ISSN 2689-0852

BIOTECHNOLOGY KIOSK

VOLUME 3, ISSUE 3
MARCH 2021

BioMEMS for Life-saving Biomedical Technologies

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Email: shyabiswas@biotechkiosk.com
shyabiswas@gmail.com

Editorial, Sales & Circulation Office

1330 NW 6th Street
Suite A2, Gainesville
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From the Publisher's Desk

Welcome to Biotechnology Kiosk!

The March' 2021 issue of BK is now online for our readers with the regular features. This issue includes a perspective on the latest advances in bioMEMS devices for medical technologies. Other features include a guest editorial on employing artificial intelligence in agriculture biotechnology and editor picks on the positive effects of SARS-CoV-2 antibodies to prevent future infections. The role of asthma in the mutations of dangerous flu virus is also highlighted in another report.

We hope our readers will enjoy reading these news and views on the current cutting-edge topics that include latest research breakthroughs in different areas of medicine and biotechnology.

We look forward to receiving your feedback. We do hope that you will enjoy reading this issue of Biotechnology Kiosk. Please do write to us with your comments. Your suggestions are always appreciated.

Dr. Megha Agrawal & Dr. Shyamasri Biswas.

Editors-in-Chief, Biotechnology Kiosk

Contents

Volume 3, Issue 3 March 2021

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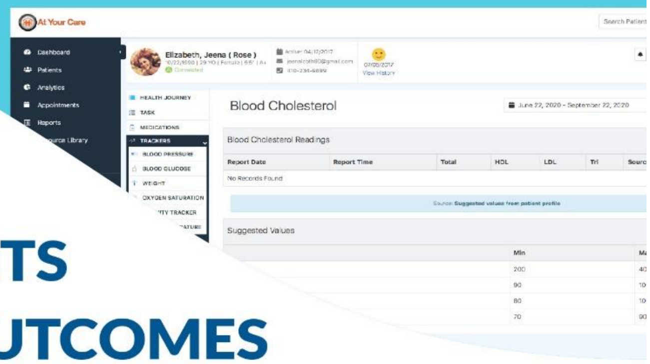

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Perspective

BioMEMS for Life-Saving Biomedical Technologies

Pallavi Tripathi*, Ashish Yadav[2], Yongling Wu[2], Zheng Hongyu[2], Habeebuddin Shaji Mohammed[3], Rajeev Gupta[4]

[1]Manchester Institute of Biotechnology, The University of Manchester, 131 Princess Street, M1 7DN, Manchester, UK
[2]Center for Advanced Laser Manufacturing (CALM), Shandong University of Technology, Zibo, 255000, P.R. China
[3]Bio-Medical Sciences Department, College of Medicine, King Faisal University, Hofuf, Al-Ahsa, 31982, Saudi Arabia
[4]Department of Physics, School of Engineering, University of Petroleum & Energy Studies, Dehradun-248007, Uttarakhand, India

DOI: https://doi.org/10.37756/bk.21.3.3.1

Article type: *Perspective*

Received: *February 2, 2021*

Revised: *February 15, 2021*

Accepted: *February 18, 2021*

To cite this article: Tripathi P., et.al., BioMEMS for Life-Saving Biomedical Technologies, Biotechnol. kiosk, Vol 3, Issue 3, PP: 5-15 (2021); DOI: https://doi.org/10.37756/bk.21.3.3.1.

Abstract

Lately, there have been huge research interests in developing micro-electro-mechanical systems (MEMS) for various biological and medical applications. These bioMEMS based devices are considered instrumental to develop many life-saving biomedical technologies. To this end, a number of studies have focused on the developments of bioMEMS in the field of molecular biology, biotechnology, medicine, biochemical and material sciences and also in microsystems technology. The applications of bioMEMS are extensive that include diagnostic research, drug delivery, therapeutics, tissue engineering, biosensors and lab-on-a-chip systems for regenerative medicine, to name a few. Here, we present a perspective on the important breakthroughs in bioMEMS including the advances in microfabrication, monitoring and modulating cellular activities along with notable applications of bioMEMS in the modern healthcare sector.

Keywords: *BioMEMS; Cardiovascular Disease; Microfabrication; Cell Culture; Therapeutics; Organ-on-a-chip*

***Corresponding Author**
E-mail: pallavi.tripathi@manchester.ac.uk

To cite this article: Tripathi P., et.al., BioMEMS for Life-Saving Biomedical Technologies, Biotechnol. kiosk, Vol 3, Issue 3, PP: 5-15 (2021); DOI: https://doi.org/10.37756/bk.21.3.3.1.

1. Introduction

Last few decades have witnessed notable research efforts to develop highly controllable microscale fabrication techniques for applications in a wide range of biomaterials substrates. These efforts have subsequently led to the development of biological micro-electro-mechanical-systems 'bioMEMS technology, which represents an emerging new area of biotechnology [1]. The field of bioMEMS technology is enabled by the combination of a number of technologies including electronics, fluidics, optics, sensors, and micro/nanotechnology. BioMEMS devices offer a vast array of life-saving biomedical technology applications. These include genomics and proteomics, early lab-on-a-chip devices for point-of-care (POC) diagnostics as well as clinical diagnostics, toxicity screening to artificial organ assist devices, implantable tissue constructs and also *in-vitro* tissue models for drug delivery systems. The design principles of BioMEMS fabrication techniques are based on low-cost, simplicity and ease of processability. These are the technology drivers of bioMEMS fabrication techniques. Researchers have leveraged these principles to build new and emerging technology platforms such as organ-on-a-chip and tissue engineering for applications in next generation regenerative medicine [2-6].

