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*Perspective*

# Biochip Systems for Intelligence and Integration

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**Abstract:** Disease is one of the major threats to human life and health, and historically there have been many cases which threatened human life due to infectious diseases. In almost all cases, specific triggers for the emergence of disease can be identified, so there is an urgent need for effective detection and identification of most diseases, including infectious diseases. Therefore, this article proposes biochip systems as a tool for disease detection and risk assessment, and explains why they are effective in detecting disease, in terms of their working mechanisms, advantages and disadvantages, specific application scenarios and future trends.

**Keywords:** biosystems; artificial intelligence (AI); biochip; intelligent; system integration

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**Citation:** Wang, J.; Sun, B.; Zhu, Z. Biochip Systems for Intelligence and Integration. *Systems* **2023**, *11*, 43. https://doi.org/10.3390/systems11010043

Academic Editor: Zhan Shu

Received: 23 November 2022
Revised: 5 January 2023
Accepted: 8 January 2023
Published: 11 January 2023



## 1. Introduction

Throughout human history, the emergence and spread of infectious diseases with pandemic potential have occurred frequently and many public health challenges have arisen. At the same time, humans are aware of the interdependence of health with animals and the environment [1]. Thus, with a common understanding of the concept of public safety, it is therefore particularly important to establish methods of detection and identification infections to stop the virus from affecting humans [2]. In the 21st century, modern bio-detection technology has been diversified in a cross-disciplinary context, with the development of 3D integration in electronics and machine learning in AI, resulting in the creation of biochips based on semiconductor technology. The long-term development and wider application of biochips has also brought about a profound revolution in public health measures such as detection and identification, as well as helping to curb the spread of infectious diseases.

Many infectious diseases that cause public health problems are caused by zoonotic pathogens, such as plague, cholera, influenza, coronavirus diseases (Acute Respiratory Syndrome, Middle East Respiratory Syndrome, COVID-19) and other pandemics that have afflicted humans for a long time [3–5]. These infectious diseases pose a threat to human health, while these pathogens can spread rapidly around the world through global trade and international travel. Therefore, the approach to disease detection requires interdisciplinary cross-collaboration. In the face of highly infectious diseases, global surveillance programmes are needed to detect and identify pathogens spilled from animals to humans, and effective non-pharmaceutical measures are needed to prevent and detect these infectious diseases in order to rapidly address global public health problems.

As early as 1999, biochips were used to analyze the gene expression time of human cytomegalovirus and HCMV [6]. In the research of wang et al., the viral DNA microarrays are used to generate hybridization signatures for the identification of known, related or novel viruses [7]. Likewise, biochips have been developed for the detection and differentiation of hantaviruses [8] and are capable of differentiating isolates with up to 90% sequence similarity. Other researchers focus on genotyping viruses, such as human immunodeficiency virus (HIV) [9]. The biochip as described above provides an accurate, rapid and sensitive method for virus detection and identification. Recently, the research showed a photonic biochip for bacterial killing through the temperature increase caused by the heating of gold nanoparticles [10]. EPFL researchers have created nanoparticles that attract viruses and, using the pressure resulting from the binding process, destroy them [11]. The work of Jiang et al. also shows that aminophenol-modified gold nanoparticles can kill bacteria with minimal ototoxicity [12]. Another study highlighted the significant contributions of nanotechnology in preventing, diagnosing, and treating COVID-19 [13]. Only by demonstrating the accuracy, speed and sensitivity of biochips in detection and identification can they play a more precise role in the prevention and control of infectious diseases.

The biochip itself has the advantages of ease of use, rapid response and low cost, so it can be a novel and preferred solution for detecting infectious diseases. On the one hand it can provide a timely and effective response in terms of rapid diagnostic testing, contact tracing, drug reuse, and biomarkers of disease severity, and on the other hand it can play an important role in the rapid detection of infectious diseases worldwide. Although biochips have great advantages in the detection of diseases, they still face the following problems at this stage: i. Chip integration problems: single biochips have low detection sensitivity, poor reproducibility and narrow analysis range. ii. Technical problems: they include sensors and low-power data transmission [14].

Biochips are mainly used in the diagnosis, treatment and prevention of specific infectious diseases, while the successful manufacturing of biochips requires a variety of technologies, such as sensing chemistry [15], microarray manufacturing [16] (electronic technology) and signal processing (information technology). Therefore, in the face of explosive medical data that comes from biochips, the demand for rapid and sensitive technologies to provide better diagnosis of infectious diseases is constantly increasing [17]. This paper focuses on a new idea for disease surveillance: the establishment of an integrated bio-detection platform solution from the perspective of AI and integration on the basis of biochips and reviewed the current status of biochip research. Thus, it is helping to address the current bottleneck by exploring new possibilities for biochips. Additionally, once available, it can serve as an efficient tool for rapid detection as well as contact tracing and isolation of infected individuals for a more effective response [18].

