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Research paper

A Technology Overview and Future Scope of Bio-Mems in Tropical Disease Detection: Review

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Abstract

From past few years, there is a revolutionary progress in biomedical sensing applications as a result of incredible growth in technological advancements. The biomedical sensors play a key role in the global market and it is estimated to reach 15.01 Billion US$ by 2022. As a worldwide research focus, there is especially a strong interest in the use of micro and Nanosystems in health monitoring. Most of the researchers applying innovative techniques to noninvasive patient monitoring and diagnostics developed with micro and nanofabricated technologies like MEMS/NEMS. Which provides more compact, inexpensive, accurate, and reliable detection tools to identify more life-threatening diseases in early times. This review paper will focus on various tropical disease detection methods and scope of the BioMEMS towards the detection of more prevalent tropical diseases.

Keywords: *MEMS,biosensors,actuators, tropical diseases, noninvasive, chemical sensing, microfluidics, biotechnology.*

1. Introduction

Nowadays Tropical diseases are widespread in the Tropical and Subtropical regions[1]. These tropical diseases are widespread in hot and cold climates leads to pathogenic agents. Which may include malaria, dengue, Tetanus, Hepatitis, yellow fever, cholera and many others. The identification of those tropical diseases contains serologic testing of infective markers like macromolecule, antigen, and protein X-rays, physical examination still as activity microorganism and fungous culture techniques. These strategies need a sample of body fluid like blood, mucous secretion (or) excretory product samples. But the identification of tropical diseases needs many challenges which incorporate prolonged work time for assessment of specimens, Controlled surroundings, extremely trained personnel and large blood (or) liquid body substance samples and conjointly this can be the foremost valuable. Not just for these tropical diseases, to look at a pathologic organ or bad of a joint during a physical structure, go across the skin and open up the body then exclusively they might verify the character of drawback and decides the course of action. However which can or might not happen throughout surgical procedures. The term exploratory surgery is employed for this kind of medical procedures and lots of risks are inherent in such strategies and these associated methods and measurements are perpetually Invasive. In Order to provide diagnostic technique more easily, Accurate, inexpensive and low turnaround time to detect this tropical diseases, recent researches and studies from past few years proposed numerous biomedical engineering approaches with non-invasive biomedical sensors. This novel minimal invasive sensing techniques ready to replace former methods and provide new insights into the physiological state [2]. This review paper concentrate on biomedical sensors developed to date in current biomedical engineering approaches and future research area of MEMS/NEMS-based biomedical sensors on detection tropical diseases. And additionally Innovative, smart solutions for sensing devices, are going to be highlighted, in conjunction with specific applications of each biomedical sensing element technologies. Finally, the paper can depict the long run perspective of MEMS/NEMS biomedical sensing element technologies and corresponding exploitation opportunities for the development of Bio-MEMS (Bio-Micro-Electro-Mechanical System) and Bio-NEMS (Bio-Nano-Electro-Mechanical System) for chemical sensing [3]. Exciting progress has been achieved as a result of the integration of Micro/Nanofabricated devices with the purposeful sensitive nanomaterial. That introduced new features and better performance to the chemical sensing systems, like higher sensitivity, higher specificity, higher throughput, and lower economic. .

2. Biomedical Sensing Technology/Approaches of Various Tropical Diseases

Current research and studies have proposed numerous biomedical engineering approaches that commit to addressing the issues featured in the diagnosing of tropical diseases. This paper focuses on present biomedical engineering approaches for the more distinguished diseases of dengue fever, malaria, cholera, schistosomiasis, lymphatic disease, Ebola, leprosy, the protozoal infection, and Chagas. The diagnosing of those tropical diseases contains various ways as well as serological testing of pathogenic markers like protein, antigen, and antibody X-rays, physical examination in addition to performing microorganism and fungous culture techniques. In this section we tend to discuss variety of sensing technology/approach is employed to detect Topical diseases from previous discussions are listed. Table 1 represents various engineering approaches to detect breakbone fever.