Organ-on-a-chip technology is a very important development in the modern healthcare sector as a result of direct impact of the applications of bioMEMS technology. A combination of different technologies consisting of microfluidics, bioMEMS, and biomaterials is employed to fabricate organ-on-a-chip devices. These devices are useful to mimic mechanical and biochemical microenvironment of tissues and simulate multi-level organ systems on a lab bench, which can be leveraged for real *in-vitro* studies. These include drug testing and disease research that helps develop implantable functional devices for practical applications. Researchers have demonstrated successful implementation of brain, liver, heart, kidney, lung, and intestine functions on a chip platform that have been integrated with a range of electronics. Microsensors play important roles in these applications of bioMEMS devices by providing assistance with many transducing functions such as temperature, pressure and force, acceleration, pH, humidity and many biological and chemical functions that are converted into an electrical signal. Capacitive sensors are usually used as common sensing techniques [7, 8].

However, the challenges of achieving a seamless integration of bioMEMS devices include interfacing electronics with a human body with minimized dimension, weight, and power consumption. It also requires the device to be safe and reliable along with circuits to be functional in all situations including harsh and humid environment [2].

In this perspective overview, we have described some of the fundamentals of bioMEMS technology and its biomedical applications.

2. Cell Capture, Modulation and Monitoring using BioMEMS Platform

Conventional microfabrication techniques that are used in microelectronics and chip making industry can be leveraged in the field of BioMEMS for manipulating liquids and biological entities at small length scales. Figure 1 shows the microfabrication process that consists of etching and vacuum deposition of thin films on the wafer. It uses reactive ion etching along with sputter etching of the exposed area of the material for removal. Vacuum deposition process is employed to coat a thin layer of material on the surface of the wafer. Several deposition methods can be employed that include chemical vapor deposition processes process, plasma enhanced chemical vapor deposition and molecular beam epitaxial growth, which is a relatively new technique that allows deposition of films with molecular thickness [8].

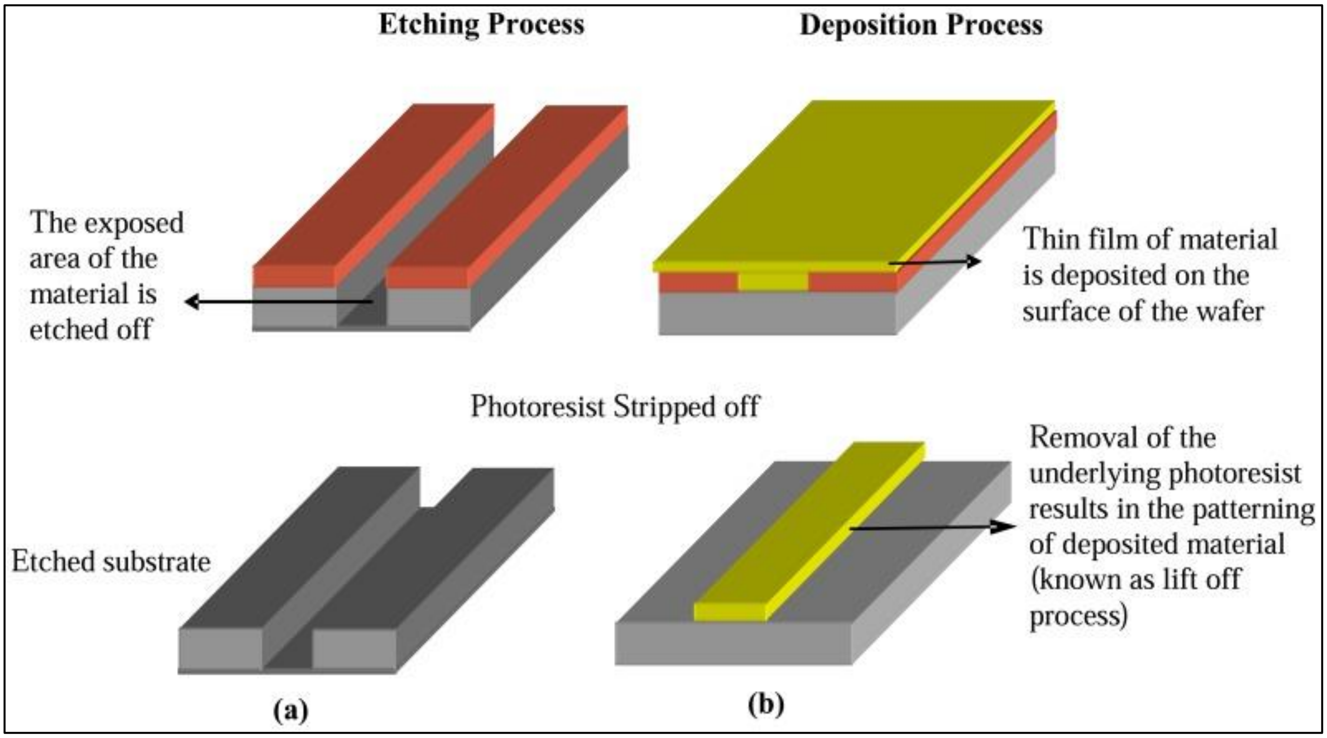

Figure 1: *Schematic depiction of various microfabrication steps for the etching and deposition process in the design and development of MEMS technology [**Source:** Sensors (Basel) (2008)].*

Researchers have shown that cell seeding, cell culture, modulation, monitoring, and analysis can be achieved on a single chip with high efficiency by employing miniaturization that allows the integration of various components with different functions on a bioMEMS technology platform (Figure 2). High-throughput platforms can be realized to build an array of microscale wells that are interconnected via fluidic channels. Microfabrication techniques can be leveraged to achieve such highly integrated arrays with fluidic control for individual wells [7].

A micropipette is used in the conventional cell culture approach. This is done to add the metered biochemical agents/products. This is a complex operation that produces a decreasing stimulation profile due to consumption of factors by the cell or via noncellular chemical degradation

[7]. However, microfluidics technology is employed in a biochemical MEMS based cell culture and modulation of cell behavior. This approach enables the critical ability to perfuse cultured cells with a well-defined stimulus pattern. This results in facilitating stimulus–response analysis that can be used to simulate nutrient concentrations in blood following fasting and feeding [7].

