MSDE

MINI REVIEW

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Cite this: *Mol. Syst. Des. Eng.*, 2022, 7, 315

A review of 3D printing technology for rapid medical diagnostic tools

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Received 29th November 2021,
Accepted 28th February 2022

DOI: 10.1039/d1me00178g

rsc.li/molecular-engineering

Early diagnosis of diseases leads to selecting the appropriate treatment method and prevention of problems, such as drug resistance. It also prevents the spread of diseases and pandemics in some cases and plays a crucial role in treating diseases. In some diseases, such as bacterial infections, effective diagnoses prevent antibiotic overuse and make such antibiotic treatments futile against infections. Additive manufacturing (AM) or 3D printing has received great attention in recent years and has been applied in a wide variety of biomedical applications, such as implants and diagnostic tools. The structures fabricated *via* this method are highly precise and economical and can have complex geometries, such as interconnecting channels, undercuts, and curvatures. Developing sensors and sensor arrays in a shorter time with high sensitivity is possible by applying AM fabrication approaches. Other fields such as dentistry also take advantage of 3D printing technology to ease the diagnosis process as it helps to fabricate complex structures with dimensions close to reality which cannot be achieved by any other method. In this review, recent advances in AM fabrication methods in producing rapid diagnosis tools have been discussed by providing a classification of advanced diagnostic tools using AM.

Design, System, Application

Additive manufacturing (AM) has attracted growing interest for different industries. This article provides a review of fabrication of biosensors and diagnostic tools *via* additive manufacturing. This mini-review will provide an applicable classification of diagnostic tools fabricated by different AM methods such as fused deposition modeling, stereolithography, and selective laser melting. The application of bioprinting for designing sensors and different mechanisms such as extrusion, inkjet, and laser-based methods are studied. This mini review summarizes design principles and mechanisms and challenges in additive manufacturing to achieve high-performance sensors. Each of the AM methods results in specific properties and characteristics of the fabricated biosensor. Some parameters including the heat source type, build orientation, thickness of the layers, raster width and angle, air gap, and feed rate, which can affect systematically the properties and characterization of biosensors, are investigated in this paper.

1. Introduction

Rapid diagnosis of diseases such as cancer,[1] infectious diseases,[2] and even dental problems plays a crucial role in choosing an appropriate treatment and will prevent serious problems. Diagnostic tests and devices based on the biosensing approach have recently received huge attention. These tools allow for economical and point-of-care testing.[3] Different types of biosensors have been developed so far, such as enzyme-based, tissue-based, and immune sensors, DNA biosensors, and thermal and piezoelectric biosensors. Compared to traditional methods, good stability and sensitivity have been achieved by applying these sensors. Biosensors have various applications in the food industry, medical field, marine application, *etc.*[4] Conventional manufacturing methods like spin coating, photolithography and screen-printing, which are mainly based on 2-dimensional fabrication processes, have several restrictions such as detrimental chemical usage, material waste, use of expensive equipment, and the impossibility of using enzymes and cells during the manufacturing process. Therefore, developing a new process to address these problems is needed.[5] As a new fabrication method, additive manufacturing has started a revolution in the generation of biosensors and medical diagnostic tools in the recent years. AM, commonly known as 3D printing, allows us to control the internal shape and micro-architecture of the produced sample, which highly improves tissue regeneration and integration and the fabrication of complex structures.[6] It has been considered a cost-beneficial and versatile approach to

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produce a complex medical application structure.[7] The physical and mechanical properties of samples can be controlled by employing multiple materials, printing at changing porosities, and applying different internal designs.[8] In recent years, 3D-printed electronic, force, motion, hearing, and optical devices have been widely studied. In particular, electronic and force sensing modules are highly investigated for additive manufacturing, and the rest of the sensor categories are fabricated by incorporating commercial components into 3D-printed constructions. Substrate boards, electronic ink, and printing process techniques are the main components of the 3D-printed sensors.[9] In this review, advancements in the fabrication of biosensors and diagnostic tools *via* additive manufacturing have been discussed. This paper aims to efficiently classify diagnostic tools fabricated *via* fused deposition modeling, stereolithography, and selective laser melting. The outline of additive manufacturing is presented in Table 1.