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Table 1: Dengue Detection Methodologies

Tropical disease	Author Reference	Type of Sensing Technology
Dengue	Ibrahim F et al. [4]	Bioelectric Impedance Analysis(BIA)
	Priyanka shrama et al. [5]	Decision Support system
	Mohit Arora et al.[6]	Echo cardio graphy
	Dr. Hasan Sadikin et al. [7]	Electro cardio Graphy
	V sravani et al. [8]	Imaging: Ultrasonic
	Amir M. Foudeh et al. [9]	Micro Fluidics and Lab on a chip
	J F Lancaster et al. [10]	Laser Doppler Velocimetry
	Leila Syedmoradi et al. [11]	Paper based Diagnostics
	Delia B. Bethell et al.[12]	Plethysmo Graphy

Dengue fever could be a mosquito-borne tropical disease caused by the dengue virus and it's most typical in the Asian nation throughout the few months after the monsoon, however, occurs within the monsoon season additionally, this can be a lot of prevailing in water stagnated areas. Meantime protozoal infection isn't a true problem in Asian country during the dry winters, however outbreaks of occurring throughout the monsoon, significantly when it's raining perpetually. The foremost severe falciparum strain of malaria is most active after the monsoon.

Table 2: Malaria Detection Methodologies

Tropical Disease	Author Reference	Type of sensing Technology
Malaria	Ibrahim F et al.[4]	Bioelectric Impedance Analysis
	Surasak Kasetsirikul et al.[13]	Die electro Pharoses
	Pallavi T. Suradkar et al.[14]	Image processing
	Shouki Yatsushiro et al. [15]	Micro Array chip
	Amir M. Foudeh et al.[9]	Micro Fluidics and Lab on a chip

Cholera is an infectious disease that causes severe watery diarrhea, which may cause dehydration and even death if untreated. it's caused by consumption food or beverage contaminated with a microorganism referred to as true bacteria epidemic cholera. Similarly, schistosomiasis could be an unwellness that is caused by parasites that enter humans by attaching to the skin, penetrating it, and so migrating through the blood vessel system to the portal veins wherever the parasites produce eggs and eventually, the symptoms of an acute or chronic disease.

Table 3: Other Tropical Diseases and Detection Methods

Tropical Diseases	Author Reference	Type of sensing Technology
Cholera	Ibrahim F et al. [4]	Bioelectric Impedance Analysis
	Amir M. Foudeh et al.[9]	Micro Fluidics and Lab on a chip
Schistosomiasis	Vivek Kumarsahet al.[16]	CT and MRI Scans
	Sabriye Sennur et al.[17]	Ultrasonic Imaging
Lymphatic and Leprosy	Frederik j. Slim et al.[18]	CT and MRI Scans
Ebola Chagas	Justin T. Baca et al.[19] María-Isabel et al.[20]	Biosensor

Ebola virus is also called Ebola viral infection or just hemorrhagic fever. it is an infective agent viral hemorrhagic fever of humans and other primates caused by Ebola. This disease was initially identified in 1976 in two simultaneous outbreaks, one in Yambuku and the other in Nzara, these are the village close to the Ebola river thence the name Ebola. The Chagas disease also called American trypanosomiasis, it is a tropical parasitic disease caused by the protest Trypanosoma cruzi(T Cruzi). it normally unfolds to humans and other mammals by the blood-sucking "kissing bugs". There are many approaches are proposed by researchers to sight those tropical diseases, during this section we tend to study about various engineering approaches

Author X. Liu demonstrates a novel gauze-based adorned electrochemical sensor, to detect above aforesaid tropical diseases that are versatile, mechanically strong and compatible with plain-woven materials. This paper [21] focused on fabricating electrochemical sensors on versatile substrates like plastic films and textiles for in vitro diagnostics and noninvasive health observation.

In this paper [22] interfacial electrochemical impedance spectroscopy (EIS) to review various surface and electrochemical processes applied to DNA chips and, biosensors. And author M. Rosu-Hamzescu et al. demonstrates two-electrode setup, permits observation of the cell-culture impedance, revealing parameters of biological processes like cell adhesion, viability, growth, motility, morphology, and internal activity of bio-tissues.

Author D. Sathyanath et al.[23] Presents in this paper on a microwave-based detector - the Split Ring Resonator (SRR) and its complementary structure (CSRR), as a minimally invasive blood glucose observation system. Here the modification in the material dielectric constant of blood owing to variation of glucose level is subject to review.