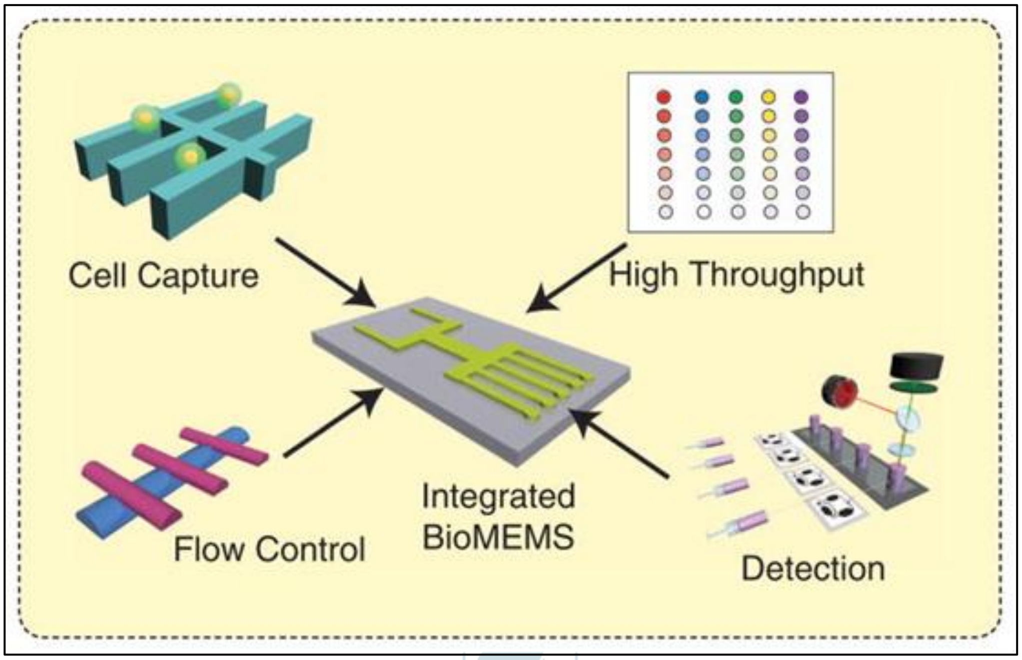

Figure 2: *An integrated bioMEMS platform is shown with its key components to monitor and modulate cellular activity [**Source:** IEEE Pulse (2011)].*

Further, in the traditional method based on electrophysiology, cells are electrically induced and tracked to study how a network of neurons collectively executes high-level functions that include memory and cognition. However, individual stimulation of neuron cells is a challenge. The bioMEMS approach overcomes this problem. In bioMEMS platform, micro-patterned electrodes that are based on microelectronics fabrication process on culture platforms can be combined with microfluidics. This can allow precise temporal and spatial exposure to biochemicals that can stimulate single neurons [7]. Optical mode of bioMEMS is an advanced version of the technology that takes advantage of the photonic structures and diodes. In this design, the integrated microoptofluidic systems can be combined with the techniques of high-content imaging that enable a variety of on-chip measurements. This can also create highly portable devices that can be used in remote settings. BioMEMS mode can be employed in mechanical perturbation. This can be applied to study cell response in various ways ranging from changes in morphology to gene expression. Microfluidics technology enables such bioMEMS mechanical mode for applying quantifiable fluidic shear forces on cells [7, 8].

3. BioMEMS for Early Detection and Monitoring of Cardiovascular Disease

Cardiovascular disease (CVD) affects the heart, veins, and arteries. CVD is a serious medical condition that causes heart attacks/coronary heart disease, strokes/cerebrovascular, peripheral arterial disease, rheumatic heart and congenital heart diseases as well as deep vein thrombosis and pulmonary embolisms. The fatalities that result from CVD are known to be quite devastating. Researchers have estimated that by 2030, more than 23.6 million people worldwide will die from CVD alone, which is a frightening scenario [9]. BioMEMS technology is considered very promising for early detection and effective monitoring of heart disease. It has been shown that one of the principle origins of heart failure is due to the increased pro- and anti-inflammatory cytokine levels. Researchers developed BioMEMS device based on silicon substrate for multiple cytokine detection. The fabricated BioMEMS consisted of eight gold working electrodes for the simultaneous detection of different cytokines. This was achieved by employing electrically addressable diazonium-functionalized antibodies [10].

Current research efforts are focused on developing innovative bioMEMS technologies for remote monitoring of heart failure patients. The goal of this research is to develop technologies for early detection of any medical conditions related to CVD. To this end, one novel idea is based on implementing wireless bioMEMS technology. This is for the purpose of implantation in the pulmonary artery using a minimally invasive procedure, which can subsequently measures and transmits data. It is believed that such a bioMEMS based detection platform would allow for early interventions before the situations can worsen in all CVD related medical conditions [11-14].

4. BioMEMS Chip for Point-of-Care Clinical Applications

Recent studies have suggested that BioMEMS can make a significant contribution in the areas of point-of-care (POC) patient clinical care as well as the affordability of providing that care to the patients. To this end, BioMEMS platform for POC clinical applications has been considered in the case of non-communicable diseases. These include detection of protein or deoxyribonucleic acid (DNA) cancer biomarkers from serum along with the detection of micro-ribonucleic acid (micro-RNA) for cancer detection and epigenetic analysis. POC clinical applications can also be extended to the collection of exosomes and collection of circulating tumor cells. POC clinical applications of bioMEMS chip are also suggested for infectious diseases. It is crucial to obtain accurate helper T cell and viral load counts at regular intervals to monitor the health of virus-infected patient's immune system. BioMEMS based rapid, POC detection of these infectious diseases offers promise and open up new therapeutic pathways to better manage these diseases [15].

With respect to the fabrication of bioMEMS chip, researchers have leveraged complementary metal oxide semiconductor (CMOS) circuits and technology that are employed in microelectronics fabrication process. They demonstrated bioMEMS chip based on planar microcoil array as both magnetic field source and the front-end inductive sensor. This bioMEMS technology was demonstrated for highly efficient magnetic beads manipulation and a quantitative detection in point-of-care diagnostics Figure 3 [16].

