MTBC) and its mutations. The Vera MTB™ is a nucleic acid-based, Lab-On-Chip (LOC) device which combines multiplex PCR and microarray hybridization assay to detect, differentiate and identify: 10 different mycobacterium strains with special emphasis on *Mycobacterium tuberculosis* complex (MTBC) and its resistance to Rifampicin and/or Isoniazid from pulmonary clinical specimens or cultivated samples. Mycobacterium tuberculosis bacilli resistant to rifampicin and isoniazid is called multidrug resistant tuberculosis (MDR-TB).

Although molecular diagnostic technologies have been around for a substantial amount of time, however they have not been found to deliver as per expectations. This calls for advanced molecular diagnostic techniques to be put into practice. Molecular diagnostic technologies have gained impetus with advancement from the conventional PCR technique to an innovative technique called Real Time PCR. Additionally, this technique when scaled down on a chip significantly reduces the sample volumes and detection times and also shows results of analyzed samples at real time. A standard RT-PCR procedure involves extraction of RNA from tissues and cells, copying it into cDNA with the help of the enzyme reverse transcriptase, carrying out a PCR reaction to give real time results that are displayed on the screen of an automated analyzer. An improvised version of this is the LOC-RT-PCR which is True Lab ™ Real Time micro PCR system developed by Mol Bio Diagnostics Pvt ltd. that works on four simple processes which can be completed rapidly. The steps involved in disease diagnosis include i) **Collection of clinical specimen**: This include sample like blood, plasma or sputum. ii) **Sample preparation**: Extraction and of the nucleic acids from specimen and purification of nucleic acid from PCR inhibitors. This is usually carried out in small extraction tubes with the help of mini kits that comprise of reagents needed for the supposed purpose. The extraction tube is placed in the holder of a sample preparation device that provides the required heat and magnetic field with the help of magnetic nano particles to carry out sequential purification and processing of the sample within twenty minutes. iii) **Automatic analysis**: A volume as low as 6 µl of the sample is loaded onto the LOC-RT-PCR chip. This chip is further inserted into the RT micro PCR analyzer which is an extremely small, bench top, portable device. The device carries out RT-PCR to give final results that are displayed on the screen at the end of the assay. iv) **Reporting results**: results of the RT-PCR reaction obtained can be printed and documented as records for further analyses and also you can directly e-mail the results to patient since this micro PCR system is Wifi, Bluetooth and GPRS compatible. True Lab ™ Real Time micro PCR system works on the following simple procedures **(1) Extract (2) Load and (3) Read**. The entire unit is extremely light weight, portable and durable and can be easily carried to the point of need to provide rapid results of diagnostic tests and therefore also called as anytime anywhere real time PCR system. It encompasses sample collection and PCR analysis along with providing near patient diagnosis within an hour's time. The True Lab ™ system integrates multiple functions on chip combining Micro-Electro-Mechanical-Systems (MEMS) with micro fluidics. Since it is chip based and utilizes micro fluidics, it assures high sensitivity and specificity of the diagnostic tests being carried out. The technique has high reproducibility and precision having nano particle based nucleic acid purification and performs reverse transcriptase as well as PCR in a single step. It does not require preparation of any PCR master mix and is also easily disposable. Such mini diagnostic chips are commercially available for detection of pathogens like H1N1virus, HIV, HBV, *Mycobacterium tuberculosis* and malaria parasites. Thus Lab on Chip RT-PCR has several advantages over the conventional diagnostic techniques as well as simple DNA chips. Thus it proposes to be one of the most innovative bio electronic tools for simpler, rapid and accurate diagnosis of diseases. In near future molbio diagnostics pvt. ltd. is planning to bring in market complete automated real time micro PCR device, where in nucleic acid isolation and real time PCR analysis are coupled together. This device can analyze 4 or more samples at a time with a multiplexing facility.