1.1. Why biosensing based methods

Biosensors are small devices that convert a biological reaction into measurable electrical signals proportional to the analyte's concentration.[4] A biosensor typically comprises a biorecognition element, a transducer, and a signal amplifier. The biorecognition element is considered the most critical part as it determines the success of biosensing.[16] It detects the analyte (*e.g.*, nucleic acids, antibodies, ions, or enzymes[17]) *via* a reaction, specific adsorption, or other processes such as physical/chemical interactions.[18] Then, the transducer converts the detected analyte to a quantifiable signal.[19] So far, various types of materials have been developed for diagnostic sensors such as metallic (particularly gold) and carbon materials, carbon-based hybrids, boron-doped diamond (BDD), and paper in paper-based devices.[20] Biosensors have been used in many fields, including medicine, the food industry, and marine sector, and their usage is rapidly expanding[4] For example, the diagnosis of infectious diseases is one of the areas where biosensors are widely employed. Pathogens or the response of the host to pathogens plays a key role in the diagnosis of infectious diseases. Besides biosensors, the most used approaches to diagnose infectious diseases in laboratories are protein-based assays like ELISA and serology, microscopy techniques such as pathological, histological, and morphological assays, mass spectrometry, and molecular diagnostics (including quantitative (q) PCR and sequencing). Generally, these methods involve an *in vitro* culture and an isolation stage. For example, hepatitis diseases can be detected by a wide variety of methods such as enzyme-linked immunosorbent assay (ELISA), chemical-based methods, real-time polymerase chain reaction (PCR), *etc.*[21] These techniques require a considerable amount of time and are highly sensitive to sample preparation. Technical restrictions due to limitations of testing a specific cell or area in a systemic sample or not having a perceptible amount of the pathogen needed for detection may result in a false answer.[22] Furthermore, these techniques are both costly and complicated and entirely dependent on expert skills.[21] Therefore, cost and design-efficient bio-sensing-based methods have been developed to address these limitations. Biosensors can also quantify non-polar molecules, which cannot be diagnosed *via* any other instrument. Relying on detection mechanisms, different biosensors such as optical, electrochemical, thermal, ion-selective, magnetic, and acoustic biosensors were developed.[21] Detection of biomarkers to diagnose cardiovascular diseases is one of the examples of the medical applications of biosensors. Cardiovascular diseases have been considered the major cause of mortality in the recent years. A biosensor based on biomarker detection has been developed for this purpose. Myoglobin, interleukin-1, interleukin-6, tumor necrosis factor-alpha, low-density lipoprotein, lipoprotein-associated phospholipase, troponin I or T, C-reactive protein, and myeloperoxidase are

Table 1 The additive manufacturing process outline[10]

Technology	Vat photopolymerization	Material extrusion	Powder bed fusion (PBF)
Method	Stereolithography	FDM/ FFF	SLS/SLM
Resolution (μm)	50–200 (ref. 10)	100–400 (ref. 11)	50–100 (ref. 11)
Layer thickness (μm)	<10 μm (ref. 12)	From 100 to 250 μm (ref. 12)	From 25 to 100 μm (ref. 12)
Principle	Photo-polymerisation	Melt extrusion	Powder sintering
Materials	Photo-curable polymers[13]/composites/cells[10]	Polymers, ceramics, metals[13]/composites/cells[10]	Polymers, metals, ceramics[13]/composites[10]
Advantages	Highly accurate Appropriate surface finishing[14] High resolution[15]	Cost-efficient[14] Facile multi-material printing[14] Widely commercially available Potential to process both amorphous and crystalline polymers[15]	Highly accurate[14] Acceptable strength and stiffness[14]
Disadvantages	Time consuming due to curing and refill intervals Poor mechanical properties[15]	Poor surface finishing[14] or mechanical properties compared to injection molded parts[15]	Slow building process[14] Limitation in size[14] Post-processing treatments needed (surface polishing, heat treatments)[15]