## 2. Biochip Working Mechanism and Industrial Value

Whether it is a communicable or non-communicable disease, 70% of medical treatment options are influenced by the results of diagnostic tests, making them the first step in public health protection [19]. As a tool for the detection of diseases, it is particularly necessary to understand the mechanisms by which biochips work. Biochips are microchip technologies that process and analyse biological information, mainly referring to the solid phase of biomolecules (oligonucleotides, complementary DNA, peptides, proteins, etc.) on a carrier such as a solid chip surface to form a miniature bioanalysis system, based on the principle of specific interactions between biomolecules in order to achieve the detection of nucleic acids, proteins, etc. Thus, the test data from the biochips will serve as an effective basis for precise and personalised treatment.

A series of indications show that biochips can be used as a testing tool for diseases. At present, biochip technology is gradually becoming holistic and systematic, and the research of corresponding supporting reagents, instruments and software is receiving more and more attention. Biochip technology not only has significant value for basic research on gene functions, but also has obvious prospects for industrialisation, and can be widely used in various aspects such as medical gene diagnosis, screening of new drugs by pharmaceutical companies, clinical precision drug use guidance, cosmetic toxicity evaluation and food safety verification. The biochip platform developed can also capture these microscopic cells, which can provide big data for precision medicine such as cell proliferation, metabolism, angiogenesis, inflammation, metastasis and drug resistance.

Many specific infectious diseases and illnesses are transmitted from animals to humans as part of the process, and zoonotic diseases pose both a major health threat and a complex scientific and policy challenge where social, cultural and political norms and values are critical to successful control of outcomes [20]. Biochips are a technology that will bring disruptive breakthroughs in genetic, immunological, microbiological and clinical chemistry diagnostics, enabling early diagnosis and prevention of many diseases that threaten human health.

## 3. Intelligent? Integrated? A Part of the Human Body? The Infinite Possibilities of Biochip Systems

Driven by the needs of life sciences and medicine at home and abroad, the development of the biochip industry is facing great challenges and at the same time is facing new opportunities. Currently, research in bio-detection technology is integrated with many aspects, such as machine learning and integration technologies. Machine learning is a method of using experience to improve the performance of a system, and it can be applied to the study of life phenomena and laws. Therefore, the whole process of bioinformatics research from "life phenomena" to "law discovery" must include data acquisition, data management, data analysis and simulation experiments, etc., and "data analysis Data analysis" is the great advantage of machine learning technology. At the same time, the interdisciplinary research direction of microelectronics and bioscience is the basis for the establishment of biochip architecture. 3D integrated circuits mainly use silicon through-hole technology to stack and bond multilayer integrated circuit chips or wafers and achieve three-dimensional integration with the help of integration technology, which greatly accelerates the growth of chip size and therefore provides a basis for the establishment of integrated chip heterogeneity [21].

### *3.1. Machine Learning Is a Prerequisite for Efficient Chip Detection*

Machine learning: Traditionally, ML is divided into 3 main categories [22–24]: (a) supervised learning, including classification and regression methods, (b) unsupervised learning, and (c) reinforcement learning. Here, medical data for infectious disease testing typically tends to incorporate supervised learning, largely due to the large amount of information and data types available in the discipline (e.g., images versus numerical versus text). However, it is important to note that these predictive analyses will evolve rapidly over time as more and more studies use ML, and as computational power and portability improve.

Machine learning-assisted analysis of etiological data makes a variety of processes more efficient [25,26], such as drug repositioning [27,28], cancer cell analysis [29,30], disease-related microRNA identification [31] and disease-associated long non-coding RNA identification. They are increasingly being used in biotechnology. It can be seen that with machine learning, it is possible to accurately analyse and predict location-related diseases as seen in Figure 1. Thus, biochips with machine learning will greatly improve the efficiency of disease detection.

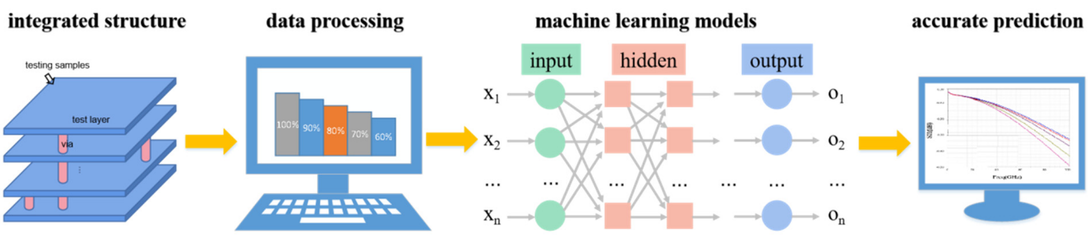


**Figure 1.** The working mechanism of the Biochip Platform Integrated System.

For example, detection of Plasmodium by traditional methods remains challenging due to the unique nature of the pathogen [32]. Rapid antigen test smears are available to experienced technicians but they may not detect or readily differentiate Plasmodium subspecies. In a study using neural network (SVM and KNN methods), the researchers were able to generate models with a sensitivity and specificity of 99.5 percent and 99.1 percent, respectively, and an accuracy of 99.2 percent using smartphone-based imaging software [32].