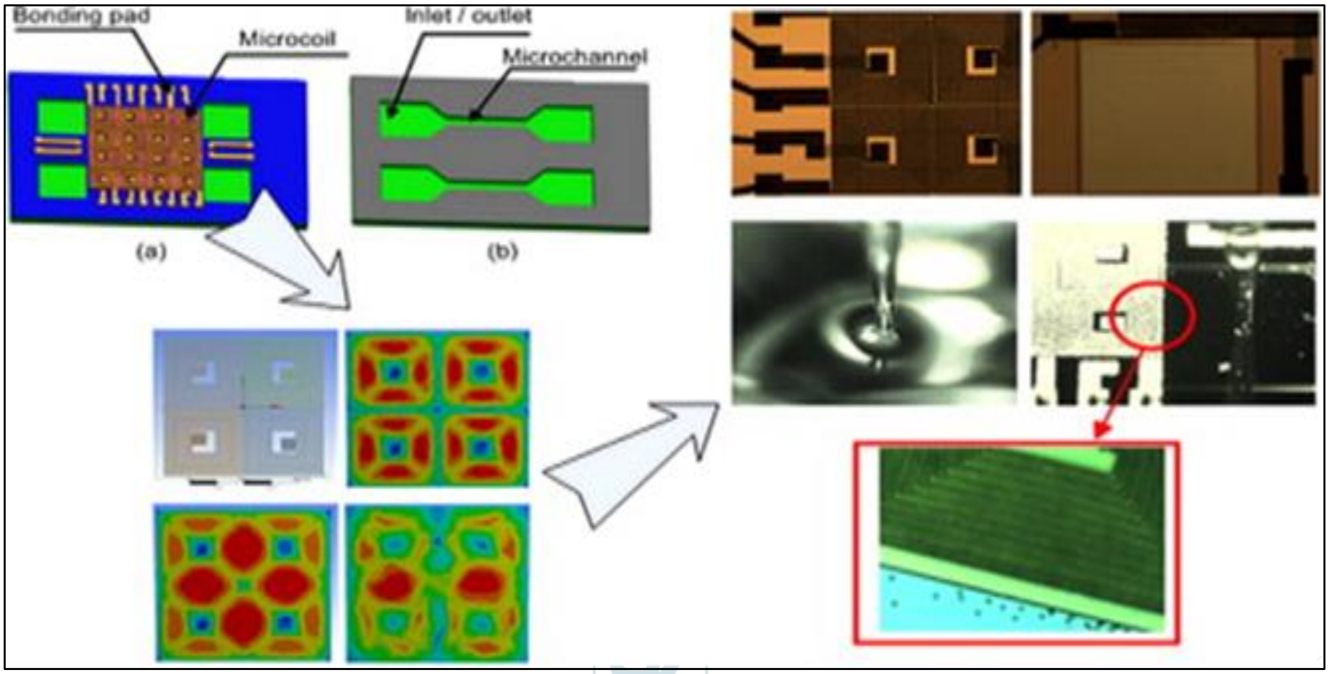

Figure 3: *(a & b) CMOS technology-based mass producible bioMEMS chip. A combination of MEMS and microfluidic technology is used in the design [**Source:** Microelectronic Engineering (2014)].*

5. BioMEMS for Specific Drug Delivery to Enhance the Efficacy of Treatments

In recent years, extensive research and developments have taken place to develop innovative drug delivery devices that have revolutionized the course of therapeutic treatment to combat complex diseases. It has been shown that these drug delivery devices have the potential to overcome the challenges of systemic administration that limits providing site-specific high drug potency especially at the body tissues that are infected. In view of the unprecedented potentials of new drug delivery systems especially that are based on bioMEMS platform, the current research efforts in the pharmaceutical industry are directed to exploring the reliable actuating mechanisms that seek to precisely control the dispensing of drugs. The overall goal of this research is to develop a process that provides therapy and dispense drugs precisely at the infected sites. This eventually controls therapeutic effects that result in minimum toxicity. An innovative concept is based on the wireless actuation of drug delivery devices. This has been considered by the researchers lately, to adopt an intervening noninvasive approach that enables easy release of encapsulated drug compounds.

Subsequently, the device is swallowed or injected and traverses through the body to reach to the desired location or specific tissue sites. A schematic illustration of the whole process is depicted in Figure 4 [17].