examples of cardiac biomarkers.[23] Although blood is the most widely used biological fluid for diagnostic applications, its collection and sampling is both invasive and painful.[24,25] Another example of the medical application of biosensors is flexible biosensors attached to the skin (Fig. 1). These sensors are capable of quick detection of different biomarkers in body fluids such as sweat and tears, which can be an effective non-invasive alternative.[26] Various types of physiological metabolites such as glucose, lactate, cortisol, and other small ions can be detected in sweat and tears.[27]

These devices can be directly attached to the skin and report accurate and real-time measurements of biomarkers.[28] These biosensors can be fabricated by different techniques such as inkjet printing, screen printing, and lift-off lithography.[29]

2. Additive manufacturing

Additive manufacturing (AM), namely 3D printing, is a technique to create three-dimensional (3D) objects layer by layer using computer-aided design (CAD) data. AM was developed 20 years ago for creating prototypes and models and has turned into a popular fabrication method owing to its various advantages such as availability of 3D design software, unique design freedom, ease of use, low cost, and short processing times.[30]

The AM technique can produce structures that are either patient-specific or hard to fabricate using other methods.[31] Compared to the conventional manufacturing processes such as injection molding, AM is cost-efficient as it eliminates extra tooling and re-fixturing and does not require a skilled operator, or even a long fabrication time. Complex geometric shapes can be designed and fabricated *via* AM technology with no additional cost, while in the conventional methods, for the more complex geometric shapes, more expensive molds are required.[32] Since traditional manufacturing processes, such as injection molding, have high start-up costs, they are better suited for mass production, whereas AM is cost and time-effective for low part numbers because no startup tooling is required. Furthermore, the amount of wasted material in the AM process is remarkably low.[32] As the AM manufacturing process involves a digital environment and samples are designed in digital files that can easily be shared or altered, time bottlenecks are eliminated. Another advantage of AM over other approaches is that it reduces risks associated with the workplace.[14] Hence, considering the capability of fabricating samples with high geometric complexity, low wasted material, shorter time to market,[14] and better efficiency of supply chains,[14] AM technology is cost-efficient.[32]

Recent studies have concentrated on developing more cost-efficient and less time-consuming approaches with higher sensitivity. For example, in many ELISA systems, microplates of various capacities and sizes are used for antibody immobilization, necessitating a significant amount of time for incubation and washing processes. Limited surface area to immobilize antibodies is one of the challenges which restricts the use of ELISA for low-cost diagnostics.[33,34] The 3D printing approach can be used to create microwells with a greater surface area, which improves the performance of microplate ELISAs. Sharafeldin *et al.*[34] developed ELISA in 3D-printed pipet tips. The required time for the assay decreased due to the high surface area. Moreover, the roughness of the 3D-printed surface resulted in a 15–50 times higher antibody loading capacity of the surface. This increase in loading capacity lowered the required time for the assay while the sensitivity was similar to that of conventional ELISA. Moreover, 3D printing can be a cost-efficient approach for fabrication of diagnostic tools such as ELISA. Bauer *et al.*[35] developed a 3D-printed ELISA device for detection of malaria and compared the required cost to that of different malaria-detection platforms including other 3D-printed ELISA devices, rapid diagnostic tests, and