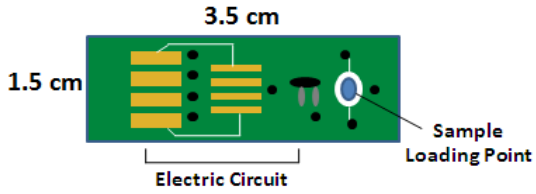


**Figure 1:** Lab-On-a- Chip (RT-PCR).

- Truenat™ Chip based Real Time micro PCR Tests are sensitive, specific.
- Sample to Real Time PCR under 1 hr
- Any where any Time real Time PCR possible
- Cost effective and Near patient diagnosis, Figure 1

## DNA Cartridge

It may be imperative to also mention about slightly variants of the DNA chip technology i.e. DNA cartridges. These are advanced devices that eliminate steps of sample purification and nucleic acid extraction. DNA cartridges have an advantage over the DNA chips as they integrate sample extraction, amplification and detection, all in one cartridge and provide results directly from samples without any manual sample processing steps. Gene Expert DNA cartridge system, marketed by Cepheid is the best example to explain DNA cartridges. It is a fully fledged integrated and automated on-demand diagnostic system that carries out test analysis within 2 hours. The Gene Expert MTB/RIF is a cartridge-based automated diagnostic test for identification of *Mycobacterium tuberculosis* (MTB) and resistance to Rifampicin (RIF) by Nucleic Acid Amplification Technique (NAAT). It is interesting to note that in December 2010, the World Health Organization (WHO) has endorsed the Gene Expert MTB/RIF for use in TB endemic countries, declaring it a major milestone for global tuberculosis (TB) diagnosis. Several other commercially available products also elucidate such type of bioelectrical diagnostic technology. The disposable cartridge by Alere NAT system for detection of Human Immunodeficiency Virus (HIV)

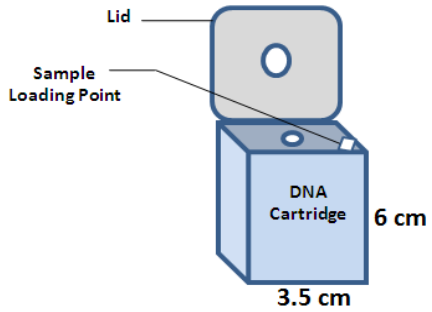


**Figure 2:** Model of a DNA Cartridge.

carries out sample collection, cell lysis, specific target capture, reverse transcription, PCR amplification and real time fluorescence detection based on reporter probe hybridization on an integrated micro probe array. The Lit ™ analyzer is yet another such DNA cartridge system designed to carry out multiplex PCR real time detection of H1N1 virus. In such a system, the sample (whole blood) is directly applied into the cartridge and inserted into the analyzer for amplification and real time detection. Thus DNA cartridges have also proved to be major breakthrough products in the field of molecular diagnostics.

## LOCs as Game Changers

It has been observed that over a period of time the use of kits and reagents has been stopped by developed countries and one finds them slowly heading towards newer bio electronic technologies. Earlier it was observed that serological diagnostic kits scrapped by the developed countries were then exported to developing countries. However, recent trends show that even the developing countries have shown keen interest in the use of these improvised and sophisticated bio electronic tools. LOCs provide a relief from the laborious and time consuming conventional diagnostic tests by providing rapid, point of care service to the patients. In case of chronic diseases like TB, serological tests (blood tests and antibody tests like ELISA) were widely used in various countries by government and private health sectors despite the knowledge of their inaccuracy. Unavailability of accurate, validated, point of care tests for TB had left patients, doctors and paramedics with no better option than serological tests for disease diagnosis. Considering global health standards, the World Health Organization (WHO) in its first ever negative policy recommendation prohibited all the governing bodies from conducting (serological tests) for TB due to their inaccuracies. Thus with the aim of improving health standards of its citizens, several developing countries like India have banned the sale, use or import of such inaccurate and irrational TB serological kits. In such situations accurate and reliable methods like DNA chips and LOC-RT-PCR based techniques have come to the rescue of the health authorities as well as the patients. Therefore in today's time, we find the developing countries heading towards the use of LOCs for trustworthy and accurate test results. Biosensors and bio electronic tools have thus gained significant market value due to their high performance efficiencies and portability. The added advantage of these tools being cost effective, user friendly and not requiring skilled professionals for their use furthermore have encouraged their usage. By providing near patient diagnosis, the LOCs have changed the traditional scenario of scientific research bringing an entire laboratory to a small chip size. This path breaking tool in the field of science and technology has been pivotal in elevating the field and is therefore preferred over the conventional lab techniques. Thus LOCs are the new booming bioectronic tools preferentially used by several doctors and researchers to deliver rapid test results.

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