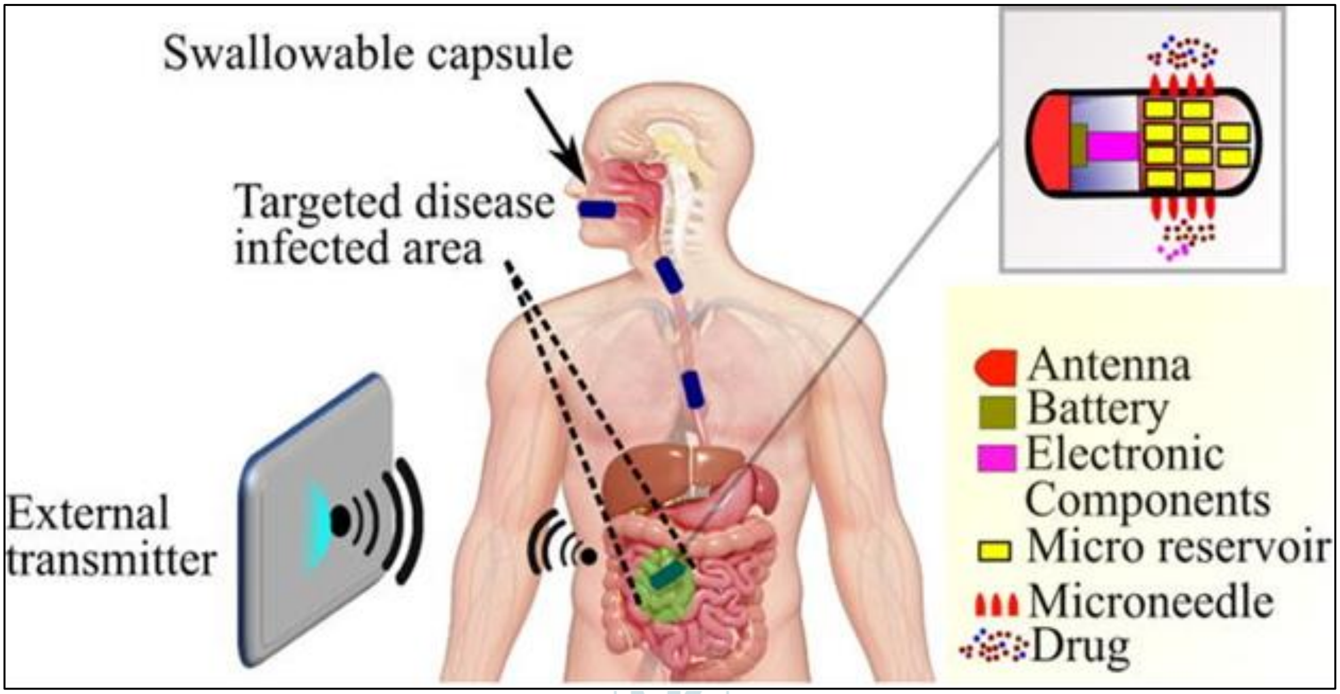

Figure 4: *An innovative concept of targeted drug delivery using a swallowable capsule drug delivery device. The device allows dispensing of drug through tiny microneedles that work by external actuation [**Source:** Appl. Phys. Rev. (2019)].*

As Figure 4 shows, the efficacy of pharmaceutical treatments can be greatly enhanced by physiological feedback from the patient using the bioMEMS based biosensors platform. In related studies, researchers demonstrated closed loop drug delivery by integrating of these systems with bioMEMS based drug delivery devices (Figure 5) [18-20].

Concluding Remarks

The BioMEMS technology offers new possibilities in expanding the horizons and scope of ever-growing drug delivery platforms that can impact a number of key areas in pharmaceutical and biotechnology industries. Recent studies have shown promise of bioMEMS technology platform for new innovative ways of modulating, monitoring, and accommodating biological entities. These novel techniques can be leveraged to create a more physiologically relevant environment to achieve realistic responses from cultured cells, which promotes new devices for life saving applications.

The BioMEMS field is growing rapidly, and there is a need for simplifying and standardizing BioMEMS tools. Seamless operations of BioMEMS devices are limited by two of the major obstacles that include complexity and unreliability. In future studies, we anticipate testing of new proof-of-concept bioMEMS devices for the reliability in operating these technologically important BioMEMS devices for real-world applications.

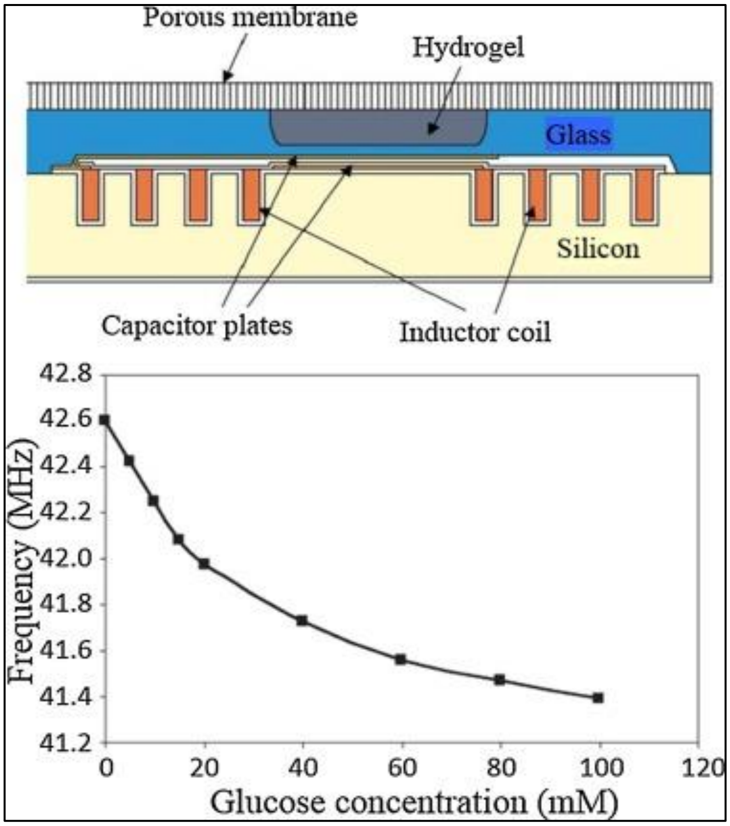

Figure 5: *A schematic illustration of bioMEMS based closed loop drug delivery platform along with the characterization data is shown [**Source:** Int J Pharm. (2018)].*

Acknowledgement

Financial assistance by Marie Skłodowska-CurieEuropean Actions Invidvidual Fellowship is thankfully acknowledged by PT.

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Guest Editorial

Machine learning tools can now help with improving Taxol production in plant cell cultures

Ranjana Sarma, PhD
Editorial Board Member
Biotechnology Kiosk, USA

DOI: https://doi.org/10.37756/bk.21.3.3.2

Chemotherapeutic intervention for cancer care is an important step. One of the most effective chemotherapy agents in use today is Paclitaxel (PTX), sold under the common name Taxol and Oxanol. Due to its ability to inhibit microtubule formation in cells, PTX is effective at all stages of the cancer and is FDA approved for treatment of many types of cancer (ovarian cancer, esophageal cancer, breast cancer, lung cancer, Kaposi sarcoma, cervical cancer, and pancreatic cancer). PTX is a plant alkaloid in the taxane family of compounds obtained from bark of the Pacific Yew tree (Taxus brevifolia) [1]. Adequate market supply of PTX has remained a challenge, as paclitaxel represents only a minor proportion of the total taxoid content of the Taxus species. Over the years, research into finding an alternate to cutting down Yew trees for PTX harvesting has been on the forefront. It is estimated that up to 60 trees may need to be harvested for the treatment of one patient.