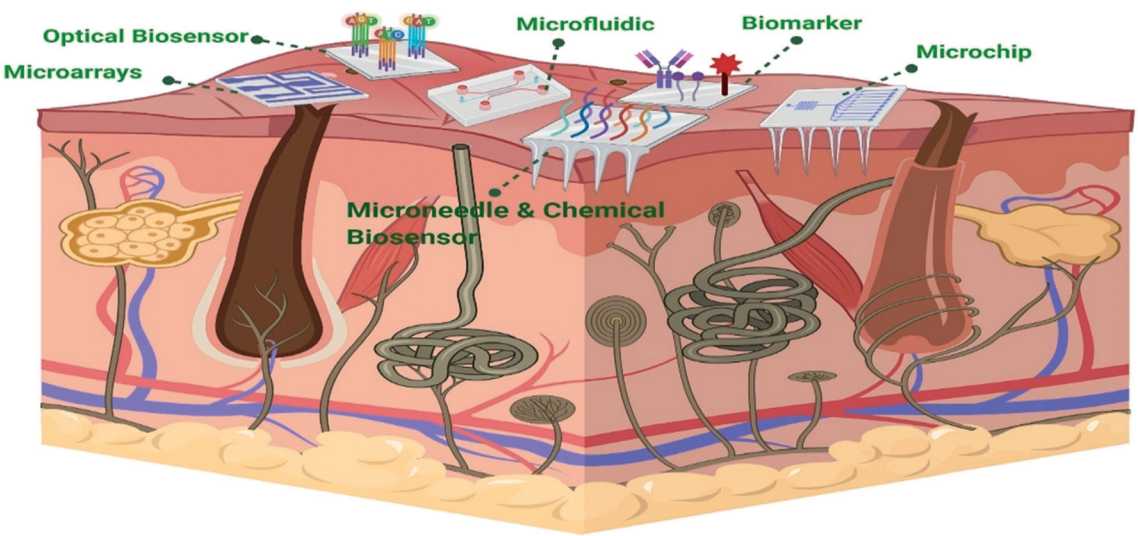

Fig. 1 Schematic representation of different types of flexible biosensors on the skin (created with BioRender).

PCR. The 3D-printed ELISA device cost less than $10 depending on the reagent and printing costs while this number for rapid diagnostic tests was around $5 and, for the PCR method, could increase to $25.

2.1. Additive manufacturing techniques and process

AM comprises various approaches and technologies, including material extrusion, material jetting, powder bed fusion, directed energy deposition, binder jetting, sheet lamination, and vat photopolymerization.[36,37] In all techniques, the sample is fabricated in a layer-by-layer manner.[9] The selection of the AM technique depends on various factors, such as the nature of the material, chemical composition, optical character, and strength. The most common techniques applied in laboratories are particularly FDM, SLA, poly jet, and SLM printing (Fig. 2).[38]

The AM procedure consists of eight general steps: 1. conceptualization and creating a CAD model. 2. Turning to STL format. 3. Conveying to the AM device and STL file manipulation. 4. Setting up the system and equipment. 5. Fabricating the sample. 6. Withdrawal and cleaning the built part. 7. Post-treatment of the fabricated samples. 8. Application.[39]

2.1.1. Additive manufacturing and biosensors. The development of 3D printing techniques has resulted in advancements in biomedical diagnosis.[40] 3D printing can be considered an efficient alternative fabrication approach for transducers where portable, more efficient, and faster biosensing apparatus with enhanced stability and controllability can be produced during the whole process. The biosensor can be produced *via* AM through three different approaches: 1: embedding the commercial device into printed constructions, 2: producing molds *via* printing for casting sensors, and 3: essentially printing the whole tool. In the last few years, 3D-printed biosensor research has focused on specific domains such as optics, electronics, and electrochemical electrodes. These specific areas deeply investigate the processability of 3D-printed optical and electrochemical devices to create high-performance biosensors using various biofunctionalization techniques. It is crucial to note that the nature of the biological components and the functionalization strategy used to integrate them on the electrode surface significantly affect the fragility and the durability of the 3D-printed biosensors.[41]

Sensors fabricated *via* AM can be highly sensitive.[42] Singh *et al.*[33] proposed a 3D printed prototype design to improve the diagnostic performance of ELISA and achieved a 2.25-fold higher sensitivity. This higher sensitivity was attributed to the larger reaction surface area in the 3D-printed samples. In another study, Guo *et al.*[43] developed a helical structure as a multifunctional 3D liquid sensor in which the structural feature of the printed sample resulted in excellent sensitivity and selectivity as it was capable of trapping more liquid