### 3.2. Integrated Technologies Are the Basis on Which Biochip Architectures Are Built

Integration technology: Circuit integration with the help of 3D integration technology, which greatly accelerates the growth of chip size and therefore provides a valid basis for the heterogeneity of integrated chips [21]. At this stage, with the development of integration technology, research on silicon-based integrated microarray biochips [33] mainly includes electrochemical biochips, magnetic tunnel junction (MTJ)-based biochips [34], giant magnetoresistive (GMR) biochips [35] and oscillator-based integrated biochips [36]. It also includes digital microfluidic biochips including full DNA sequencing [37] and protein crystallization for drug discovery [38] and additionally, magnetic nanostructures integrated in biochips [39]. Thus, embedded systems, microfluidic technologies and more diverse integration options bring new dimensions of research to biochips.

### 3.3. Precision Medicine Is a Specific Application Scenario for Biochips

Of course, in the future, biochip technology will work directly on human organs [40] and so far some researchers have succeeded in creating "lung chips" [41,42], "liver chips" [43,44], "heart chips" [45], "intestinal chips [46,47], among others showed in Table 1. A key advantage of organ-on-a-chip is its ability to control cellular and tissue-specific structures, enabling precise control of the biochemical and cellular environment, simulating the environment and responses in the body, and providing high-resolution, real-time imaging and in vitro analysis of the biochemical, genetic and metabolic activities of living human cells in a functional human tissue and organ environment [48]. In the near future, the chip may be able to work directly inside the human body, and if the biochip can be effectively used for personalised precision medical analysis and testing, it will significantly improve the effectiveness of patient treatment and condition monitoring.

**Table 1.** Organ biochips.

| Type | Materials | Advantages | Disadvantages | Main Function | Processing Technology | Culturing Cells |
|---|---|---|---|---|---|---|
| Lung chips [41,42] | PDMS | Low cost; High throughput | Bacterial contamination; Limitation | Pneumonia model; Nano-particle toxicity; Alveolar respiratory process | Cast molding | Alveolar epithelial cells |
| Liver chips [43,44] | Glass PDMS PCL COC Glass+PDMS | Alternative | Poor absorption; Difficult to industrialise | Drug metabolism; Hepatic lobule structure; Drug Hepatotoxicity Testing | Cast molding; 3D printing; Photo-lithography | Hepatoma cells; Liver parenchymal cells |
| Heart chips [45] | PDMS Glass+PDMS Hydrogel PLA ABS | Low cell volume; Low consumption; Dynamic culture | Technical stability; Manufacturing materials | Drug testing; Myocardial ischemic response; Cell contractility measurement; Cell beat frequency measurement | Cast molding; 3D printing; Laser corrosion | Cardiomyocytes; Fibroblasts |
| Intestinal chips [46,47] | PDMS Hydrogel | Stability Continuity | Long incubation time | Intestinal absorption; Intestinal motility; Intestinal villus structure | Cast molding | Colorectal adenocarcinoma cells |

## 4. Discussion

As a new health approach to the detection of infectious diseases and disorders, biochip detection technology has positive implications for diagnosis, treatment and prevention in addressing precision medicine, with its associated manufacturing basic theory and applied research. Ideally, in the face of detection of infectious and related diseases, these interventions should adequately show the speed and sensitivity with which they can detect viral infections while minimising social and economic disruption. To facilitate this, ongoing research should focus on the following areas.

### 4.1. Performance Sensing

For the high efficiency of disease detection and identification, biochip integrated systems need to exhibit long-term stability under sweat erosion, fluctuations in body and environmental temperature, mechanical deformation and many other environmental influences. Therefore, precise packaging of biochips may be a key research direction. Additionally, the potential use of biochips as organ-integrated chips and studies of organ bionics, drug activity/toxicity, etc. will require the integrated system to be adapted to more extreme operating conditions.