Genetic manipulation tools have offered researchers a handle to shift from cutting down trees to PTX production in cell suspension cultures. Agrobacterium mediated transformation of taxus cell in suspension cultures has been one way towards developing high yield cell cultures for large scale biomanufacturing [2]. However, setting up in vitro cultures of Taxus species is anything but straightforward and the search for high yielding cell cultures is on. One promising candidate is cell suspension culture of hazel plant (Corylus avellana), which is being actively researched on. Given that hazel is a dicotyledonous plant, it is expected to be more amenable to genetic manipulation by the Agrobacterium mediated transformation method. Researchers at Tarbiat Modares University, Tehran, have recently published findings that offer new insights into improving PTX levels in the total toxoid content of the plant culture [3].

PTX biosynthesis is complex, multifactorial and non-linear, involving of many pathways. To get plants to produce bioactive molecules and secondary metabolites, many factors need to be optimized. Testing so many parameters sequentially by laboratory methods is not only time consuming, but also commercially non-viable. PTX biosynthesis requires, among others parameters, fungal elicitors. The PTX concentration in the secondary metabolite produced by the cell suspension culture, is affected by the type and concentration of the fungal elicitor, and the specific adding day the fungal elicitors are added. The exact harvesting time of the cell suspension cultures is an additional factor that needs to be optimization but is difficult to predict based on the input parameters. Forecasting PTX bioproduction by calculating the optimized value of so many factors is a difficult as the prediction of the precise effects of each factor and how they interact needs multifactorial analysis. Artificial neural networks (ANNs) and deep learning methods offer promising leads to improving plant biotechnology methods.

ANNs are brain-inspired systems that consist of an input, an output, and several hidden layers [4]. Since the 1940s, ANNs have been researched as machine learning tool, to solve complex relationships amongst input and output data. Deep Neural Networks (DNN) are relatively recent branch of ANNs that are being robustly developed with more hidden layers, with much improved prediction power. Deep learning methods have become a mainstay in plant biotechnology, e.g., to identify multi-dimensional genome-wide phenotypes and create new genetic elements with desirable traits. For such predictions, specific types of DNNs are used called Convolutional Neural Networks (CNN) which have the ability automatic feature extraction from a continuous signal like weather data as a time series, or plant image or DNA/RNA sequence. Recurrent Neural Networks (RNNs) are another subset of ANNs that have the advantage of handling inputs with different size. In RNNs, outputs of some layers are fed back into the inputs of a previous giving the ANN memory capabilities [4]. Each ANN has its own workflow and specific training sets are required for machine learning. (fig.1)

Conventional computational methods are inefficient for modelling secondary metabolite production in plants due to the requirement of multifactorial analysis, as mentioned above [3]. Problems requiring optimization, can be solved using search-based algorithms, like genetic algorithms (GAs) [5]. GAs are heuristic search algorithms that employ the concept of genetics and natural selection to provide solutions to problems, making GAs more intelligent than random search algorithms. For machine learning, it is a regression problem whenever the final output requires prediction of a quantity. PXT biosynthesis, being a non-linear regression problem, requires ANNs that can handle multifactorial analysis. The research group in the current study, had already tested machine learning algorithms such as multi-layer perceptron, genetic algorithm, adaptive neuro-fuzzy inference system to forecast and optimize paclitaxel biosynthesis with relative success. In the present study, the researchers expanded on their repertoire by testing General regression neural network (GRNN) optimized using fly optimization algorithm (FOA) [3].

GRNN is a special case of radial basis function (RBF) that has been successfully used to find difficult and unknown solutions in various fields. Due to its highly parallel structure and a memory-based robust network, GRNN has an ease of implementation. However, the challenge of the predictive performance depends on best estimate of smoothing (spread) parameter (σ) in GRNN architecture. The research group for the current study used the Fly Optimization Algorithm (FOA) to solve the issue to finding the optimal smoothing parameter to be fed into GRNN. [3]. FOA is an evolutionary algorithm that uses fruit fly food searching behaviour to search for the best smoothing parameter to be fed into the GRNN architecture. Data from previous studies on PTX biosynthesis using different growth conditions were used as training sets for GRNN.

This study considered four different parameters as input variables into the ANN to generate forecasting data – concentration levels of culture extract and culture filtrate, fungal elicitor adding day, and harvesting day of the culture. The success of growth conditions were evaluated using output variables to measure - dry weight (DW), intracellular (μg g−1 DW), intracellular (μg l−1), extracellular yield of PTX and total yield of PTX. GRNN-FOA was used to forecast the optimized input variables and expected the output variables of the predictions were validated against experimental data [3]. The quality of predictions made by the GRNN-FOA confirm the power of Artificial Intelligence in being able to provide solve multifactorial forecasting of growth and paclitaxel biosynthesis in hazel cell culture (fig 2&3).