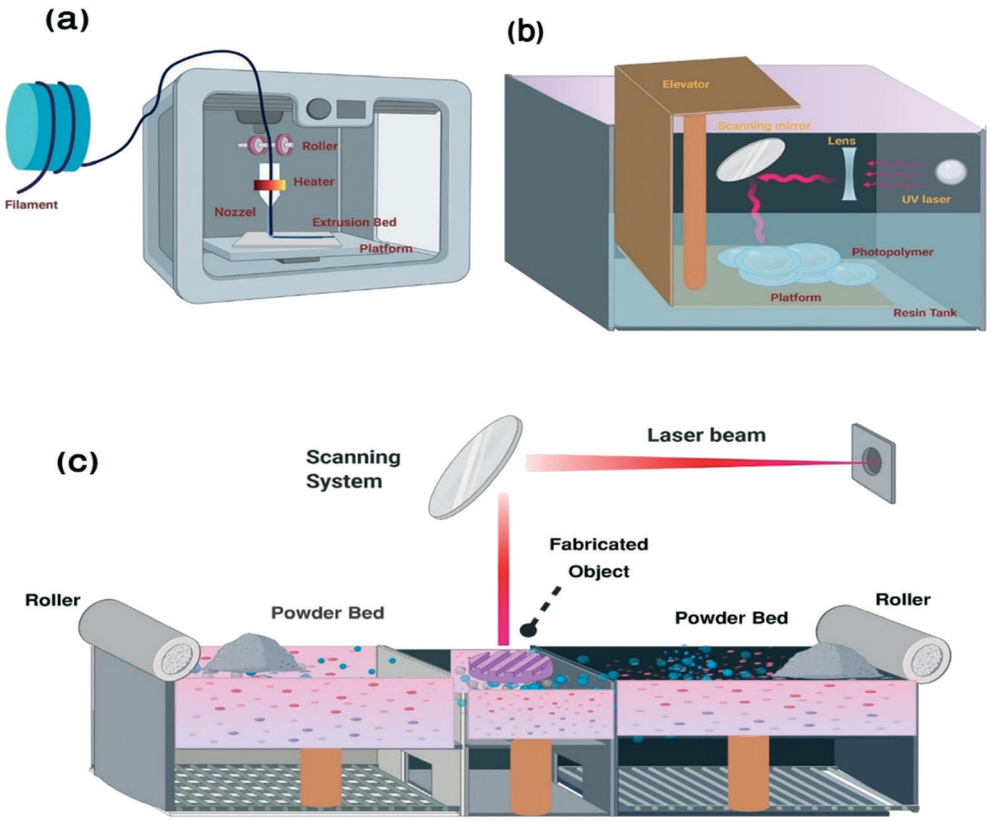

Fig. 2 Schematic representation of AM fabrication processes: (a) fused deposition modeling, (b) stereolithography and (c) selective laser melting[48] (created with BioRender).

components. Petroni *et al.*[44] fabricated an electrochemical sensor based on a graphite/acrylonitrile butadiene styrene conductive composite. The outcomes indicated better analytical performance compared to commercial carbon black/PLA conductive filaments. This is due to the production technique, which allowed for the insertion of greater amounts of conductive material in the matrix.

