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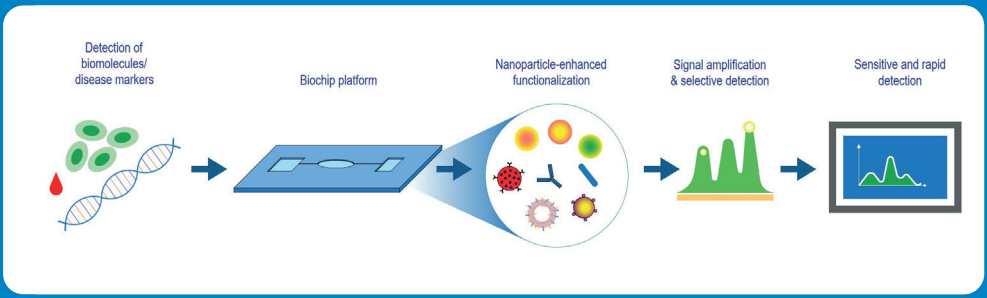

Wydawnictwo Uniwersytetu Medycznego w Łodzi

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SYSTEMY MIKROELEKTROMECHANICZNE W BIOCHIPACH OPARTYCH NA NANOTECHNOLOGII. ZASTOSOWANIE W FARMACJI I MEDYCYNIE

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WYDANIE PIERWSZE

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Abstract: The development of microelectromechanical systems (MEMS) contributed to the production of silicon-based microfluidic systems made of miniaturized objects. Owing to microfluidic systems small (10^{-9} to 10^{-18}) amounts of fluids can be used, thus allowing laboratory analyses to be scaled down to micro-sized chips. It provides comprehensive multiplexed detection, diagnostics, and high-throughput screening. Due to their unique physical and chemical properties which result from their surface-to-volume ratio, nanoparticles (NPs) have been increasingly used in the production of these devices. Electrical conductivity or surface chemistry of nanomaterials can be regulated, which makes them useful in a range of industrial sectors. In NP biochips, the sensitivity, specificity, detection limits and time necessary to perform analysis are improved, and the costs are reduced. By conjugation with biological particles (e.g., antibodies), they can receive signals that sometimes cannot be detected in normal conditions. They can be easily adapted to identify other toxins, bacteria or viruses.

This review aims to provide consolidated knowledge about the development of biochips that led to the production of advanced nanoparticle biochips. These devices are applied in different pharmaceutical and medical fields and allow for performing comprehensive analyses, which contributes to an improvement in human health and quality of life.

Keywords: biochips, nanoparticles, nanomaterials, microfluidics, microarray technology, micro-electro-mechanical systems

Abstrakt: Rozwój systemów mikroelektromechanicznych (MEMS) przyczynił się do powstania mikrofluidycznych systemów opartych na krzemie, zbudowanych ze zminiaturyzowanych elementów. Systemy mikrofluidyczne posiadają zdolność wykorzystywania niezwykle małych objętości cieczy (od 10^{-9} do 10^{-18}), co umożliwia przeniesienie analiz laboratoryjnych na mikroskalę z wykorzystaniem biochipów. Umożliwia to kompleksową, wielokrotną detekcję, diagnostykę oraz badania wysokoprzepustowe. Coraz częściej w produkcji tych urządzeń wykorzystuje się nanocząstki (NP), co wynika z ich unikalnych właściwości fizycznych i chemicznych, będących efektem dużego stosunku powierzchni do objętości. Przewodnictwo elektryczne, a także właściwości chemiczne powierzchni nanomateriałów mogą być regulowane, co czyni je użytecznymi w wielu sektorach przemysłu. Biochipy z nanocząstkami charakteryzują się wyższą czułością, swoistością, niższą granicą wykrywalności oraz krótszym czasem potrzebnym do przeprowadzenia analizy. Jednocześnie ich użycie wiążę się z niskimi kosztami. Poprzez sprzęganie ich z cząsteczkami biologicznymi (np. przeciwciałami) możliwe jest odbieranie sygnałów tam, gdzie w normalnych warunkach byłoby to niemożliwe. Można je również łatwo dostosować do wykrywania toksyn, bakterii lub wirusów.

Celem niniejszego przeglądu jest przedstawienie skonsolidowanej wiedzy na temat rozwoju biochipów, który doprowadził do wytwarzania zaawansowanych urządzeń z wbudowanymi nanocząstkami. Biochipy w połączeniu z nanotechnologią znajdują zastosowanie w różnych dziedzinach farmacji i medycyny oraz umożliwiają przeprowadzanie kompleksowych analiz, przyczyniając się do poprawy zdrowia i jakości życia pacjentów.

Słowa kluczowe: biochipy, nanocząstki, nanomateriały, mikrofluidyka, technologia mikromacierzy, mikroelektromechaniczne systemy

List of abbreviations

Ag-NPs – Silver nanoparticles
ANNs – Artificial neural networks
AuNIs – Gold nanoislands
Au-NPs – Gold nanoparticles
AuNPs-FTO – Gold nanoparticle-decorated fluorine-doped tin oxide
BBB – Blood-brain barrier
BoC – Body-on-a-chip
CMOS – Complementary metal–oxide–semiconductor
CNT-FET – Carbon nanotube field-effect transistor
COVID-19 – Coronavirus disease 2019
CRISPR – Clustered regularly interspaced short palindromic repeats
DMAP – Dissolving microarray patch
DOX – Doxorubicin
EDC – 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
EBL/IBL – Electron/ion beam lithography
EBV – Epstein–Barr virus
EV – Extracellular vesicle
FDM – Fused deposition modeling
FUS – Focused ultrasound
HDL – High-density lipoprotein
HoC – Human-on-a-chip
IC – Integrated circuit
LAPAP – Laser-assisted protein adsorption by photobleaching
LOC – Lab-on-a-chip
LFIA – Lateral flow immunoassay
LNPs – Lipid nanoparticles
MCE – Microfluidic capillary electrophoresis
MERS-CoV – Middle East respiratory syndrome coronavirus
MH-IgG – Mouse anti-human IgG antibodies
MSNs – Mesoporous silica nanoparticles
MST – Microsystems technology
MTX – Methotrexate
MUA – Mercaptoundecanoic acid
NHS – N-hydroxysuccimide
NIL – nanoimprint lithography
OOC – Organ-on-a-chip
PCB – Printed circuit board
PDMS – Polydimethylsiloxane
PEI – Polyethyleneimine
POC – Point-of-care
PS-NPs – Polystyrene nanoparticles
PUF – Physical unclonable function
R-IgG – Rabbit IgG
rRT-PCR – Real-time reverse transcriptase polymerase chain reaction
RT-LAMP – Reverse transcription loop-mediated isothermal amplification
SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2
SWCNTs – Single-layer carbon nanotubes
MWCNTs – Multilayer carbon nanotubes
SPRi – Surface Plasmon Resonance imaging
TE – Tissue engineering
ZIKV – Zika virus

1. Introduction

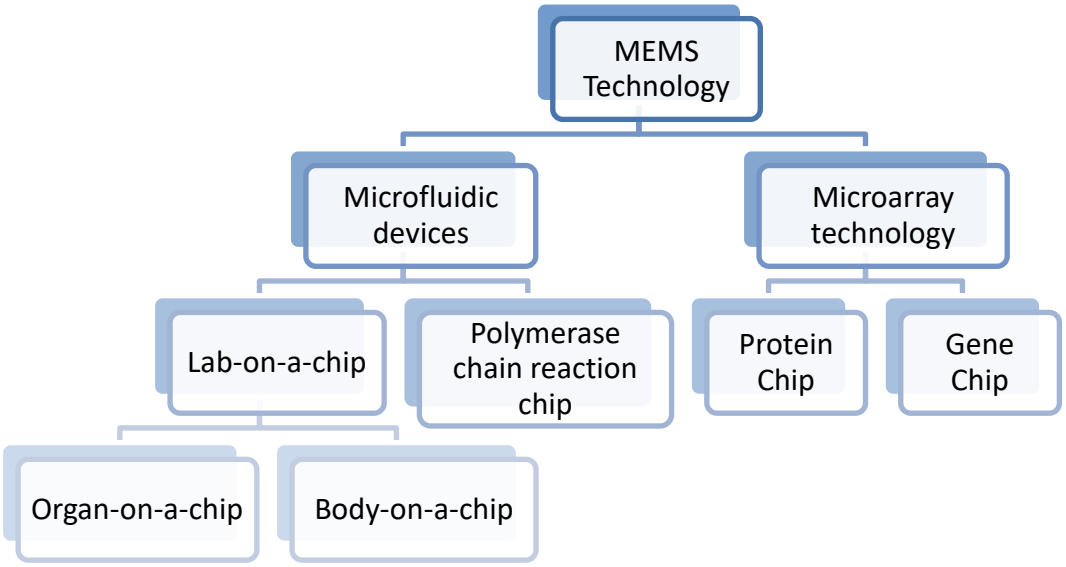
Over the past few decades, microelectromechanical systems have gained tremendous importance in various medical and pharmaceutical fields. Electrical and mechanical components form an integrated device that conducts tasks on a model of macroscopic systems. Time-consuming and inaccurate diagnostic techniques are thus being replaced at an accelerating pace with new efficient solutions that allowed testing methods to be moved to the micro scale (Putrino et al., 2016). Biological or biomedical MEMS (BioMEMS) have gradually become more and more popular in scientific areas such as diagnostics, therapeutics, drug delivery or biosensors (Grayson et al., 2004a).

Microfluidic devices for biomedical applications are designed based on technologies using micro- and nanoelectromechanical systems (MEMS and NEMS). MEMS and NEMS have allowed for the development of high-performance devices that meet strict medical criteria. Microfluidic drug delivery systems provide an alternative to conventional methods of drug administration. They ensure precisely controlled drug release or real-time observation of drug delivery (Ma et al., 2022).

Biochip is a broader term and refers to miniaturized scale laboratories where multiple biological reactions or analyses can be conducted on a single chip. Biochip technology has been developing owing to microfluidics and MEMS technology. Nowadays, many varied types of biochips exist. They differ in terms of their purpose, construction or research material. They can be divided according to their structure, the presence of special elements or their application, e.g., diagnosis, DNA sequencing, drug discovery and real-time bio-molecular recognition. Based on their architecture, they can also be divided into two main categories, i.e., microfluidic-based biochips and microarray-based biochips (Zhu et al., 2001).

Biochips based on nanotechnology solutions are becoming increasingly important. Nanoparticles used as biochip components provide higher analysis efficiency and detection of specific biomolecules. For example, surface-enhanced Raman scattering (SERS) technology has gained substantial recognition for its ultrahigh sensitivity, serving as a pivotal analytical tool in the fabrication and functionalization of biochips. Lin et al. reported the development of a novel sandwich immunoassay that combines surface-enhanced Raman scattering (SERS) with magnetoplasmonic nanoparticles (MPNs), thus allowing for significantly enhanced detection sensitivity for biomolecular analysis (Lin et al., 2024).