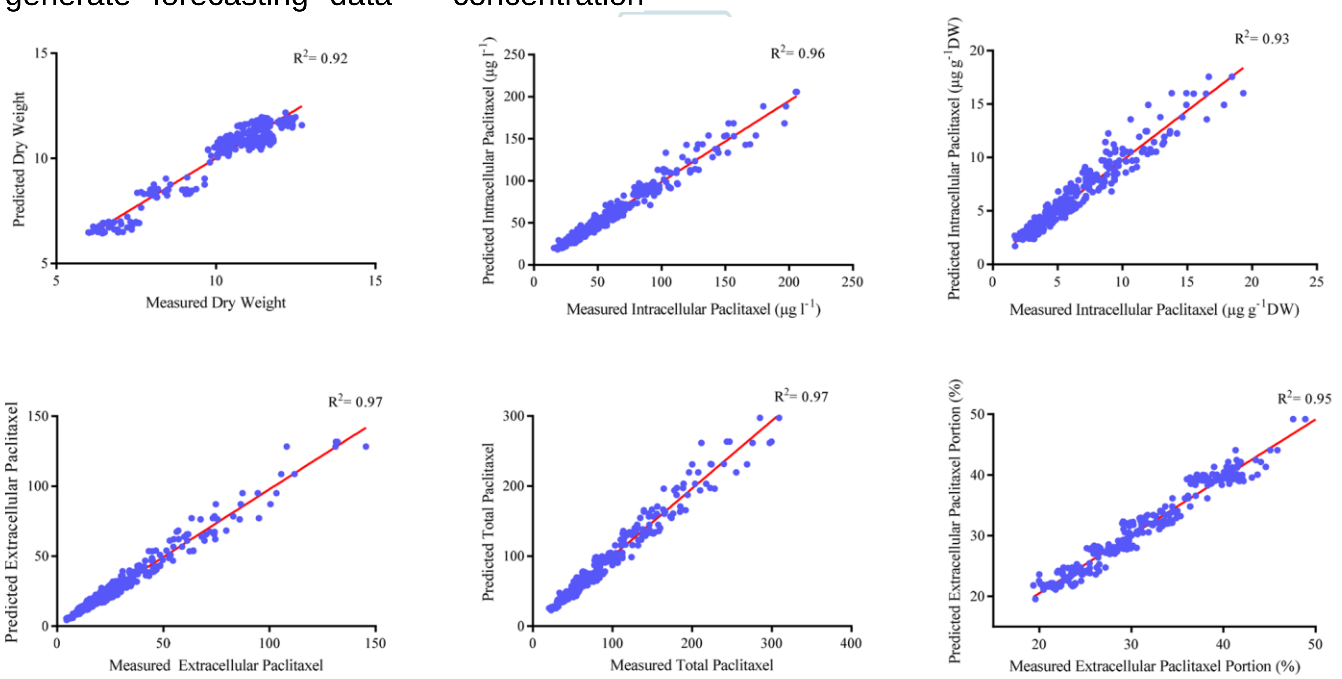

Figure 1: *Scatter plot of actual data against predicted values of dry weight, intracellular (μg g−1DW), intracellular (μg l−1), extracellular and total yield of paclitaxel, and extracellular paclitaxel portion in Corylus avellana cell cultures using general regression neural network-fruit fly optimization algorithm (GRNN-FOA) models in training subset. The solid line shows fitted simple regression line on scatter points [**Source:** Plant Methods (2021)].*

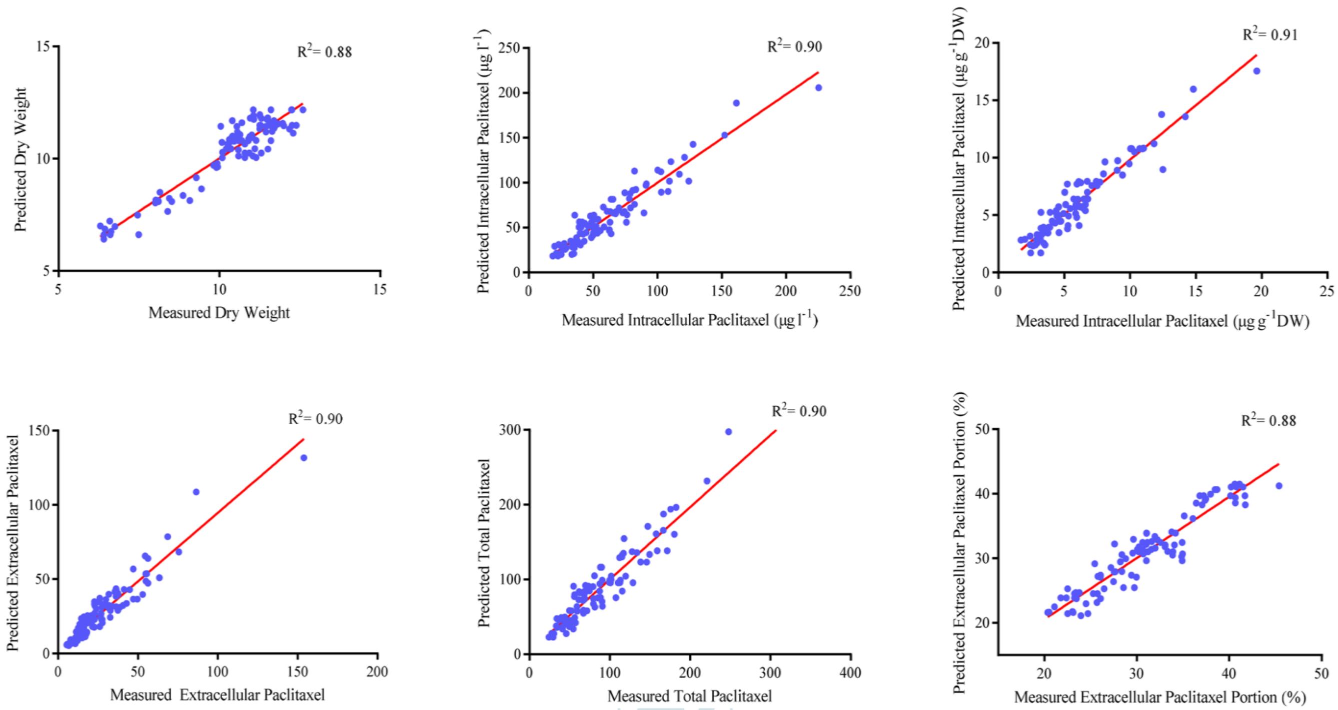

***Figure 2**: Scatter plot of actual data against predicted values of dry weight (DW), intracellular (μg g−1DW), intracellular (μg l−1), extracellular and total yield of paclitaxel and extracellular paclitaxel portion in Corylus avellanaI(hazel) cell cultures using general regression neural network-fruit fly optimization algorithm (GRNN-FOA) models in testing subset. The solid line shows fitted simple regression line on scatter points [**Source:** Plant Methods (2021)].*

The data mining approach to of the present study improves plant biotechnology process using ANNs to help reduce the infrastructural cost of trials in laboratory setting. The research group also compared the prediction accuracy of GRNN vs the predictive power of multilayer perceptron-genetic algorithm (MLP-GA) to be able to select the most efficient ANN for future cases. The results of the study show great accordance between what the algorithm predicted and what was harvested as dry weight of PTX in hazel cells suspension cultures. One only has to look the shift in the cancer care scenario during the pandemic to realise the importance of tools that offer ways to improve industrial scale production of an important chemotherapy drug like PTX. With many missed screenings, early-stage cancers would have been missed and the demand for PTX is bound to rise in the coming years. ANN driven boost of plant biotechnology methods are taking the 'unknown' out of production and replacing it with predicted outcomes and a promising future.