The performance of the sensor (such as gauge factor and linearity) can be controlled by printing parameters during the fabrication process.[45] These parameters are the printing-line directions,[46] needle diameter,[47] ratio of components in the composites,[45] and printing speed.[45] Abshirini *et al.*[47] fabricated highly flexible strain sensors by extrusion-based 3D printing. This sensor was constructed from multi-walled carbon nanotubes (MWNTs) and polydimethylsiloxane (PDMS). The influence of the needle diameter and MWNT concentrations on sensor performance was investigated. The piezoresistive sensitivity was improved when the diameter of the needle was reduced. Because the needle diameter can potentially modify the shear flow generated during the printing process, the MWNT distributions and alignment were altered as a result. Therefore the piezoresistive sensing performance of these sensors was different. Furthermore, by decreasing the amount of the MWNTs, the piezoresistive sensitivity of the printed nanocomposites was enhanced. The piezoresistive sensing mechanism depends on the MWNT network reorganization under external load and an appropriate amount of MWNTs resulted in an effective connection of MWNTs which consequently led to higher sensitivity to external loads. Vu *et al.*[46] studied the effects of the printing-line directions (45°, 90°, 180°) on the performance of a strain sensor fabricated *via* the FDM method. The results showed that all three samples had acceptable performance in terms of sensitivity (GF) with the sample printed at 45° exhibiting the highest GF among the samples. The effect of other parameters such printing speed has been also studied. A change in the printing speed altered the line width of the 3D-printed sensor.[45]

2.1.1.1. Diagnostic tools fabricated via fused deposition modeling. Fused deposition modeling (FDM) is a 3D printing technology that uses the melt extrusion method to deposit extruded thermoplastic filaments into individual layers according to a specific pattern (Fig. 2a). FDM is a complicated process. Many parameters are involved in determining the quality of the final product and understanding how these parameters interact is typically difficult. The orientation of the structure, the layer thickness, the raster angle and width, the air gap, the infill density and design, and the feed rate are all considered critical aspects in this approach.[49]

In 2017, Gaal *et al.*[50] used FDM techniques to fabricate biosensors composed of integrated, sealed and transparent polylactic acid (PLA) microchannels. The highlighted features of this construct were its appropriate transparency and reasonable price, the availability of raw material (PLA), the printing of microchannels without destroying the structures, and also the ease of combining other materials during the process. By way of illustration, pliable interdigitated electrodes were placed in a microfluidic e-tongue that could detect the basic tastes below the human threshold. Microfluidic devices is consist of polydimethylsiloxane (PDMS) because of its optical transparency, chemical inertness, non-toxicity, and gas permeability. However, microfluidic device production using PDMS has limitations, such as the cost, handling, and additional step requirements. Therefore, 3D printing to fabricate microfluidic biosensing devices enables the use of a wide range of materials and produces complex structures by avoiding multi-step processing. In 2018, Palenzuela *et al.*[51] developed highly sensitive graphene-based electrodes for electrochemical sensing using the FDM method. They 3D-printed ring- and disc-shaped electrodes and used different redox probes (ferrocene monocarboxylic acid, $K_3Fe(CN)_6$:$K_4Fe(CN)_6$, ascorbic acid, $FeCl_3$, and $Ru(NH_3)_6Cl_3$) to study the electrochemical performance of the probes. They reported increased electroactivity by a simple activation protocol, which includes DMF-assisted limited dissolution of the insulating polymer polylactic acid. Marzo *et al.* (2020)[52] also employed graphene and PLA to develop an enzymatic biosensor using the FDM approach in another study. The biosensors were produced by horseradish peroxidase (HRP) immobilization to create electrostatic interactions for H_2O_2 detection, and their results showed that the direct electron transfer of immobilized HRP was highly efficient. They further modified the biosensor by applying gold nanoparticles (AuNPs) to facilitate heterogeneous electron transfer and reported an enhanced biosensor performance. In 2020, Cardoso *et al.*[53] developed other graphene–PLA (G–PLA) based amperometric biosensors for detecting glucose in biological fluids. The glucose level was measured using glucose oxidase and ferrocene-carboxylic acid (FCA) at a 15 μmol L^{-1} detection limit. They could also modify the surface of the same system (by solvent immersion and mechanical polishing) to detect nitric acid and uric acid to analyze saliva and urine. The G–PLA sensors developed *via* the FDM approach are flexible, biodegradable, and biocompatible. Furthermore, these types of biosensors can be fabricated on a large scale with various dimensions at a low cost. FDM techniques can also be used for disease/injury diagnosis purposes. Frizziero *et al.* (2019)[54] reported the use of computed axial tomography (CAT) data which are converted into 3D-printed models, and these models are used to characterize the anatomical structure of fractures and lesions to provide a complete pre-surgery evaluation.