This review article is aimed to examine the evolution of microtechnology, with a particular focus on cutting-edge biochip technologies integrated with nanoparticles, as well as their applications across diverse industrial domains, especially pharmacy and medicine.



Scheme 1. The origin of biochips and classification based on application and technology used in production.

2. MEMS and nanotechnology

Microelectromechanical systems have been developing rapidly since the early 1960s. They show considerable potential in a wide range of fields. Among these, biological and biomedical MEMS (bioMEMS) have aroused particular interest because of their use in the pharmaceutical industry, diagnostics, therapeutics or tissue engineering. The systems are also known as microelectronic in the United States, micro machines in Japan and as microsystems technology (MST) in Europe. They allow conventional analytical techniques, such as sample preparation and detection, to be applied in biochips on the micro- or nano-scale, thus providing a wealth of information at the molecular level (Grayson et al., 2004b).

The design of MEMS is consistent with integrated circuit (IC) technology, with the systems ranging in size from micrometers to millimeters. Early systems (used between the 1960s and 1970s) focused on anisotropic single crystalline silicon etching (Yi et al., 2000). The first products, made of silicon-based micromachining, were pressure transducers (Eaton & Smith, 1997). By the 1980s, thin-film microstructures were formed by selective sacrificial etching, and electrostatic micromotors were used in the second half of the 1980s (Fan et al., 1989). Micromechanisms based on polycrystalline surface micromachining were designed. A groundbreaking revolution in 1990s brought the introduction of fully integrated MEMS. Sensors, actuators and control functions were connected using micromatching and IC processing (Bustjllo et al., 1998).

Nowadays, microsystem-based devices are used in among others airbag trigger system (Elaidy et al., 2024), GPS system (Hanse, 2004), micro-machined ultrasound transducers (Hajati et al., 2012a), biochips for micro total-analysis (Louizos et al., 2012), inkjet printers, accelerometers in modern cars or consumer electronics devices such as game controllers, MEMS gyroscopes to detect yaw, silicon pressure sensors, high performance steerable micro-mirrors, disposable medical devices, DMD chip in a projector based on DLP technology (Mishra et al., 2019).

MEMS require moving components to allow for performance of physical or analytical functions. Moreover, the system has favorable electrical properties, a small size, the ability to work on a short timescale and low power consumption. Additionally, by allowing production of thousands of miniaturized objects simultaneously, it can reduce manufacturing costs.

However, unlike electronic and microelectronic circuits, MEMS devices are constructed from membranes, channels, holes and cavities (Louizos et al., 2012). Microfabrication techniques employ a range of repeating sequences of photolithography, etching and deposition steps (Grayson et al., 2004b). Most importantly, micro-devices produce micro-scale results (Agbo and Fabricius, 2018). The aim of the technology is to offer higher volume efficiency with lower costs (Pattanaik and Ojha, 2021).

MEMS have unique characteristics, such as optical and electrical sensitivity, and a feature size comparable to relevant biological structures. These have been used in the development of retinal implants to treat blindness, microneedles for painless vaccination, or neural implants that can be used for stimulation and recording from the central nervous system (Grayson et al., 2004b). Additionally, with MEMS microsurgery devices surgery can be performed inside the human body without interruption of the continuity of the skin (Hajati et al., 2012).

The integration of MEMS technology with functional nanoparticles has provided a chance to develop sensors that can detect a wide range of gases. Hsueh and Wu (2021) synthesized Co_3O_4 nanoparticles (Co_3O_4-NPs) using ultrasonic wave-assisted grinding, followed by the surface functionalization with gold (Au) nanoparticles through adsorption. The Au-decorated Co_3O_4-NPs were subsequently integrated onto a MEMS platform to construct a high-performance NO_2 gas sensor. The Au-functionalized Co_3O_4 nanoparticles were evaluated for their NO_2 gas sensing capabilities.

Due to their miniaturized dimensions and compatibility with integrated system architectures, MEMS-based gas sensors, incorporating ZnO nanoparticles as active sensing elements, have recently attracted considerable attention for low-level H_2S detection. Zhu and Xie (2022) fabricated MEMS-based microhotplate chips onto which ZnO-1 nanoparticles were deposited as the active sensing layer. Optimized ZnO-1-based MEMS sensors exhibited broad linearity, strong selectivity, and robust repeatability in H_2S sensing, with a detection threshold as low as 50 ppb at 220 °C.

Another example of sensor – based MEMS, integrated with Pt-loaded SnO_2 monodispersed nanoparticles, for the detection of toluene gas. The synergistic effects of Pt-induced electronic and chemical sensitization on the SnO_2 sensing layer, along with the efficient gas diffusion and compact design provided by the MEMS platform, facilitated rapid response and ultra-sensitive toluene detection. These findings pave the way for the advancement of highly integrated, energy-efficient, and portable gas sensing technologies (Liu et al., 2023).

Wang et al. (2025) constructed microelectromechanical systems ethanol sensor combined with Pt-modified SnO2-TiO2 composite nanomaterials. Precision ethanol sensing technology has become essential in some of the emerging domains including intelligent transportation, digital healthcare, and advanced manufacturing, where its role is both irreplaceable and critical to system performance and safety (Zhao et al., 2024).

MEMS-based biosensors have achieved significant progress in both engineering and medical science, creating numerous future opportunities. They have enhanced the accessibility of point-of-care testing, facilitating early disease detection in healthcare.

3. Integration of microfluidics with nanoparticles

The origins of microfluidics trace back to the early 1950s, coinciding with the foundational development of modern inkjet technology. During the 1980s, the extensive adoption of silicon-based microelectromechanical systems catalyzed significant advancements in the design and fabrication of silicon-based microfluidic devices (Kikuchi et al., 1992). Microfluidics has made a significant contribution to various fields of science over the last few years (Abgrall and Gué, 2007).

A microfluidic system may be defined as one that has the ability to manipulate small (10^{-9} to 10^{-18}) amounts of fluids, thus allowing laboratory analyses to be scaled down to micro-sized chips (Alrifaiy et al., 2012). This is a key advantage of these systems, which translates into lower costs of analyses. Microfluidic systems are made of miniaturized objects (microwells, microchannels, valves, pumps) fabricated by semiconductor microfabrication technology such as photolithography and soft lithography. The microchannels range in size from tens to hundreds of micrometers. This facilitates laminar flow of fluids, thus allowing their concentration to be controlled in space and time (Whitesides, 2006).

In addition to providing economic benefits, miniaturization offers new functions that cannot be performed in a different scale, such as switching optical signals by micromirrors (Estibals et al., 2004). It also allows surface effects to be observed, e.g., intermolecular forces that may change the viscosity. It was demonstrated that decreasing the height of the channels from 40 microns to about 10 microns lowers the surface effects, improves convective and radiative heat transfer (Ho and Tai, 1998).

A microfluidic chip consists of diverse components, responsible for different functions: simple microstructures such as electrodes, post and filters, biological components (enzymes and proteins), sophisticated sensors and actuators (microstirrers, optical lenses, micropumps, and microvalves), coating layers (hydrophobic or hydrophilic coatings, self-assembled monolayers) (Leslie et al., 2009).

Most microfluidic biochips are used in biological analyses. They should be composed of biocompatible components such as polymers with high mechanical strength, porosity, hydrophobicity and biocompatibility (Song and Lee, 2006).

Owing to special characteristics, microfluidics can be used to study the mechanical behavior of cells, including the following:

- possibility to create an in vitro environment which simulates physiological conditions;
- delivering determining factors which affect cell shape, substrate topography, fluid flow or stiffness;
- exposing cells to growth factors or drugs that alter their mechanical behavior;
- measuring intracellular mechanical properties by high-throughput biochemical analysis, using only small quantities of samples and reagents;
- controlling drop size, generation and manipulation;
- performing tissue engineering experiments (Yin and Marshall, 2012).

Hence, droplets can be used as analogues of living cells and their physicochemical environment, and help determine the connection between physicochemical factors and the cell biochemical response (Vanapalli et al., 2009). However, to accurately mimic the in vivo cellular microenvironment, it is necessary to assess the degree of cell viability under certain conditions (Kim et al., 2007).

High sensitivity and integration capabilities of microfluidic systems may play a critical role in the detection of nanoparticles. For example, microfluidic capillary electrophoresis (MCE) platform with LED-based fluorescent (LEDIF) detection facilitated the separation and fluorescence detection of engineered magnetic nanoparticles and ensured real-time monitoring of their interaction with dopamine, providing insight into their viability as drug delivery nanocarriers (Zafar et al., 2025).

Hosseini-Kharat et al. (2025) developed PEI-LNPs hybrid system (PEI – polyethyleneimine, LNPs – lipid nanoparticles) for DNA complexation and delivery using microfluidic technology. Microfluidic mixing effectively mitigates the inherent limitations of conventional batch synthesis by ensuring controlled and continuous integration of lipids and polymers, thereby promoting the formation of structurally stable nanoparticles with enhanced encapsulation efficiency.

The development of microfluidic systems for the controlled synthesis of biopolymeric nanoparticles is of growing importance, considering their potential in nanotechnology and nanomedicine, especially as theranostic agents. Aşık et al. presented a microfluidic device, designed and fabricated specifically for the synthesis of chitosan-based nanoparticles incorporating an iron oxide core (Aşık et al., 2021).

In another study, microfluidic reactors and green chemicals were used to produce silver nanoparticles that have been successfully tested as excellent antibacterial agents against Escherichia coli (Giorello et al., 2018).

Khayati et al. (Khayati et al., 2025) reported the evaluation of the cytotoxic activity of chitosan–zoledronic acid (CS-ZA) nanoparticles synthesized via microfluidic technology, aimed at developing novel cancer therapy strategies by using pharmaceutical nanotechnology. The microfluidic synthesis method exhibited significantly higher drug entrapment efficiency compared to the conventional bulk method and demonstrated a more controlled in vitro drug release profile.

A combination of microfluidic technology and 3D printing has emerged as a promising approach for the fabrication of advanced drug delivery systems. Fused deposition modeling (FDM) was employed to design and fabricate four distinct microfluidic channel configurations, e.g., Y-shaped, T-shaped, baffle, and staggered herringbone micromixers. These microfluidic channel configurations were utilized for the preparation of chitosan–hyaluronic acid polyelectrolyte nanoparticles encapsulating rivastigmine hydrogen tartrate, a therapeutic agent used in the treatment of Alzheimer's disease. The applied solution allows for scalable, reproducible, and cost-effective production of drug delivery systems (Atashbasteh et al., 2025).