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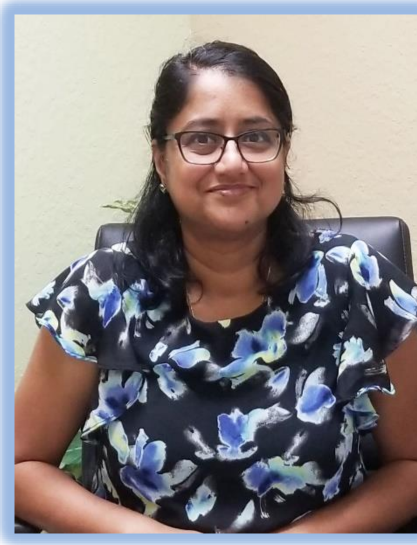
Biotechnology Advances around the World

Editor's Picks

Every issue of Biotechnology Kiosk presents select latest research news picked by the editors-in-chief on significant research breakthroughs in different areas of biotechnology around the world. The aim is to promote further R&D in all of these cutting-edge areas of biotechnology. The editors have compiled and included the following innovations and breakthroughs to highlight the latest biotechnology advances.



Dr. Megha Agrawal
Co Editor-in-Chief

Dr. Shyamasri Biswas
Co Editor-in-Chief

Antibodies

Presence of SARS-CoV-2 antibodies could lower the risk of future infections

Antibody tests that are known as serology tests are widely employed to detect serum antibodies. These antibodies are essentially immune system proteins that are made to counter a specific foreign substance or infectious agent, for example, SARS-CoV-2.

A new study conducted by the researchers in the US suggested that people with prior infection with SARS-CoV-2 could develop antibodies that could protect against being re-infected with the virus for a few months. Their findings were published in JAMA Internal Medicine (Association of SARS-CoV-2 Seropositive Antibody Test With Risk of Future Infection. *JAMA Internal Medicine*, 2021; DOI: 10.1001/jamainternmed.2021.0366).

The data reported by the researchers suggested that people with a positive result from a commercial antibody test could show substantial immunity to SARS-CoV-2. This could potentially result in lower risk for future infection. This finding provides explanation of relatively rare cases of reinfection. This could pave the way to adopt future public health implications and measures that include decisions about school attendance and returning to physical workplaces. It could also help prioritization of vaccine distribution, and other healthcare activities.

In this study, researchers focused on about 11% of the seropositive individuals. Later, 9.5% of the seronegative individuals received a nucleic acid amplification test (NAAT) known as PCR test for SARS-CoV-2. Subsequently, researchers investigated what fraction of individuals in each group showed a positive NAAT result to understand the new infection. The NAAT results were then reviewed at several intervals that included 0-30 days, 31-60 days, 61-90 days, and >90 days. The chosen intervals were due the reason that some people who recovered from a SARS-CoV-2 infection could still shed viral material (RNA) for up to three months.

In this process, it was found that between 3% and 4% of the seronegative individuals had a positive NAAT test during each interval. However, for people showing originally seropositive, the NAAT test positivity rate declined over time. Researchers investigated the results obtained over 90 or more days after the initial antibody test, it was revealed that only about 0.3% of those who had been seropositive had a positive NAAT result. It was about one-tenth the rate in those who had been seronegative.

These results supported the viewpoint that antibodies associated with SARS-CoV-2 could protect from future infection.

Asthma

Asthma could promote influenza viral variants and dangerous flu mutations

Past studies have identified asthma as the most common underlying medical condition in individuals that are hospitalized with flu. Further, these individuals are found to be at a greater risk of intensive care unit 'ICU' admission. A new study has revealed that a subtype of asthma in adults could cause higher susceptibility to influenza that could result in dangerous flu mutations.

Researchers in Australia conducted animal studies and found that paucigranulocytic asthma (PGA), a non-allergic form of the condition, could promote the flu virus to flourish in greater numbers in sufferers. It was attributed to the asthma's suppression of the immune system. They recently reported their work in eLife (A paucigranulocytic asthma host environment promotes the emergence of virulent influenza viral variants. *eLife*, 2021; 10 DOI: 10.7554/eLife.61803).

This study reported that non-allergic asthma, or PGA, could potentially suppress immune response to flu. With a compromised immune system, the virus is then left unchecked that can replicate more compared to a situation in a healthy individual. Further, most of the time, the flu cannot proof read its genetic code when replicating. This results in a lot of mistakes that only grow with more replication. This generates more opportunity for mutations to emerge.

To address this issue and study the underlying mechanism, researchers used an asthmatic mouse model with influenza virus. The computer-driven analysis of the virus genome was used to identify mutations that emerged exclusively in the asthmatic group. The preliminary tests that were conducted in animals were important as these tests could potentially reflect a broader phenomenon in humans.

The study produced findings that were in agreements with the existing knowledge about a suppressed immune response and the emergence of influenza virus variants.

This study paves the way to new understanding of asthma that can influence the evolution of the influenza virus, and also transmission. Such transmission could further lead to the emergence of more pathogenic strains into the community.

It is believed that the new understanding would help remember bidirectional nature of host-viral interactions that could give new insights into host co-morbidities that are considered influencing factors of the evolution of influenza virus.

Compiled and Edited by Dr. Megha Agrawal & Dr. Shyamasri Biswas.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