In this paper [24] versatile deep tissue microvasculature blood flow imaging systems exploitation near-infrared diffuse correlation techniques were demonstrated by C. Huang et al. They developed setup known as noncontact speckle contrast diffuse correlation imaging.

Here Authors N. Chudpooti et al.[25] Reports on a miniaturized lab-on-a-waveguide liquid-mixture detector. that provides extremely accurate Nanometric capacity unit liquid sample characterization, for biomedical applications. This small fluidic-integrated mm-wave detector developed supported a near-field transmission line technique designed with one loop slot antenna that is working at the frequency of 91GHz. an equivalent is made-up into the lid of a photo laser-based subtractive manufactured WR-10 rectangular waveguide.

In this paper [18] D. Mishra et al. developed non-contact, non-invasive, a real-time device “polarized imaging-based integrated solution for SpO2 measurement”. In comparison to the present SpO2 measuring techniques, the proposed technique uses a single source of illumination.

This paper [26] gives an outline and highlights the distinctive benefits optical sensors. Here, authors, S. O'Keeffe et al. presents advancements in optical technology and range of various sensor systems appropriate to be used within the biomedical industry. Non-invasive monitoring techniques are created attainable by the penetrating characteristics of an optical signal, whereby the attenuation of light travel through a patient's tissue will give a lot of data concerning the patient's well-being. Such non-invasive techniques are vital for permitting continuous, real-time observation of the patient and reducing the chance of infection led to by invasive procedures. in addition, the immunity of optical fibers to electromagnetic interferences makes optical fibers appropriate for monitoring harsh environments, like areas of high radiation.

Of course, a number of the Authors discussions on detection of tropical diseases conferred here, have made substantial progress in recent years, yet, continuous efforts should need to further analysis and improve the performance of existing bioengineering approaches/sensors. however, during this twenty-first century, MEMS/NEMS sensors technology revolutionize the biomedical industry like semiconductor devices in the electronics industry in the last century, as a result of their miniaturized fabrication technology, light-weight weight, low power consumption and high functionality, economical compared to conventional devices.

3. MEMS/NEMS Technology in Medical Applications

MEMS (Micro-Electro-Mechanical Systems) are miniaturized devices and systems fictitious by micromachining processes [27]. MEMS have important dimensions within the range of 100nm to 1000µm. This MEMS technology belongs to more widespread VLSI Technology deals with Nanomaterials termed as nanotechnology. And it refers to science, engineering, and technology but one hundred nm the atomic scale. MEMS devices with these dimensions in the millimeter range are referred as meso or macro-scale MEMS devices. Figure one shows relevant dimensional scale aboard biological matter.

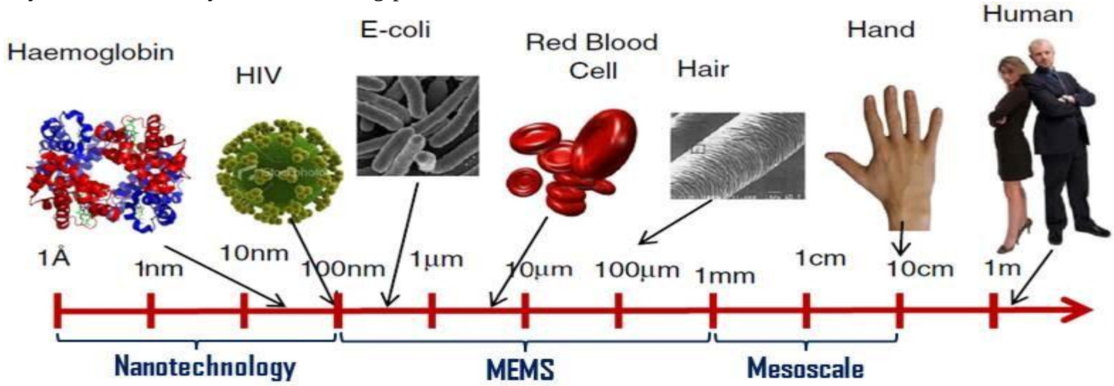

Fig. 1: Dimensional scale of MEMS and NEMS Technology (Source:http://electroiq.com/blog/2013/10/mems-devices-for-biomedical-applications)

These MEMS devices will actuate on a µ-scale and may operate together with different devices to come up with effects of meso or macro scale. Major advantages of MEMS devices embody tiny in size, light-weight in weight, Consumes terribly less power and high functionality as compared with typical devices [27]. This MEMS technology offers more economical as a result of batch processing techniques like semiconductor integrated circuit (IC) manufacturing. In earlier days, MEMS technology emerged as a branch of the semiconductor industry and eventually established itself as a special field of study with a major market share in the medical field because of the BioMEMS. This BioMEMS have a worldwide market share is anticipated to nearly size in triple, from \$1.9 billion in 2012 to \$6.6 billion in 2018 consistent with the survey conducted by Yole [28].