Gold nanoparticles (AuNPs) were synthesized with the use of ripping-regime segmented-flow microfluidic reactor (Khorsand et al., 2025). A key advantage of employing segmented flow in two-phase microreactors (TPMR) is the significant reduction in mixing time of the reactive species, enabling it to approach the nucleation time of gold particles. Jiang et al. (2023) applied microfluidic reactor systems for continuous synthesis of size-controlled nano-Fe_3O_4, whereas Yuan et al. (2025) reported the synthesis of dasatinib nanocrystals using microfluidic reactor.

Another research (Yu et al., 2025) focused on the design, simulation and optimization of diverse microfluidic channel configurations for the fabrication of poly(dimethylsiloxane) (PDMS) microfluidic chips, with the objective of producing lipid nanoparticles (LNPs) encapsulating green fluorescent protein messenger RNA (GFP mRNA). The proposed solution is an alternative to conventional method of LNP preparation, which is time-consuming and is often associated with poor reproducibility.

Y. Wang et al. (2020) conducted a study with a new polymeric nanoparticle material (anti-CD63 conjugated magnetic nanoparticles) which provides rapid and sensitive quantitative exosome detection. The proposed chip allows easy capture of exosomes through a mixing channel of a staggered triangular pillars array. Enriched exosomes are magnetically attached to the Raman detection region and probe, consisting of EpCAM-functionalized Raman beads with high densities of nitrile; these allow

quantitative detection of exosomes from prostate cancer cells and healthy prostate cells by monitoring the intensity of the SERS peak.

Lin et al. (2022) examined whether self-assembled zinc oxide (ZnO) nanopillars have anti-biofouling properties —either by minimizing initial cell attachment, enhancing cell detachment from the surface, or achieving both effects. Microfluidic approach was implemented to avoid difficulties related to manual evaluation of bacterial adherence to nanopillar surfaces.

4. Nanoparticles as components of microarrays

Microarrays are very popular in gene expression or genotyping studies. They allow simultaneous identification of different mutations. The first information about the use of DNA microarrays for conducting genomic research was published in the 1990s (Maskos, 1992; Mirzabekov, 1994; Chee et al., 1996), whereas protein arrays for protein–protein interaction, ligand binding and biochemical investigations were recorded by MacBeath and Schreiber in 2000 (MacBeath and Schreiber, 2000). In 2001, Zhu et al. (2001) presented the yeast proteome array: a ground-breaking development that has been applied in many different ways. In this study, a large-scale proteomic analysis was performed by expressing and presenting 5800 yeast open reading frames on a single glass side (Aşık et al., 2021). Thousands of assays could be undertaken quickly and cheaply, thus reducing the amounts of reagents and lowering the costs of analysis. Microarray chip architectures based on a flat reaction surface reduce the washing and incubation steps and allow for higher sample density (Dove, 2005).

Peptide microarrays are mostly used for epitope-mapping, substrate profiling and probing peptide-ligand interactions (Panicker et al., 2004). Unlike proteins, peptides may be synthesized and applied on a microarray as large, defined library sets; they are also more stable than proteins (Uttamchandani et al., 2005).

The integration of peptide microarrays with nanoparticles is becoming increasingly popular in various research studies. Jabir et al. (2022) conducted a study employing a nanoparticle-based platform to induce both humoral and cellular immune responses against Coxiella burnetii, the etiological agent of Q fever. Antigen microarrays were utilized to assess the antibody responses generated by the formulation comprising the immunodominant outer membrane protein antigen (CBU1910) and the E2 nanoparticle.

Biochip microarray technology is a promising tool for multiplexed detection, diagnostics, and high--throughput screening, with potential for miniaturization and parallel operation (Uttamchandani et al., 2006). It provides stable immobilization and presentation of biomolecules such as nucleic acid (Heller, 2002), proteins (Bertone and Snyder, 2005), peptides (Panicker et al., 2004), antibodies (Angenendt, 2005), small molecules (Duffner et al., 2007) or carbohydrates (Ratner and Seeberger, 2007), on planar supports (e.g., glass). Additionally, cells and tissues have been studied as microarrays, and chemical manipulations and serological assays have been performed (Rimm et al., 2001).

Stimson et al. (2025) reported a study utilizing electrode microarray within a microfluidic channel to detect protease activity carried by extracellular vesicle (EV) nanoparticles. EV-based detection of protease activity is extremely useful for cancer identification, as protease activity levels are often increased in tumor tissue compared to healthy tissue. This study presents a method that leverages two distinct electrokinetic phenomena, generated by a single electrode microarray within a microfluidic channel, to manipulate extracellular vesicle (EV) nanoparticles and charged molecular byproducts resulting from protease activity. Manipulating different sized and charged analytes in a single device is possible owing to dual-electrokinetic chip-based technology.

In another study (Li et al., 2025), the protein microarrays with a low background and high signal intensity were developed based on the polystyrene nanoparticles (PS-NPs) assembled substrate. The characteristics of 3D protein-microarrays are high protein loading capacity and controllable density, provided by patterned surfaces incorporating PS-NP. The assembly density can be precisely tuned by changing the concentration of the PS suspension, which allows for effective control over the density of surface-immobilized proteins.

Febrianti et al. (2024) developed smart nanoparticles (SNP) loaded with methotrexate (MTX) and integrated them with a dissolving microarray patch (DMAP) to achieve selective-targeted delivery for the treatment of rheumatoid arthritis. The integration of SNP with DMAP can control the release of MTX through the skin, as it was demonstrated in ex vivo testing. Hemolysis and irritation tests indicated safety of the formula, showing no potential for toxicity or irritation.

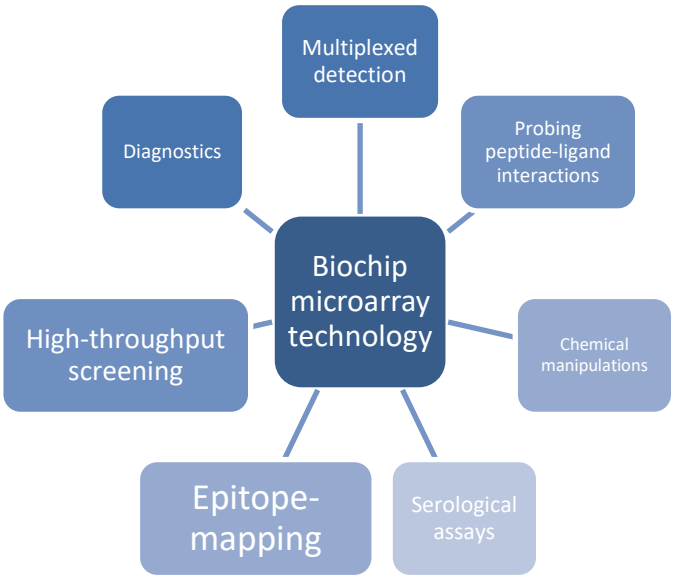
Ren et al. (2024) developed a sensitive label-free oblique incidence reflectance difference (OIRD) microarray chip by using gold nanoparticle-decorated fluorine-doped tin oxide (AuNPs-FTO) slides as a chip substrate. Oblique incidence reflectance difference (OIRD) emerged as a promising technique for real-time, label-free detection of bio-affinity interactions on microarray platforms, offering advantages in sensitivity and dynamic monitoring over traditional labeled methods.

The mesoporous silica nanoparticles (MSNs), conjugated with fluorescein, streptavidin and seven detection antibodies-biotin, were employed to enhance the fluorescence signals on the microarray, forming fluorescein doped mesoporous silica nanoparticles conjugated with detection antibodies (MSNs-Flu-SA-Abs) complexes (Hormsombut et al., 2024). An antibody-aptamer array, labeled with MSNs-Flu-SA-Abs, facilitated both visual and quantitative detection of foodborne bacteria.

Yang et al. (2024) developed a high-throughput, rapid, and highly sensitive surface-enhanced Raman spectroscopy (SERS) microarray for screening multiple mycotoxins. The microarray components consisted of a three-dimensional silver nanoparticle-porous silicon (3D AgNP-Psi) structure. The 3D AgNP-Psi active SERS substrate was prepared with electro-chemical etching and magnetron sputtering technology.

Presnova et al. (2023) conducted a study aimed at enhancing color intensity in DNA membrane microarrays by employing a seed-mediated growth strategy for gold nanoparticle (AuNP) labels, both in solution and on the porous nitrocellulose membranes widely used as a support for DNA detection by the microarrays and lateral flow analysis. The method demonstrated enhanced sensitivity in detecting both short oligonucleotides and long DNA sequences, including full-length β-lactamase genes associated with bacterial resistance to β-lactam antibiotics.

It is worth remembering that the use of nanoparticles in research has both many advantages and disadvantages. Unique optical characteristics, such as a high extinction coefficient and a size-dependent surface plasmon resonance (SPR) band position (Fan et al., 2020), are undoubtedly extremely useful in combination with microarrays. In the case of colorimetric studies, AuNPs smaller than 15 nm in diameter cannot produce an intense color, whereas those with a diameter larger than 60–70 nm are unstable for conjugation (Rodríguez et al., 2016).



Scheme 2. Diverse applications of biochip microarray technology.

5. Fusion of selected types of biochips with nanoscale technologies

The significance of disease detection at its early stage has been recognized for a long time. Early identification and correct diagnosis are crucial for successful treatment and quicker recovery. As a result, there is a strong demand for diagnostic methods that are fast, easy to use, accurate, and affordable – especially in the context of lifestyle-related conditions like diabetes and high blood pressure, as well as infectious illnesses such as flu.

Biochips incorporate biological materials extracted from biological species or synthesized in a laboratory (Carrara et al., 2012). Biochips have also been defined as a collection of miniaturized test sites (microarrays or microfluidic grid) placed on a solid substrate where thousands of biological reactions and chemical tests can be performed in one second (Haddad et al., 2018).

5.1. Protein chip

Protein microarrays are used to analyze gene function and regulation, among others. For this purpose, it is necessary to prepare protein formats in which protein molecules are organized. This can be challenging, as the functionality of proteins is dependent on modifications, partnerships with other proteins or reversible covalent modifications. Proteins and antibodies can be attached to microarrays by chemical or physical interactions, depending on the nature of the surface. These processes include adsorption or absorption (Cahill, 2001), covalent cross-linking (Zhu et al., 2000), affinity binding (Zhu et al., 2001b), diffusion (Guschin et al., 1997), or hybridization (Winssinger et al., 2002).