### 4.2. System Integration

Biochip integrated systems contain a variety of biomarkers for disease diagnosis, monitoring and management. However, current biochips are stand-alone biochemical sensing tools and are limited to single biomarker detection. The development of an intelligent biochip system for simultaneous disease diagnosis, monitoring and management will provide comprehensive analysis of disease monitoring tools, ultimately facilitating personalised medicine for service and treatment effectiveness and quality of condition monitoring. At the same time, an integrated system of instant biochips with embedded data processing circuits and wireless transmission modules will allow for personalised analysis at any time scale, facilitating accurate disease prediction and prevention. Additionally, as a summary of future solutions, it is important to address the increasing sensitivity of the chip to the application environment, especially in the in vivo environment of the body surface, where influencing factors are variable [49,50]. Therefore, this will require the integration technologies to be more adaptable to the application environment.

### 4.3. Data Analysis

As mentioned above, the integrated biochip system can provide a large amount of medical data, and machine learning can be used to analyse the data effectively. Figure 2 shows the working mechanism of this integrated system, but the biochip heterogeneous integrated system is still in its infancy and therefore has a long way to go before it can be truly applied in practice.

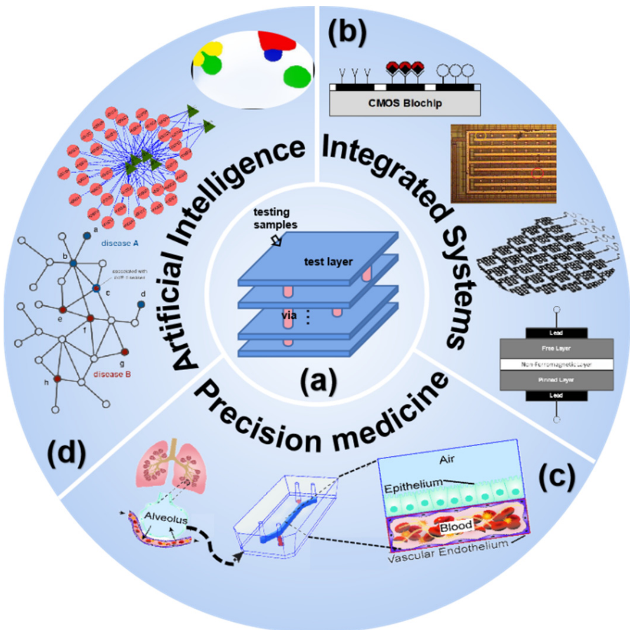


**Figure 2.** Bio-detection system solutions in artificial intelligence and integrated systems. (**a**) Conceptual model of an integrated bioassay platform based on big data. (**b**) Biochips in the field of integrated systems [34]. (**c**) Biochips in the field of precision medicine [42]. (**d**) Biochips in the field of artificial intelligence [28,30].

In the 21st century, infectious disease detection has largely leveraged information technology. Large amounts of medical data create a state of "information overload" for medical personnel [51], but computers can overcome these limitations because they can simultaneously process a wider range of medical data. Therefore, the use of predictive analytics through AI could enhance our ability to identify infectious diseases [52]. On the contrary, for diseases with a small amount of data and fragmentation, the learning ability of AI will have a large deviation [53,54], so it is not applicable for those diseases, such as colds and fevers.

On the one hand an in-depth understanding of machine learning pathways, biochip screening and data analysis will be further improved and optimised. On the other hand, regulatory mechanisms for the collection, publication, sharing and utilisation of clinical data should be proposed [55]. For better application, more accurate analysis of data by machine learning techniques in order to increase population applicability more broadly in the face of individual health status differences may be required.

## 5. Conclusions

This mini review discusses the detection mechanisms and development of biochips and looks at future trends in the deployment of AI and integrated systems in biochips. Biochip technology is considered to be one of the leading tools for disease detection, precision medicine solutions, and the technical challenges facing biochips at this stage can be surpassed beyond the limits of conventional biochips using AI and 3D integration technologies. After reviewing the existing research literature, we envisage in the future that the biochip systems will integrate machine learning-based approaches with efficient detection performance, especially where cross-disciplines have been applied to address these challenges in biology. A rational exploration of potential research avenues and emerging trends through machine learning and integrated systems leads to the innovative idea of an integrated machine learning-based biochip systems, which can also be used to effectively drive the development of efficient disease detection devices.

**Author Contributions:** J.W.: Literature research, Data curation and analysis, chart-making, and manuscript writing. B.S.: Data investigation and validation. Z.Z.: Analysis and guidance of literature data, correctness and finalization of manuscripts. All authors have read and agreed to the published version of the manuscript.

**Funding:** This paper is funded by open funding from Guangdong Key Laboratory of Intelligent Information Processing and Shenzhen Key Laboratory of Media Security.

**Data Availability Statement:** All data are included in this published article.

**Conflicts of Interest:** The authors declare no conflict of interest.

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