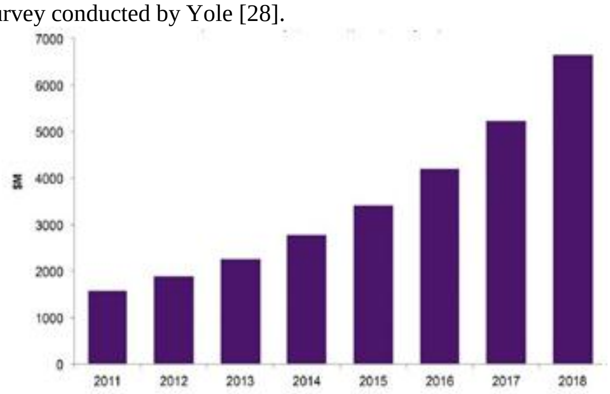

Fig. 2: BioMEMS market forecast by Yole Development (Source: http://www.yole.fr/).

3.1 What is BioMEMS?

A sensor is a device whose function is to detect changes in its surroundings and send the data to other electronics for further processing. A sensing element is usually used with other electronics, whether it is simple as the light or as complicated as the laptop. This sensing element converts the physical amount into the decipherable signal of the instrument or user, whereas transducer converts one type energy to a difference which will or might not perceive by the instrument or user.
A MEMS/NEMS biomedical sensor may be a device that contains a biophysically derived sensor integrated with a physical-transducer that transforms a measurand into an identical electrical output. the basic necessities for any sensible biomedical sensors are specificity i.e the power to choose out fascinating parameter without interference of the other parameters, sensitivity i.e the potential to measure slight changes during a given measurand, and accuracy i.e. closeness to the true measurement, latent period, biocompatibility, aging characteristics, size, ruggedness and hardiness, and economical. Together with these characteristics, the sensing element should are compatible with the chemical, optical, optoelectronic, or electronic integrated circuit technology.
Typically, electronic systems are used to interface MEMS/NEMS devices from its practical domain (i.e., Physical, Chemical, or Biological) to the electrical domain for signal transduction and recording. It ought to be noted that the term MEMS was originally conferred with miniaturized sensors and in operation between electrical and mechanical fields. This MEMS technologies permit the micro or nanometer scale construction of the many forms of devices and therefore hold great potential for biomedical sensing applications are termed as BioMEMS or BioNEMS [29]

3.2 MEMS Technology - Basic Principles:

In MEMS Technology micro cantilever primarily based systems play a major role within the field of biosensors for the detection of ultra-small masses like proteins and other biomolecules attributable to their little size, light weight, high surface-to-volume ratio, and attainable multiplex application[30]. Cantilever-based sensing involves the transduction of a Biomolecular interaction to a measurable mechanical change. whereas the cantilevers don't possess their inherent property for chemical and biological agents, moieties for specific binding features ought to be used for coating consistent with the ultimate application the optimum transducer response is formed when the target reacts specifically with just one facet of the cantilever, the sensing surface. Immobilization of the moieties to the other facet of the cantilever needs to be stripped-down as ought to nonspecific binding of the target on the surface. This MEMS technology provides the advantages of tiny size, low weight, high performance, simple mass-production, and low cost. Sensing techniques are usually based on piezoelectric, capacitive, electromagnetic and piezoresistance principles [31]. These sensing technologies are concisely mentioned here.