Protein chips vary in terms of their structure or functionality. One group includes 3D surface structure, nanowell and plain glass chips; to obtain high density, protein chips are manufactured using glass microscope sides or derivatives to attach proteins to the surface. The glass surface can be modified by photolitography technology with the use of reagents, including polyacrylamide gel packet or agarose thin film. The surface provides various porous and hydrophilic matrixes that capture molecules, which are then immobilized by cross-linking to ligands. Further analysis can then be conducted by adding analytes to these 3D arrays. The 3D matrixes on glass surface allow higher capacity protein immobilization than a 2D surface (Zhu and Snyder, 2003).

The nanowell chip was first fabricated by Zhu et al. (2000). In this case, a standard glass side is supported by a polydimethylsiloxane (PDMS) surface. The open nanowell structure reduces evaporation and cross-contamination, allows for sequential addition of components and buffers and performance of multiple-step biochemical assays. Also, the captured molecules can easily be recovered. However, these chips are expensive.

Protein microarrays can be divided into analytical and functional types. Analytical microarrays are used to detect and profile proteins in a complex mixture, as well as to describe epitope expression, whereas functional protein chips are better for basic research, such as identifying drug targets or conducting enzymatic assays (Zafar et al., 2025).

Zajac et al. (2007) presented a method for identifying cancer biomarkers using quantum dot-based protein microarrays. Quantum dots, such as CdSe and core shell type ZnS/CdSe, are resistant to photo- and chemical degradation as well as to photobleaching. However, quantum dots, when positioned and aggregated in live cells, can kill the cells (Abdellatif et al., 2022), which may limit their use in bioimaging.

Lee et al. (2024) developed Protein Corona Sensor Array Nanosystem for detection of coronary artery disease. A panel of chemically diverse nanoparticles was utilized to selectively enrich distinct subsets of the plasma proteome, each capturing unique molecular profiles. Nanoparticles (NPs), exposed to biological fluids, adsorb a layer of proteins, the “protein corona” (PC), on their surface. These proteomic subsets have been demonstrated to exhibit disease-specific alterations. PC-based analysis of plasma allowed discovery of protein markers associated with both asymptomatic stage of Alzheimer’s Disease and its progression (Hadjidemetriou et al., 2021). They also contributed to identification of low-molecular weight and low-abundance cancer biomarker (Hadjidemetriou et al., 2019).

Cristina-Cassiana Andrei et al. (2020) designed a SERS-based biochip (sensitive and reproducible surface-enhanced Raman spectroscopy) with bound anti-fimbrial E. coli antibodies. They used positively charged gold nanorods to catch a negatively charged E. coli cell membrane on the surface,

thus allowing detection of SERS. Gold nanorods were chosen due to their anisotropic optical properties that guarantee better control of resonance wavelength and stability at room temperature, as well as high SERS sensitivity.

In some cases, different kinds of particles can be mixed. For example, Y. Wang et al. (2021) combined gold nanoparticles with magnetic microparticles. An antibody and bio-barcode were assembled onto the surface of the gold nanoparticle using electrostatic forces. The surface was covered by a small molecule hapten of the target analyte associated with carrier protein. The NPs allowed good isolation of the analyte.

Chen et al. (2021) (described a magneto-optical biochip created using γ-Fe2O3@Au core/shell nanoparticles, which have great biocompatibility and can be conjugated with biomolecules owing to their gold shell. Furthermore, the biochip has strong magneto-optical properties and magnetism due to the maghemite core. It can also be easily modified for detecting other diseases). The production of each biochip costs around $2, however, an external optical measurement system is also required. Despite this, the biochip is easily portable.

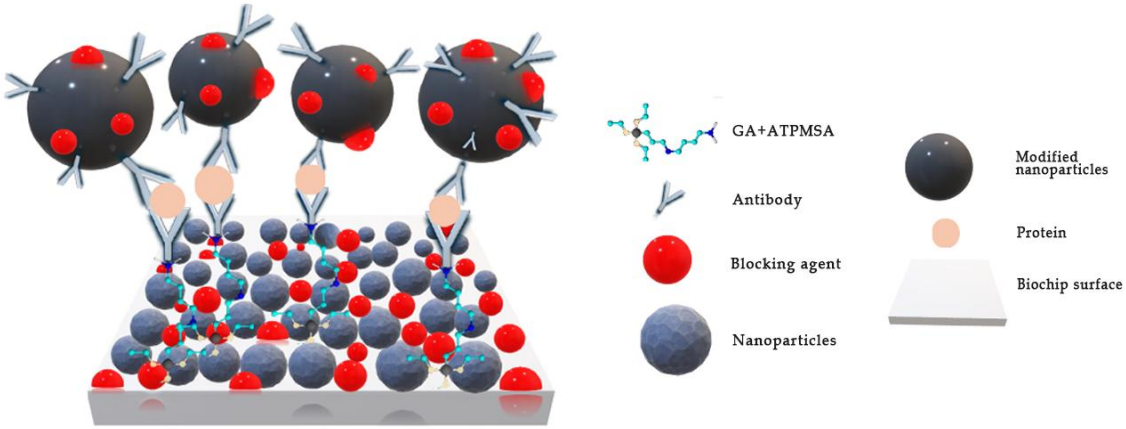


Figure 1. An example structure of magneto-optical biochip with nanoparticles, applicable in many fields such as immunoassays. The chip is functionalized using APTMS ((3-aminopropyl)-trimethoxysilane) and GA (glutaraldehyde); the blue atoms represent carbon atoms, the yellow denote oxygen, the navy blue indicate nitrogen, the black represent silicon, and the white atoms correspond to hydrogen. A blocking agent is used to block the remaining reaction sites. Antibodies are chosen for a specific protein. Modified nanoparticles enhance the signal and enable the detection of proteins (fig. Aleksandra Lis).

5.2. Gene chip

Gene chip, also known as DNA microarray, has become a promising tool to monitor a whole genome and observe interactions between thousands of genes at the same time. It is composed of a two-dimensional array of small cells, manufactured on a solid platform composed of silicon wafer, nylon membrane, plastic or a thin sheet of glass. The analyzed fragment of DNA (complementary to cDNA) may consist of short sequences of bases (20 to 25), or longer ones. It may be assumed that the mechanism of action involves unknown fragments of single-stranded DNA (targets) which react with the probes on a chip to form double-stranded DNA. The reaction proceeds wherever targets and probes are complementary (Ratner and Seeberger, 2007).

There are two types of DNA microarray:

- Format I (DNA microarray): probe cDNA, composed of 500~5000 alkalis, is applied on the solid surface using special robots.
- Format II (DNA chips): oligonucleotide (20~80 mer-oligos) or peptide nucleic acid are synthesized on-chip, or in the traditional way and then immobilized onto the chip (Ratner and Seeberger, 2007b).

Moreover, gene chips are commonly used to detect hundreds of genetic markers in a single test. Such a technology, connected with special software, significantly improves test accuracy in clinical applications (Lobenhofer et al., 2001). For comparison, real-time quantitative PCR, a highly-sensitive method, only detects a single type of a genetic molecule at one time (Mocellin et al., 2003).

Gogianu et al. (2023) developed a microarray platform for enhanced DNA detection. Microarray chips were assembled on silicon nanowires, coated them with SU-8 polymer, and ornated with carbon quantum dots. A study demonstrated that carbon dots significantly enhanced the sensitivity and efficiency of DNA detection. A possible explanation resides in the optical and physicochemical properties of CDs.

Su et al. (2023) presented a cost-effective fabrication method of nanoparticle microreactor array chip for high-throughput DNA synthesis. A substantial expansion in the available reactive surface area leads to a marked improvement in synthesis efficiency compared to planar or porous substrates.

Zhu and Xie (2022) designed a biochip that uses gold nanorods to amplify optical signal intensity, enhance the accuracy of measurement results and ensure label-free detection of RNA viruses. The use of gold nanorod dimers in the gold nanorod dimer-quartz substrate system allowed for obtaining extremely complex plasmonic resonance modes. This kind of a system can also be used to detect biomolecules, e.g., DNA and RNA. Additionally, moving away from the classic metal electrode reduces the impact of the quality of the electrode on detection results and improved detection sensitivity.

Lipoplex nanoparticles have also been combined with molecular beacons to specifically capture extracellular vesicles and measure their mRNA content, which is considered a potential biomarker for cancer. Studies have shown that the resulting lipoplex nanoparticle-based biochip offers greater sensitivity for detecting circulating mRNA compared to traditional qRT-PCR methods (Wang, Kwak, et al., 2018).

5.3. Polymerase chain reaction chip

On-chip PCR platforms are microfluidic devices. They allow small-volume and highly efficient bioassays to be performed for point-of-care diagnostic applications. On-chip PCRs provide miniaturization and integration of point-of-care (POC) testing systems (Chin et al., 2012).

Appropriate temperatures for PCR cycling are achieved using different resistive microheaters. For example, ultrafast real-time nanoplasmonic on-chip PCR has been developed using nanoplasmonics and vacuum-assisted microfluidics to allow rapid and quantitative molecular diagnostics (Kang et al., 2021).

Hsieh at al. (2022) produced a SPR nanoslit chip for detecting the DNA sequence of latent membrane protein 1 (LMP1), extracted from Epstein-Barr virus (EBV)-positive cells, using a laser scribing technique (hot-embossing nanoimprinting lithography). The analytical procedure was completed in around 36 minutes, compared to 105 minutes required in the case of a traditional machine.

Kang et al. (2021) reported ultrafast, real-time, and on-chip nanoplasmonic PCR for rapid and quantitative molecular diagnostics at the point-of-care level. The plasmofluidic PCR chip consists of glass nanopillar arrays integrated with gold nanoislands and gas-permeable microfluidic channels, which house reaction microchamber arrays, a precharged vacuum chamber and a vapor barrier. PCR biochip provides rapid amplification for plasmids expressing SARS-CoV-2 envelope protein.

One of the most commercialized nanomaterials used in industry are the silver nanoparticles (AgNPs), mainly due to their antibacterial properties (Brzóska et al., 2018). Jia et al. (2018) used silver decahedra nanoparticles to enhance the sensitivity of Surface Plasmon Resonance imaging (SPRi) signal. Proteins, such as lactoferrin, were immobilized on the SPRi chip by injecting them into the channels and incubating the chip for 50 minutes to allow covalent binding between carboxylic and

amine groups of protein and the pre-prepared Au film. Subsequently, the unreacted active sites were blocked with ethanolamine. The researchers conjugated an ssDNA library consisting of a 20nt fixed primer sequence and a central 40 sequence with a decahedra nanoparticle. This method allows rapid aptamer selection by SPRI-SELEX with real-time assessment.