Piezo Electric Sensors:

Substances, like barium titanate, single-crystal quartz, and lead-zirconate-titanate (PZT) will generate an electrical charge and an associated electric potential when they are subjected to mechanical stress or strain. This piezo effect is employed in piezoelectric transducers. The governing equation of a piezoelectric element is

$$\boldsymbol{D_n = e_{nm}s_m + \varepsilon_o \varepsilon^s_{nk} E_k} \quad (1)$$

$D_n$is the displacement of dielectric in the n[th]orthogonal direction (*Note:* n = 1, 2, 3 are three orthogonal directions in 3-dimensions) due to six mechanical strain components S_m(3-normal strainsand 3-shear strains) and three orthogonal electric field components E_k(in 3-dimension). Also **e**denotes the piezoelectric strain coefficient.$\boldsymbol{\varepsilon^s_{nk}}$Is the permittivity (dielectric constant) of a vacuum, and is the relative permittivity of the material betweenDifferent pairs of directions n and k, at constant strain (denoted by the superscript S). The constant$\boldsymbol{\varepsilon_0}$ is equal to 8.854×10^{-12} farads per meter (F/m). An equivalent circuit of a piezoelectricmicro sensor is given in Fig. 3.The dielectric displacement in the direction (denoted by 3) normal to a pair of parallel plates of a piezoelectric capacitor of facing area A and carrying a charge Q is given by

$$\mathrm{D} = \frac{Q}{A} \quad (2)$$

This is indeed the charge per unit area. When there is no external electric field E, equation (1) may be written for axis 3 as

$$D_3 = e_{31}s_1 + e_{32}s_2 + e_{33}s_3 \quad (3)$$

Note: $e_{32}s_2 = e_{33}s_3$

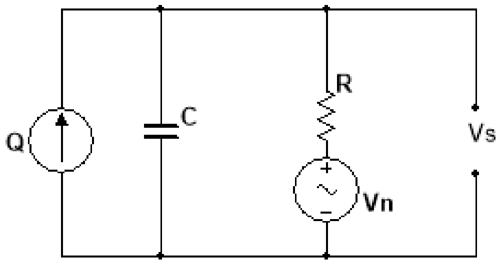

Fig. 3: Equivalent circuit of piezoelectric sensor

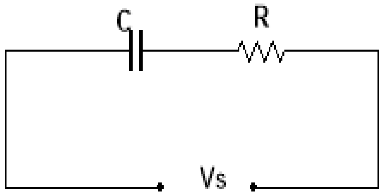

Fig. 4: Equivalent circuit of piezocapacitive sensor

Piezo Capacitive Sensors:

A capacitor is created by 2 plates which might store an electrical charge. The charge generates a potential difference which can be maintained using an external voltage. The capacitance C of a two-plate capacitor is proportional to A, the common (overlapping) area of the 2 plates, and e, the dielectric constant (or permittivity) that depends on the dielectric properties of the Medium between the 2 plates. C is reciprocally proportional to d, the gap width between the 2 plates. A modification in any one of those three parameters could also be utilized in the sensing method. Capacitive sensors are compatible with most mechanical structures, and that they have high sensitivity and low-temperature drift. An equivalent circuit for a capacitive sensor is shown in Fig. 4. The capacitance of a parallel plate capacitive transducer is given by:

$$\mathrm{C} = \frac{\varepsilon o \varepsilon r A}{\mathrm{d}} \quad (4)$$

Where Ɛrand Ɛo denote the relative and free space permittivity, respectively.

Piezo Resistive sensors:

Piezoresistive sensors use the change of the electric resistance in the material when it has been mechanically distorted. The resistance of a piezoresistor is given by:

$$\mathrm{R} = \frac{\rho \mathrm{l}}{\mathrm{A}} \quad (5)$$

Whereρ, and l denote the resistivity and length, A denotes Surface area of material i.e A = t x w; here t is the thickness andw is the width of contact. ρdepends on the doping concentration of the piezoresistor.

Electromagnetic Sensors:

The Sensors that use the principle of electromagnetic induction are termed variable-inductance or electromagnetic sensors. Those variable-inductance transducers that use a non-magnetized ferromagnetic medium to change the reluctance (magnetic resistance) of the flux path are called variable-reluctance transducers. Magnetic force on a magnet placed in an external field of force is given by:

$$F = \frac{B^2 A}{2\mu o} \quad (6)$$

WhereF denotes the magnetic force, μ_0 is the permeability of freespace, which is equivalent to $4\pi \times 10^{-7}$ $_{\mathrm{H/m.}}$ and B and A are the magnetic field intensity and area ofthe ferromagnetic material perpendicular to the magnetic field.

4. Biorecognition Molecules for Disease Detection:

Biosensors able to give fast, more specific and sensitive and quick detection of microorganism diseases. Typical parameters in the design of biosensor function are an improvement of the specificity, selectivity, and affinity that may identify the success rate of the complete detection technology. So, it's very tough to see that biorecognition element might be used for a given pathogen [32]. There are 2 kinds of biorecognition methods, they are the detection of infectious agent nucleic acid (NA) sequence and detection of specific infective agent biomolecules like surface proteins or antigens. MEMS/NEMS-based biosensors able to show high sensitivity and specificity when labeling with metallic element probe, antibody, or another specific molecule with the affinity with the target structure.

Nucleic Acid (NA):

Insensible cases this nucleic acid-based detection is more specific and sensitive than remaining detection strategies, whereas the second methodology i.e infective agent biomolecule detection is quicker and sturdier. For detection, the probe is labeled with a special labeling molecule like electro active substances, enzymes, radioisotopes, fluorophores, and more recently, haptens (to that antibodies are available). Similarly, hybridizing biosensors are able to acquire higher sensitivity and selectivity than conventional ways. This hybridizing potency will be improved by the distribution and orientation of probes on the transducer surfaces. However these days, as a result of technological advancements nanomaterials used for fabrication of transducers has become more and more popular. Nanotubes, Quantum dots, nanowires, magnetic and nanoparticles more recently, Nanopillars are the foremost attentive signal transducers [33]. The applications of nanotechnology, with distinctive properties, will construct novel biosensors, are systematically being dilated upon by researchers.

Proteins/antigens:

Most of the tropical and sub-tropical diseases cause viral infections, those are usually related to the presence of generic, and not specific thence their origin is difficult to diagnose. The appearance of the particular antibodies and antigens provides the detection of specific viral infectious agent and it allows to begin the suitable treatment [34]. These Antibodies are one amongst the foremost often used bio-recognizing parts for biosensor fabrication as a result of the presence of foreign molecules and organisms. This antibody primarily based diagnostics market remains improving and provides innovative, rapid, and accurate immunodiagnostic strategies are established. In the olden days, polyclonal antibodies were used first; however recently, they were pushed out by high-affinity monoclonal antibodies. For the purpose of analysis, monoclonal or polyclonal antibodies are often raised for a whole virus and might bind with high affinity (Kd=106−109 M). Similarly, Peptides (polymeric amino acids) will bind viral proteins or antibodies, too. Alternate means of detection of virus relies on glycan-protein interactions and it is necessary for many biological processes [35]. This methodology will give the fundamental keys for species with high affinity "lock-in" recognition related to a good range of pathologies conferred in tropical and sub-tropical diseases.

4.1 Disease Detection through C - reactive protein:

C-reactive protein (CRP) is generated by the liver and it enhanced when there is an inflammation throughout the body. this can be one quite supermolecule known as acute-phase-reactant in response to inflammation[36]. the degree of acute part reactants rises in response to some inflammatory proteins referred to as cytokines. These proteins are generated by white blood cells throughout inflammation and proportion of the C-reactive protein varies in accordance with sort of virus infection or illness.

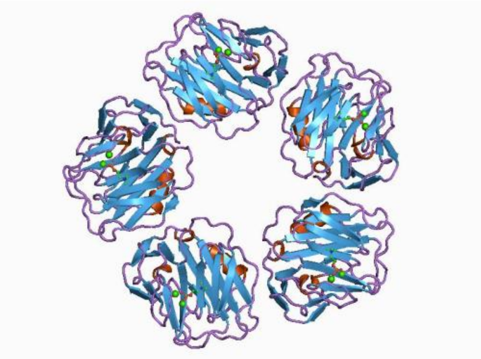

Fig. 5: C - reactive protein
(Source:https://en.wikipedia.org/wiki/C-reactive-protein)

Proteins have more biological functions within the flesh. These proteins catalyze the biochemical reactions to move, store nutrients and provide protection from viruses or bacterium and transfer various biological signals. This C-reactive protein concentration in human liquid body substance is below 1μg/mL in a very healthy body. If C-reactive protein will increase to 100 and, in some cases it is raised up to 500 times as a result of the infection or diseases. This Increasing C-reactive protein rate within the blood could result in disorder and should cause coronary failure. Development of economical C-reactive protein detection is very important for human health observation and it permits detection of biological molecules. Fluorescence-based sensing technique is that the most typical methodology of biological molecule sensing. However, this method needs a complex labeling method of target molecules with dye and therefore it is costly.