The most popular type of nanoparticles is the modified AuNPs. B. Wang et al. (2020) used AuNPs to strengthen the surface plasmon resonance imaging signals of antibodies in an immunoassay sandwich biochip. Based on the methods previously described in the literature, AuNPs were chosen to enhance the SPRi signals to detect low concentration of antibodies (Stx1a, Stx2a), present in real-life samples. Various antibodies against Stx1a and Stx2a have been tested in SPRi.

The biochip was covered with mercaptoundecanoic acid(MUA) A), and subsequently activated by 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and N-hydroxysuccimide (NHS) coupling reagents (EDC-NHS), and spotted with antibodies by the microarrayer capillary pin. Changing the diameter of the capillary pin used to spot the antibodies on the biochip surface to 700 µm (compared with 500 µm) allowed greater repeatability of size and shape of each antibody spot on the gold film. The obtained results indicate that AuNP – based immunoassay was rapid and sensitive for detection of Stx1a.

5.4. Lab-on-a-chip

Lab-on-a-chip (LOC) devices are microfluidic systems; unlike macroscopic systems, they have laminar and sometimes turbulent fluid flow characteristics. Laminar flow (streamline flow) is characterized by liquid flowing in smooth and regular pathways. Velocity and pressure are time-independent at each point (Currie & Currie, 2002).

Microfluidic channels also have a dimensionless Reynolds number (Re) which estimates the tendency of a fluid to develop turbulences. With a Re number lower than 10, which is possible in microfluidic e<500 µm in diameter, laminar flow can be achieved (Kovarik et al., 2011).

Luo et al. (2024) conducted a study utilizing a portable millifluidic nanogenerator lab-on-a-chip device for measuring blood conductivity at low frequencies. The complex interactions between generated voltage, electrolyte concentrations, and blood conductivity were characterized using a sophisticated AI modeling approach. Nevertheless, this solution has certain limitations. For practical clinical applications, a significantly larger dataset is required to calibrate the AI models, and thus improve the accuracy and reliability of blood conductivity measurements.

Wang and Gao (2012) conducted a study, utilizing synthetic nanomotors to organize and test biological samples on LOC tools.

Yaqiong Gao et al. (2019) anchored soybean peroxidase, cholesterol oxidase and gold-luminol nanohybrid onto cellulose acetate membrane. The use of this nanohybrid not only enhanced the signal value but also allowed the luminescent agent to be immobilized, which is a prerequisite for the analysis. Using electrostatic interaction, an Au@luminol / Au-luminol nanohybrid was synthesized by sequential assembly of PDDA/luminol and Nafion on the nanoparticle surface without any significant increase in particle size.

Current limitations of lab-on-a-chip (LOC) technology include the lack of multiplexing capability, challenges in detecting and measuring very low concentration levels (below the micromolar range), and the use of complex, expensive fabrication and biofunctionalization procedures that are hard to replace. Sample preparation, component separation, and signal detection are the most essential elements integrated into analytical LOC platform (Wongkaew et al., 2019).

A major challenge associated with many lab-on-a-chip (LOC) devices is their reliance on external equipment such as fluidic pumps, power supplies, and signal acquisition tools (e.g., microscopes, spectrometers). The size of components is usually larger than LOC devices, which makes complete miniaturization impossible, and all the equipment takes up a considerable space. Additionally, LOC technologies typically require skilled operators, leading to complications in user training and the implementation of standardized protocols, i.e., factors that hinder widespread commercialization (Mohammed et al., 2015).

5.5. Organ-on-a-chip

Although investment in drug development and discovery has been on the rise, the number of drugs approved by the Food and Drug Administration (FDA) has declined in the recent years. Preclinical examinations of therapeutic compounds are time-consuming (about 10 years), extremely expensive, (reaching the cost of approximately two billion dollars) and have low performance (<20 %) (Dimasi et al., 2010). Animal models are limited because of physiological and pathophysiological differences between animals and humans. Moreover, trials with the use of animals are fraught with ethical concerns, low throughput and high costs (Hooijmans and Ritskes-Hoitinga, 2013). A promising alternative for conventional drug development is the organ-on-a-chip (OOC), i.e., a physiologically relevant preclinical model capable of predicting human responses to new drugs (Moraes et al., 2012).

The OOC represents a new generation of 3D cell culture models that mimic tissue-level and organ-level physiology enabled by the development of microscale technologies, stem cell biology and biomaterials (Ahadian et al., 2018). Advanced technology, such as tissue engineering (TE), makes it possible to obtain cells derived from humans, recreate functional tissues and organs in vitro and produce OOC platforms. Pharmaceutical trials measure tissue activity and functions (Huh et al., 2013).

To design and create an OOC platform, it is necessary to possess suitable cell types from an appropriate source. For years, animal cells have been used for TE, however, this approach was inefficient. Only human cells can represent human functionality and complexity. The human cells most frequently used in OOC platforms are:

- primary cells – extracted from an organ or tissue and not evaluated in modifications (Huh et al., 2013),
- immortalized cell lines – prevented from reaching senescence by e.g., blocking or losing (Huh et al., 2013) the function of telomeres. These lines of cells are safe and can produce replicable results (Polak & Bishop, 2006),
- stem cells (SCs) – capable of self-renewal and differentiation to various cell types. They can be classified as totipotent, pluripotent or multipotent lines (Srinivasan et al., 2004).

So far, lung-on-a-chip models have been created, as well as cardiovascular-on-a-chip (Marsano et al., 2016), brain-on-a-chip (Kilic et al., 2016), liver-on-a-chip (Powers et al., 2002), kidney-on-a-chip (Jang et al., 2013), gut-on-a-chip (Kimura et al., 2008), skin-on-a-chip (Abaci and Shuler, 2015), tumor--on-a-chip (Kwak et al., 2014), and breast-on-a-chip (Grafton et al., 2011).

OOC systems are designed to serve as alternatives to animal testing by utilizing human cells and tissues. These systems are developed using a combination of microfabrication and bioengineering techniques. However, to be effectively used for toxicological and metabolic drug testing, they still need improvements in feasibility, reliability, control, and monitoring capabilities (Lee et al., 2013).

Zervantonakis and Arvanitis (2016) combined focused ultrasound (FUS) and nanomedicine drugs to enhance glioblastoma treatment. They designed an acoustofluidic platform that allows for obtaining the 3D culture of glioblastoma cells and facilitates the application of FUS therapy within this controlled environment. Doxorubicin (DOX) nanoparticles encapsulated in temperature-sensitive liposomes were utilized in the study, with the heat produced by focused ultrasound (FUS) enhancing the cellular uptake of the drug. This combined treatment led to increased cell death and reduced cell proliferation compared to therapies using either the drug or FUS alone.

Tricinci et al. (2020) used the two cell types that form the blood–brain barrier (BBB) and glioblastoma spheroids to create a 3D-printed model of brain tumor. Antibody-functionalized, nutlin-loaded nanostructured lipid carriers were evaluated as a potential therapeutic approach for cancer treatment. The authors reported that approximately 70% of the glioblastoma cells internalized nanoparticles, indicating effective cellular uptake for potential cancer treatment.

Lee et al. (2021) constructed a microfluidic chip to simulate the angiogenic formation that takes place in tumors in vivo and to assess the efficacy of an RNAi-based anti-angiogenic nanomedicine. Mesoporous silica nanoparticles were used as the delivery carrier and small interfering RNA for vascular endothelial growth factor (siVEGF) was chosen as target for the siRNA therapy. To evaluate the drug efficacy, three different cell types, HepG2, SW620, and A549, were selected.

5.6. Human body-on-a-chip systems

Body-on-a-chip (BoC) or human-on-a-chip (HoC) platforms may provide an insight into interactions between different tissues and overcome the limitations of traditional bioassay models (Shuler, 2012).

It is possible to construct a model composed of two or more coupled organ-on-a-chips. Its main goal is to determine reciprocal communication between or among the organ components using a common medium. This enables particular organs to maintain their own identity and stimulates prodrug metabolism (Li and Tuan, 2022). Moreover, body-on-a-chip technology could be used to estimate pharmacokinetic processes, such as ADME (A – absorption, D – distribution, M – metabolism, E – excretion), connected with drug administration routes. The obtained data can be used to design mathematical models to predict drug efficacy (Kimura et al., 2018).

Few studies utilizing BoC models for the screen of nanomedicines have been published, mainly because these microphysiological models are still in the early stages of development and have not yet been widely accepted as standard preclinical screening tools. An example of such studies is an article published by Ahn et al. (2020) designed a neuromimetic platform recapitulate key-structures and functions of the human BBB to 3D mapping the distributions of NFs (nanoformulations) in the vascular and perivascular regions. High-density lipoprotein (HDL)-mimetic nanoparticles with apolipoprotein A1 (eHNP-A1) were utilized in the study.

Palma-Florez and colleagues published a study (Palma-Florez et al., 2023) on theranostics of Alzheimer's disease with the use of blood-brain-barrier on a chip (BBB-on-a-chip) and targeted gold nanorods (TGN). Overall, the authors found the BoC device to be a promising alternative to animal testing used for the assessment of the brain permeability of nanocarriers in a physiologically relevant environment using human cells. They also highlighted its advantages associated with lower costs, improved reproducibility, and lack of ethical concerns.

At present, the primary challenge facing multiorgan systems is attaining consistent reproducibility and physiologically relevant outcomes. Critical issues that need to be addressed include the creation of effective blood substitutes, precise regulation of the incubation environment, reduction and characterization of drug adsorption and absorption by platform materials, as well as the incorporation of physiological parameters into the overall system design (Y.I. Wang et al., 2018).

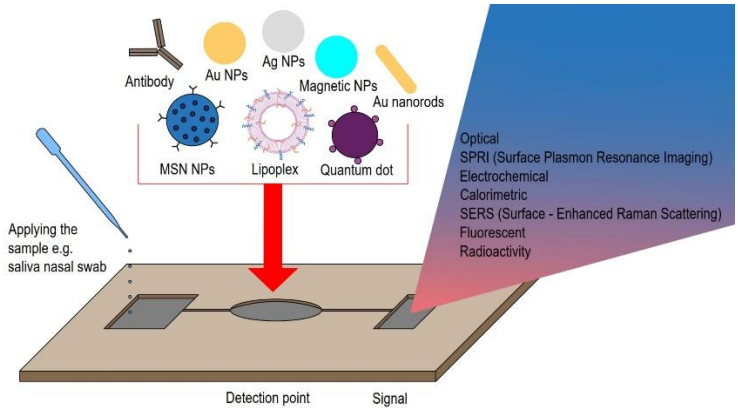


Figure 2. Illustrative image of a lab-on-a-chip biochip utilizing nanoparticles (fig. Aleksandra Lis).

Table 1. Summary of advantages and disadvantages of different types of biochips and their application

Biochip	Types	Application	Advantages	Disadvantages	References
Protein chip	Analytical protein microarrays, antibody microarrays, functional protein microarrays.	Detecting proteins in a complex mixture, assaying for a wide range of biochemical activities (e.g., protein-protein, protein-lipid, protein-nucleic-acid) drug and drug target identification	High protein binding capacity; use of small amounts of reagent; high-throughput discovery applications	Necessity to purify large numbers of proteins in a high-throughput manner; random orientation of surface-attached proteins	(Wang et al., 2024)
Gene chip	Probe cDNA (500~5,000 bases long), an array of oligonucleotide (20~80-mer oligos), peptide nucleic acid (PNA) probes	Genetic identification purposes; cancer, infections, genetic diagnostics; screening for chromosomal aberrations; detection of DNA contamination can help monitor adulteration in food products	DNA biochip eliminates the need for radioactive labels used for detection; excellent selectivity and sensitivity; performing a multitude of biochemical reactions simultaneously; easy access to critical information regarding DNA damage from cancer-producing compounds	Extremely sensitive biosensor	(Dimasi et al., 2010)
Polymerase Chain Reaction Chip	Stationary chambers with cycling temperature; dynamic continuous-flow microchamber (MC) devices	Rapid detection and genotyping; analyzing biological samples	Sample preparation is automated; small sample volume high surface-to-volume ratio, resulting in fast heating/cooling rates and short reaction time	Necessity to use resistive microheaters to achieve appropriate temperature	(HE et al., 2016)

Table 1. Summary of advantages and disadvantages of different types of biochips and their application (cont.)

Lab-on-a-chip	A single chip level which is further categorized into passive fluidic component and active electromechanical control structure; a multiple chip module system level that consists of multiple modules of different lab-on-a-chip functions	Perform biological/chemical analysis in automated, integrated and parallelized way such as: measurements of cholesterol, level of blood glucose; opportunity to perform protein analysis and integrate extraction from the cell, separation by electrophoresis, digestion and analysis using mass spectrometry; point-of-care (POC) diagnosis	Cheap, fast, more efficient than traditional analysis; small volume of sample	Leakage and exposure of electrical points to fluids need to be taken care of during fabrication	(Chin. et al., 2012)
Organ-on-a-chip	Lung-on-a-chip, cardiovascular-on-a-chip, brain-on-a-chip, liver-on-a-chip, kidney-on-a-chip, gut-on-a-chip , skin-on-a-chip, tumor-on-a-chip, breast-on-a-chip, vessel-on-a-chip.	Mimicking human tissues and organs, which provides an opportunity to observe the activities, mechanics, and physiological responses as observed for human organs; performing toxicological and metabolic test of drugs; providing information about interactions between the cells	Replacing animal testing; reducing the time and cost of the development of novel drugs and treatment; reducing the amount of testing determined before and during clinical trials in human patients	Automation of organ-on-a-chip system need to be standardized; limited working time; lack of capability to direct interpretation of human pharmacodynamic data obtained using the chip	(Douville et al., 2011)
Body-on-a-chip	Heart, liver, bone and skin	Used in parallel to human trials for the purposes of dose adjustment, PD assessment, or patient specific screening (iPSCs); possibility to direct interpretation of human pharmacodynamic data obtained using the chip	Considering inter-organ interactions in the steady state; mimicking physiologically based pharmacokinetic (PBPK) models	Parameters such as residence time need to be considered to achieve the physiological conversion/production	(Abaci and Shuler, 2015)

Nanoparticles play a significant role in the detection process with the use of biosensors. Different kinds of nanostructures, such as nanoparticles, nanotubes, nanowires, nanopores, self-assembled monolayers, and nanocomposites, may be incorporated into sensor designs to enhance their performance and operational efficiency. The following are the potential benefits of using nanoparticles in biochip-based detection:

- Adsorption of biomolecules on the surface is enhanced because of the large specific surface area and high surface free energy (Wang et al., 2014).
- Nanoparticles enhance the performance of electrochemical sensors through their electrocatalytic properties and by promoting efficient electron transfer (Abedini and Zhang, 2025).
- Biocompatibility and high adsorption power (Kyriakides et al., 2022).
- Direct attachment of the enzyme to the electrode surface (Song et al., 2018).
- Enhancement of the detection signal (Gao et al., 2024).
- Enhancement of the electrochemical sensor response through electrocatalytic activity and improvement of electron transfer processes (Jalalvand and Karami, 2025).
- Stabilization of biomolecules on the surface of biosensors (Huang et al., 2021).
- The surface charge of nanoparticles allows them to attract molecules with the opposite charge (Huang et al., 2021).
- High surface activity means that most nanoparticles, particularly metal ones, exhibit strong catalytic properties and can be used as catalysts in many chemical reactions (H. Wang et al., 2018).
- Nanoparticles, especially metallic ones, have conductive properties, which makes them a useful medium for electron transfer between the electrode and the active site (Wang et al., 2013).

Additionally, labeling biomolecules with nanoparticles allows for highly sensitive electrochemical biosensing. It preserves biological activity and ensures trace-level analyte detection through electrochemical measurement of nanoparticle-derived signals. Dissolved ions may be analyzed via stripping voltammetry (Xun et al., 2026).

Due to their high surface energy, nanoparticles are more reactive than bulk materials and can exhibit altered chemical properties in some cases (Hublikar et al., 2026).

6. Safety Considerations Related to Biochips

Counterfeiting affects many industrial sectors, including specialized technologies, medical devices or pharmaceutical products.

Ensuring the safety of biochips is crucial, especially when it comes to medical aspects and patients' health. Data inaccuracy can result in false diagnosis. Biochips become an essential tool in point-of-care diagnostics or cancer research, providing substantial advantages over traditional laboratory methods (Singh Baban et al., 2023). The microfluidics market is estimated to reach $32.6 billion by 2029 (Microfluidics Market Growth…). The importance of biochips security has been emphasized by recent regulatory actions, especially in the United States. The U.S. Medical Device Security Law, part of the Consolidated Appropriations Act of 2023 enforced by the FDA, enhanced essential cybersecurity safeguards for medical devices, including microfluidic biochips (Kolbasuk-McGee, 2023). Fraudulent medical equipment, introduced into the $1.7 trillion international counterfeit market, may pose a serious threat to public health and undermine confidence in medical products (Medical Devices…).

Biochips are exposed to various risks such as structural tampering, material degradation, biochemical interference, and intellectual property theft. There are methods used to minimize the emerging attack vectors, including machine learning (ML)- and deep learning (DL)-driven anomaly detection, mechano-responsive watermarking, molecular barcoding, and physically unclonable functions (PUFs). DL-based detection enables optical distortion assessment, triggered by height variations in microscopic images. ML detection is a type of artificial intelligence. ML-models analyze

complex connections in material properties and make predictions based on data. Thus, deviations might be detected faster and more precisely (Ramesh et al., 2022). Watermarking techniques integrate hidden ownership signatures into the biochip layout, allowing for tamper detection and authenticity verification. Molecular barcoding techniques allow for traceability and secure sample authentication. It is crucial in terms of tampering or contamination of biological samples (Baban et al., 2025). A physical unclonable function (PUF), based on encryption and cryptography, is a device that uses the randomness introduced during manufacturing to create a unique 'fingerprint' or trust anchor for a physical entity (Gao et al., 2020). A PUF tag is based on a unique physical object that is generated through chemical methods, providing virtually endless possible combinations and remarkable encoding capability (Moglianetti et al., 2022).

Nanotechnology finds application against anticounterfeiting, especially in combination with PUFs. Nanomaterials combined with physico-chemical techniques. The encoding capacity of PUFs may be limited. This can occur if there are not sufficient unique tags required to protect a large number of items. Generating PUFs by nanotechnology-based methods allows for providing large encoding capacity owing to the randomness and extensive parameter space of nanomaterials combined with physico-chemical techniques (Solanki et al., 2011).

Some nanomaterial-based PUFs have been recently reported such as glass microbead random speckle patterns (Li et al., 2016), gold nanoparticle or silver nanowire random patterns (Kim et al., 2014), and inkjet-printed unclonable quantum dot fluorescent labels (Liu et al., 2019).

Moglianetti and colleagues (2022) integrated nanotechnology, chemistry, and artificial intelligence to develop new interdisciplinary approaches designed to address important safety and sustainability issues (Solanki et al., 2011). They presented reversible PUF tag, with huge encoding capability (> 10 300) and ability to create unique patterns along with a visual colorimetric display, visible to the eye or evaluated using a smartphone.

Wang et al. (Wang et al., 2024) reported optical PUFs based on nanostructured silica (SiO2)/polydimethylsiloxane composite films. The complexity of the Raman signals produced by the optical PUFs was increased through an interaction between the irregular PDMS structure and the uneven distribution of SiO_2 nanoparticles. Biocompatibility and accuracy of biochip were preserved. The efficacy of these optical PUFs was assessed by randomness, stability, individuality reproducibility, and high information-carrying potential. Microfluidic devices, microarrays, and other types of biochips are small-scale tools employed for biological and chemical testing; however, they vary in their structure, purpose, and the ways they are used. As shown in the Table 2, the devices described in this paper differ from each other.

Table 2. Assessment and comparison of various biochip technologies

Characteristic	Biochip	Biosensor	Microfluidic	Microarray
Key function	Comprehensive biological analysis	Conversion of information into a measurable effect, such as an electrical signal (Vo-Dinh and Cullum, 2000)	Manipulation of small amounts of fluids, thus allowing laboratory analyses to be scaled down to micro-sized chips	Immobilization and detection of molecules
Biological component	Two types of bioreceptors: a biological molecular species (e.g., an antibody, an enzyme, a protein, or a nucleic acid) or a living biological system (e.g., cells, tissue, or whole organisms)	Enzyme, antibodies, cells, nucleic acids, and/or lipids (Kulshreshtha et al., 2016)	Enzymes and proteins	Protein/DNA
Response signal	Optical, SPRI signal	Electrochemical, optical, calorimetric, piezoelectric (Ramesh et al., 2022)	Optical, fluorescent, bioluminescence, surface-enhanced Raman scattering	Fluorescent, radioactivity signals
Involves fluid flow	Yes	Yes	Yes	No
Practical use	Multiple bio-chemical evaluation methods utilized for clinical research, diagnostics, drug development, toxicology studies, and patient selection for clinical trials	Biological monitoring and environmental sensing	Biological analyses, creation an in vitro environment which simulates physiological conditions, tissue engineering experiments, POC diagnostics	Epitope-mapping, substrate profiling and probing peptide-ligand interactions
Role of nanotechnology	Improves the integration of multiple functions, reduces size, and enables data encoding (such as PUFs and nanosensors)	Strengthening sensitivity and selectivity with nanotech-based transducers	Support precise manipulation of fluids and surfaces	Improves signal density and sensitivity through nanoparticle labeling

Table 2. Assessment and comparison of various biochip technologies (cont.)