4.2 Microcantilever Based Biomems:

The Microcantilever (MCL) primarily based sensing element systems plays a key role in the field of BioMEMS for the detection of ultra-small changes present in the proteins and different biomolecules. this is often attributable to their compactness, light in weight, and high surface-to-volume magnitude relation and capable to multiplex applications. It uses the one among the principle of MEMS already discussed on top of. This cantilever-based sensing technique involves the transduction of a bio-molecular interaction to a substantial mechanical modification (Piezoelectric). For a while the cantilever is unable to possess their inherent property for chemical and biological agents, then special binding features are used for coating according to the ultimate application or detection of specific disease. The optimum response of transducer is formed when the target responds specifically with just one facet of the cantilever of the sensing surface. Immobilization of the moieties to a different facet of the cantilever will be stripped-down as could not be specific binding of the target on the surface [37]. Fig. 6[38] shows the result of biological interaction in terms of displacement.

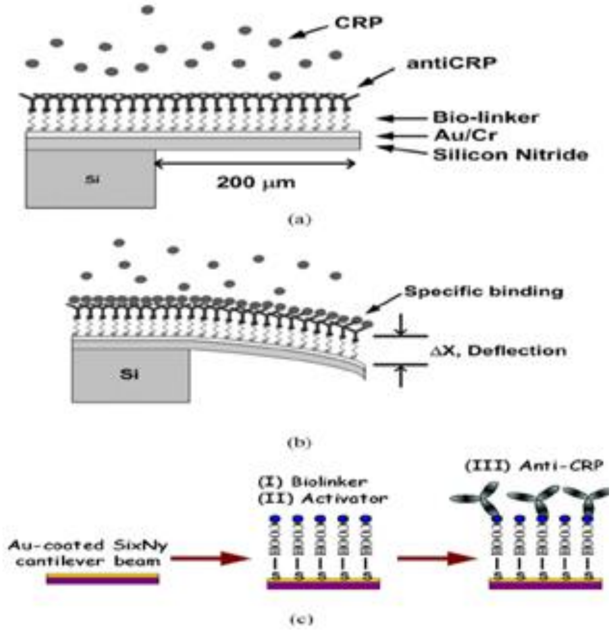

Fig. 6: (a) Cantilever before biological interaction (b) Cantilever after biological interaction (c) Cantilever beam with CRP and antiCRP

By using this MCL based BioMEMS sensors we have a tendency to are ready to detect vital changes in the C-reactive protein. Cross-bio linker binding on the sensing element is performed by Inserting self-assembled molecules into the sensing element adhere to a gold-coated (Au) chemical element compound (Si3N4) Microcantilever. Similarly opposing C-reactive protein is then injected into the sensing element and adheres to the cantilever surface. Biomolecular interactions between C-reactive protein and opposing C-reactive protein change the intermolecular nanomechanical interactions within the biolinker layer there happens a bend within the cantilever in response to the Biological interaction. This deflection of the micro-cantilever is measured optically or using Piezoresistive techniques or capacitive technique. This detectable signal is further amplified and processed to display that diseases it is further electronic integration is needed. Above figure could be a schematic of a bio-MEMS sensing element for C-reactive protein detection. It's the foremost accurate, highly sensitive, economical technique to comprehend the sensible system to sight tropical diseases.

5. Conclusion

BioMEMS/NEMS devices can become more powerful tools for the measuring of biological and biomedical functions. During this twenty-first Century, BioMEMS sensing element plays a very important role in development in the biomedical industry the same as that of semiconductor devices in the industry in the last century. As evident from the market trend, there are tremendous opportunities for MEMS/NEMS in the biomedical industry. The Review work bestowed in this paper is meant to provide useful beginning guidelines in the implementation of reliable, compact, and cost-effective BioMEMS sensor system for detection of Tropical Diseases.

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