Applied nanomaterials	Quantum dots, gold nanorods, lipoplex nanoparticles, AgNPs, liposomes	Metal nanomaterials: AuNPs, AgNPs, PtNPs, PdNPs, CoNPs, FeNPs, CuNPs, as well as metal oxides NPs like ZnO, TiO2, MnO2	Polymeric nanoparticles, lipid nanoparticles (LNPs) nanotubes (Ghasemi et al., 2017), nanoporous membrane, nanopillars	Extracellular vesicle (EV) nanoparticles, polymeric nanoparticles, AuNPs, mesoporous silica nanoparticles (MSNs), AgNPs
Fabrication method	Photolithography, soft lithography, nanoimprint lithography (NIL), electron/ion beam lithography (EBL/IBL)(Altissimo, 2010), scanning probe lithography (Garcia et al., 2014)	Inkjet-based bioprinting, extrusion-based bioprinting, light-based bioprinting, volumetric bioprinting, laser-assisted bioprinting, stereolithography (Raman et al., 2016)	Micro-cutting; ultrasonic machining, electrodischarge machining, microelectrochemical machining, laser ablation, electron beam machining, focused ion beam (FIB) machining (Scott and Ali, 2021)	Direct printing, photolithography, chemical etching, ion beam lithography, soft lithography and colloidal lithography, laser-assisted protein adsorption by photobleaching (LAPAP) (Kling et al., 2023)

7. Applications of point-of-care devices for diagnostics in the era of the Coronavirus disease 2019 (Covid-19) pandemic

7.1. Biosensors used in Coronavirus disease diagnostics

Progress in healthcare supported by nanotechnology has made it possible to manage diseases and pandemics effectively from the earliest stages. The absence of adequate diagnostic methods and therapeutic options contributed to the worsening of the SARS-CoV-2 outbreak, which resulted in its rapid spread worldwide. Comparable viruses had already led to major epidemics, such as SARS-CoV in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 (Loeffelholz ang Tang, 2020). The genetic material of SARS-CoV-2, SARS-CoV, and MERS consists of RNA, which classifies them as RNA viruses. Compared to DNA viruses, RNA viruses tend to be more infectious because they introduce their RNA genome into host cells, where it can rapidly replicate and spread within the host (Narayanan and Makino, 2001). This characteristic of RNA viruses makes early detection of the infection particularly challenging.

The Covid-19 pandemic period was associated with the necessity to isolate affected individuals to prevent spread of the disease. Patients referred to emergency departments (ED) should undergo testing without delay, to allow appropriate therapeutic decisions to be taken. Multiple testing methods have been developed so far. The current reference standard for detection of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is real time reverse transcriptase-polymerase chain reaction (rRT-PCR) characterized by high sensitivity and specificity (Corman et al., 2020). There is also a second category of tests that use isothermal amplification protocols. These tests do not require thermal cycling (De Puig et al., 2021). RT-PCR is the technique through which RNA sequences are amplified; it is used for the detection of COVID-19.

The Xpert® Xpress SARS-CoV-2 test is developed by Cepheid and based on real-time PCR assays (Bruijns et al., 2022). The test is integrated with GeneExpert Instrument Systems which provides an automatic process of sample preparation, nucleic acid extraction, amplification and detection of the specific sequence. Their Xpert Xpress SARS-CoV-2 test is approved for use at the point of care. It can be applied in patient care environments that hold a CLIA Certificate.

Rong et al. (2022) assessed the validity of the Cepheid Xpert® Xpress SARS-CoV-2 for testing both upper and lower respiratory tract. The Xpert® Xpress is a comprehensive, one-time use cartridge-based real-time RT-PCR test operated on the self-operating GeneXpert® System.

Typically employed rRT-PCR assays are not quick enough for near-patient testing. However, Abbott ID NOW™ COVID-19 2.0 assay (Abbott Diagnostics, Chicago, IL, USA) proved to be an alternative to PCR tests (Iglesias-Ussel et al., 2025). It is a rapid point-of-care (POC), isothermal molecular test for qualitative detection of SARS-CoV-2. The test is designed to detect the RNA-dependent RNA polymerase gene, using isothermal nucleic acid amplification.

Barnacle et al. (2022) conducted a study to evaluate the diagnostic performance of ID NOW as a COVID-19 assessment tool for clinical admissions from ED, Northwick Park Hospital (Barnacle et al., 2022). It is a near-patient testing device that uses only dry nasal swabs, which is a considerable advantage. Moreover, it does not require additional equipment and is eco-friendly. A positive test result is obtained within five minutes and a negative one within 13 minutes.

Clustered regularly interspaced short palindromic repeats (CRISPR)/Cas are components of adaptive microbial immunity in molecular diagnostics. (Barnacle et al., 2022b) SHERLOCK (specific high--sensitivity enzymatic reporter unlocking) (Gootenberg et al., 2017) and DETECTR (DNA endonuclease--targeted CRISPR trans reporter) (Chen et al., 2018) were used to provide molecular diagnostics for different targets. Helena de Puig et al. developed miSHERLOCK, a low-cost, CRISPR-based POC diagnostic platform. Multiple CRISPR/Cas diagnostics have been created to target severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The miSHERLOCK platform combines an optimized one-pot SHERLOCK reaction with an RNA paper-capture method well-matched with in situ nucleic acid amplification and Cas detection. The entire process takes one hour (De Puig et al., 2021).

The reverse transcription loop-mediated isothermal amplification (RT-LAMP) has been developed to detect viral infections, e.g., Zika Virus (ZIKV), as an alternative to RT-qPCR which is costly, requires lab-based equipment and highly trained technicians (Da Silva et al., 2019). Contrary to RT-qPCR, RT-LAMP has the ability to amplify genes at stable temperature of approximately 65C°, it is easy to use and provides results in 30 minutes (Huang et al., 2020). Several studies have demonstrated that RT-LAMP can be applied as a POC test to detect low copies of SARS-CoV-2 RNA (Ganguli et al., 2020). The Detect Covid-19 test from Detect Inc. is based on RT-LAMP and lateral flow strip technology which targets the ORF1ab part of the SARS-CoV-2 genome.

Visby Medical developed the Visby COVID-19 that combines RT-PCR with a lateral flow assay, targeting the N1-gene. It allows for sample preparation, complementary DNA production, amplification and detection. After 30 minutes, obtained results can be interpreted. A positive result for SARS-CoV-2 is indicated by visible color change (a spot) (Katzman et al., 2023). Another test that integrates RT-PCR with a lateral flow immunoassay is the Accula SARS-CoV-2 test from Mesa Biotech. This type of test has a special docking station that controls temperature of the reaction, time and fluid movement (Curative SARS-Cov-2 Assay).

Nanobiosensors have been designed to detect COVID-19. They may remove the limitations and challenges found in earlier detection techniques, such as ELISA. Nanomaterials typically range in size from 1 to 100 nanometers. They have remarkable properties, including responsiveness to optical, magnetic, chemical, and thermal stimuli, as well as high mechanical strength. In biosensor applications, these materials can include metal nanoparticles, magnetic nanoparticles, carbon-based nanostructures, or quantum dots (Bukkitgar et al., 2020).

The advantages of biosensors for SARS-CoV-2 include (Pradhan et al., 2021):

- long self-life,
- easy to use,
- high sensitivity,
- high selectivity,
- quick response time
- multiplexing capabilities,
- multiple sensing modes.

Utilizing a specific transducer in a biosensor offers a valuable approach compared to more complex techniques like CT scanning or RT-PCR.

Inspired by virology, nanotechnology is advancing novel delivery systems to target viruses causing epidemics and pandemics, allowing devices to be engineered at scales from a few to several hundred nanometers. On the nanoscale, novel nanostructures and nanosensors demonstrate distinct properties and functionalities not available at the macroscopic level, which makes them particularly effective in detecting nanoscale events (Takemura et al., 2017).

Gold nanoparticles are a commonly used material in the production of biosensors for the detection of the SARS-CoV-2 virus.

Qiu and colleagues (Qiu et al., 2020) designed two-dimensional gold nanoislands (AuNIs). They functionalized it with complementary DNA probes, thus providing sensitive detection of specific SARS-CoV-2 sequences through nucleic acid hybridization.

Moitra et al. (2020) developed a colorimetric biosensing approach with the use of AuNPs capped with thiol-modified antisense oligonucleotides (ASOs) [AuNPs-ASOs] The AuNPs-ASO–based biosensor selectively recognized the nucleocapsid phosphoprotein (N-gene) in RNA extracted from oropharyngeal swabs, allowing for SARS-CoV-2 detection in under ten minutes.

Roberts et al. (2020) described an electrochemical biosensor based on gold nanoparticles (Au-NPs) for detecting the COVID-19 spike S1 protein antigen. The biosensor was fabricated on a fluorine-doped tin oxide (FTO) substrate, with Au-NPs employed as signal enhancers due to their excellent electrical conductivity.

Chen et al. (2020) designed a lateral flow immunoassay (LFIA) for the diagnosis of SARS-CoV-2. The biosensor is based on lanthanide-doped polystyrene NPs, prepared by mini-emulsion polymerization method. The technique is used to detect anti-SARS-CoV-2 IgG in human serum samples. Additionally, the surfaces of the LNPs, which served as fluorescent probes, were modified with mouse anti-human IgG antibodies (MH-IgG) and rabbit IgG (R-IgG).

Z. Zhao et al. (2020) developed carboxyl polymer-coated magnetic nanoparticles (pcMNPs) and utilized this nanosystem for efficient RNA extraction to detect COVID-19 infection.

Zamzami et al. (2022.) developed a user-friendly, affordable, and quantitative electrochemical biosensor utilizing a carbon nanotube field-effect transistor (CNT-FET), designed for digital detection of SARS-CoV-2 S1 in fortified saliva samples, thus providing rapid and precise identification of SARS-CoV-2 S1 antigens.

Zhao et al. (2021) developed the first smartphone-based platform for rapid and accurate electrochemical detection of SARS-CoV-2 without RNA amplification, employing a super-sandwich biosensor made from SCX8-functionalized reduced graphene oxide (rGO).

7.2. Nanoscale technologies

Nanoscale technologies have significantly advanced modern diagnostic methods by providing exceptionally high biochemical sensitivity, which is essential for disease monitoring.

Nanowire and nanotube technologies have gained significant attention in the field of nanoscale electronic devices, serving as interconnects in ultra-miniaturized circuits.

Carbon nanotubes-based (CNTs) biosensors are used in both optical and electrochemical biosensing applications (Ferrier and Honeychurch, 2021).

CNTs can be divided into two groups, i.e., single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs).

Nanowire technologies allow detection of biomolecules such as:

- proteins (Qin et al., 2024),
- viruses (Li et al., 2023),
- DNA (Gogianu et al., 2023).

The interaction between the target molecule and the sensing element on the surface can be directly converted into an electrical signal (such as changes in conductance). The specificity of detection is determined by the selected recognition element, including antibodies, DNA, aptamers, peptides, or engineered proteins with high affinity for target molecules.

Complementary metal–oxide–semiconductor (CMOS) technologies take advantage of the well-established microelectronics manufacturing processes to produce low-cost, energy-efficient electronic components. CMOS provides highly dense, large-scale integration of many transistors on a small chip (Rai et al., 2025). Moreover, it integrates transducers and signal processing units on the same chip. Thus, the two important functions of a biosensing cell, i.e., transducing, by seamlessly handling electrical signal, and ultra-fast signal processing are combined.

Different type of nanoscale technology is Printed Circuit Board (PCB), which provides scalable biosensing device (Cuncha et al., 2025). It integrates control electronics and sample handling module via low-cost technique. As a platform, PCB comprises fluidic system integrated with electronic circuits. It allows for monitoring of various metabolites using a microdevice biosensor array, while also managing fluid operations such as transport, mixing, flow control, and heating, as well as tracking properties like temperature, viscosity, density, and pH (W. Zhao et al., 2020) It has led to the development of portable and automated diagnostic devices for biomedical applications, characterized by rapid response times, minimal sample volumes required, and a reduced effective area of the diagnostic system.

The memristor technology was first theoretically introduced by L. Chua (Chua, 1971). This technology, which includes a wide range of materials and structural designs, has been applied in numerous areas, primarily in memory, logic, and computing systems, as well as in artificial neural networks (ANNs). The memristor's state variable can also be altered by a chemical stimulus acting as

an excitation parameter. In such chemical memristors, chemical and biological species containing charged groups modify the overall charge and the effective local potential. A combination of many such events leads to electrochemical biosensing systems for antigen-specific signal transduction. Sensor specificity is defined through biofunctionalization, allowing for imitation of natural neurotransmitter behaviors as well as for the compression and sorting of electrical neuronal activity. Figure 3 presents the described nanoscale technologies.

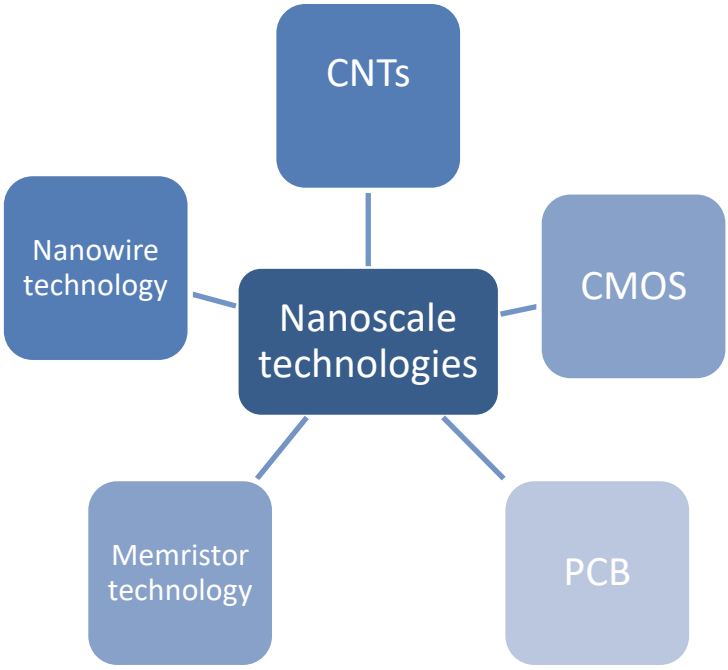


Figure 3. Nanoscale technologies used in the fabrication of biochips.

8. Challenges, limitations and future perspectives for nanotechnology-based biochips

Designing biosensors involves numerous challenges, including low sensitivity, slow response times, limited reproducibility, and poor limits of detection. The limit of detection (LOD) of biological analytes is the major challenge in the development of biochips (Szunerits and Boukherroub, 2018).

Nanotechnology has undeniably played a pivotal role in advancing biosensor capabilities. These state-of-the-art biosensors can rapidly identify target analytes, achieve single-molecule detection, and significantly amplify transduction signals. As a result, several barriers to the broader adoption of biosensors have been reduced. Nonetheless, this technology also has some downside. One of the major concerns is the inevitable release of nanoparticles into the environment (Simon et al., 2019). The response of these sensors to certain analytes can sometimes be cross-sensitive, nonlinear, and difficult to predict. Although materials like graphene show great promise for biosensing applications, efficient large-scale production remains a challenge. Until these limitations are addressed, the full potential of nanotechnology in biosensor development cannot be fully realized (Kailasa et al., 2020). Many devices reported in the literature do not progress to the final stages of development. One of the obstacles that limits the utility of nano-biochips in real life is safety and toxicity of nanomaterials, their composition and particular properties. Nanomaterials used in biochips may have toxic effects, depending on base material, shape, coatings etc. Various studies on the same nanomaterial – using different cell lines, dosages, shapes, and other parameters – can produce inconsistent toxicity results, which makes it extremely challenging to assess whether the observed cytotoxicity is biologically significant (Mahato et al., 2018).

Additionally, many technologies focus on analytical sensitivity and detection limits, omitting critical parameters such as long-term stability, accuracy and precision. To estimate how sensitive a sensor is, the most common method is to compare the change in its signal to the original signal level. Another important point refers to lack of attention regarding the time of response. Also, lack of scalable production methods for nanomaterials remains a major barrier to the commercialization of these products (Barbosa et al., 2021).

Outstanding biocompatibility of gold NPs contributes to their widespread application in various fields. There are important studies that explore how gold nanoparticles affect different organs, which was analyzed in toxicity studies. It has been proved that 33 nm citrate-capped gold nanospheres are not toxic to any hamster kidney and human hepatocellular liver carcinoma cells (Patra et al., 2007), however, they exert harmful effects on human carcinoma lung cell line (Fratoddi et al., 2015).

The recent pandemic outbreak of coronavirus disease 2019 (COVID-19) contributed to the growing interest in the field of biochip devices. Initiating research on the application of biochips in diagnostics is still a challenge for scientists. Appropriate biomarkers, platforms or detection strategies are crucial for achieving research goals. Researchers are focused on developing devices with typical characteristics such as sensitivity, selectivity, linearity, stability, and reproducibility. On the other hand, medical personnel expect diagnostic tools that enable quick results, necessary for making an accurate diagnosis.

Translation of lab-on-a-chip/microfluidic devices into clinical practice is still limited. It requires expertise across a wide variety of sectors – pharmaceutical, chemical, electrical, mechanical and bio-engineering, materials science, optics, clinical laboratory science and others. Development of micro-fluidic-based devices is an alternative to cell cultures or animal-based studies which provide reliable human models necessary for drug discovery, toxicological studies, in-vitro pre-clinical evaluation or diagnostics. Interest in this branch of technology is constantly growing but several challenges need to be faced to achieve its full capability. A common problem is the lack of standardization and proper procedures. The development of standards is based on collaboration of specialists from various fields. Successful standardization requires stakeholders to offer guidance to metrology laboratories and regulatory bodies, presenting specific suggestions for standardizing the technology and validating current models (Mastrangeli et al., 2019). Standardization should include terminology, measurement protocols, and external components that control internal conditions within the system (Mastrangeli et al., 2019).

In April 2023 “Workshop on Standards for Microphysiological Systems” was held at Michigan State University (USA). The event, organized by the OoC/ToC Engineering Standards Working Group (USA), was attended by members of the academia, industry, representatives of the Food and Drug Administration (FDA), National Institute of Standards and Technology (NIST), National Institutes of Health (NIH), and the European Commission. Such collaboration improves the clarity and focus of each group’s work (Patra et al., 2007).

When it comes to microfluidic systems, several factors need to be considered before they are commercialized (e.g., ensuring that shear stress levels fall within the expected physiological range). Another important factor is the flow direction, required capacity, mechanical activation, electric impulse stimulation, air–liquid contact surface, simultaneous cell growth capacity or cellular interactions (Wang et al., 2024).

In 2021, the European Commission's Joint Research Centre, in collaboration with the European Standardization Organizations Comité Européen de Normalisation (CEN) and Comité Européen de Normalisation Électrotechnique (CENELEC), made a decision to initiate the process of standardization of microphysiological systems by organizing a workshop “Putting Science into Standards” (Wang et al., 2024).

Biochips based on nanotechnology have made great contribution to diagnostics, addressing many challenges. However, if the aim is to provide their commercial application, researchers should focus on fabrication techniques which are readily up-scalable as well as designs that reduce both the complexity and the number of steps involved in backend processing. Additionally, considering not only

cost-effectiveness and application-specific properties but also the potential toxicological effects of the nanomaterials, another very important issue is material selection.

MEMS-based biosensor applications in engineering and medicine may have some limitations. The biocompatibility of MEMS-based devices is the main challenge in medical research. Materials and coatings need to be carefully selected because they come into direct contact with biological fluids. Therefore, it is crucial to prevent adverse reactions and preserve sensor function. Methods for calibration and adjustment are also crucial for maintaining the long-term accuracy of the sensor (Reyes et al., 2024).

9. Conclusion

This review discusses the development of micro-electromechanical systems, microfluidic systems, and various types of nanotechnology-based biochips. Increasingly advanced technology allows for creation of increasingly advanced devices such as lab-on-a-chip or body-on-a-chip. The incorporation of nanoparticles into biochip architecture significantly enhances analytical sensitivity and specificity, facilitating the precise detection of target biomolecules. These advanced devices are capable of rapid identification of target analytes, achieving single-molecule sensitivity and significantly enhancing signal transduction. Consequently, several limitations that previously hindered the widespread implementation of biosensor technologies have been effectively eliminated. Biochips have emerged as essential tools in point-of-care diagnostics and cancer research, offering significant advantages over conventional laboratory techniques, including reduced analysis time, miniaturization, and high-throughput capabilities. However, many devices described in the literature do not progress to the final stages of development because of toxicity of nanomaterials, their composition and particular properties. The primary challenges in translating nanobiosensors from the laboratory into industrial applications include the following:

- developing nanobiosensors that are simple, cost-effective, rapid, highly sensitive, and suitable for early on-site diagnosis,
- improving diagnostic accuracy through multitasking nanobiosensor designs,
- enhancing reliability and reproducibility by integrating machine learning–based signal processing for accurate and safe result interpretation.

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