Aerosol jet printing (AJP) is a type of direct-write printing working in a contactless manner by using a directed aerosol stream where the polymer is deposited on the substrate at 1–5 mm offsets. AJP can fabricate fine features on complex substrates that generally cannot be reached by any physical nozzles and can be used in diverse applications, such as fabricating active and passive electronic components, actuators, and sensors.[55] In 2016, Yang *et al.*[56] developed silver

microelectrode arrays (MEAs) using AJP techniques at a 15 μm resolution. The developed sensor was successfully applied to detecting hydrogen peroxide and glucose levels as model analytes to illustrate the system's performance. This study shows the potential of AJP as a fabrication tool for custom-shaped low-cost microelectrode arrays for a wide range of biosensor applications, including touch sensing, bio-sensing, and strain sensing. In 2018, Zachariah *et al.*[57] reported the use of AJP to develop flexible hybrid electronics (FHE) that are wearable, comforting the human body, and light. For this purpose, they employed a silver nanoparticle (AgNP)-based ink and reported that the produced electronics could extend over 10 times their primary length without losing conductivity.[58]

2.1.1.2. Diagnostic tools fabricated via stereolithography. Like most 3D printing techniques, stereolithography relies on the additive fabrication process of CAD files that describe the size and geometry of the model. First, an STL file format of the model is developed and then sliced (virtually) into layers to enable layer-by-layer fabrication at high resolution (50–200 μm). The stereolithography apparatus (SLA) produces 3D objects based on the spatially controlled solidification of the liquid resin through photopolymerization.[10] It is both efficient and economical in design.[59] Fig. 2b shows a schematic representation of stereolithography.

In 2019, Kuo *et al.*[60] developed a microfluidic device based on a stereolithography approach using low molecular weight poly(ethylene glycol) diacrylate (M_W = 258) at sub-millimeter resolution. They reported the production of complex 3D microfluidic devices such as an active micro-mixer with pneumatic micro-valves and microchannels with a high aspect ratio (37 : 1), and this resolution is not available in any other conventional rapid prototyping methods. These types of complex microfluidic devices can be applied to many different research areas, including patch-clamp chips, biosensors, organ-on-a-chip, and tumor-on-a-chip.

Miller *et al.*[61] (2011) investigated inorganic–organic hybrid microneedle-shaped materials for transdermal biosensor applications using micro-mirror device-based stereolithography instruments. The sensing mechanisms are placed in the perforation of the microneedles, and the carbon fiber electrodes are located within the hollow microneedle array created by the lithography instrument (Fig. 3). Their studies showed that the microneedles were intact after puncturing into cadaver skin. The performance of the developed ion-selective electrodes was evaluated by chemically modifying the carbon fibers to allow the detection of molecules, such as ascorbic acid and hydrogen peroxide, and measuring the current electrochemically.

In the same year, Narayanan *et al.*[62] fabricated a dual-mode electrochemical biosensor using the SLA technique to diagnose glucose and H_2O_2. The developed structure was made of tungsten coated with gold nanoparticles (AuNPs) and gold micro-wire electrodes coated with colloidal platinum (colloidal-Pt). AuNPs and colloidal-Pt acted as a support matrix to immobilize the horseradish peroxidase (HRP) and the non-enzymatic glucose biosensor, respectively. This platform was capable of identifying both glucose (with a linear range of 0.5 mM to 8 mM) and H_2O_2 (linearity up to 70 μM) simultaneously. This product can be considered a potential device for real-time identification of glucose and H_2O_2 in clinical, biological, and environmental applications.

2.1.1.3. Diagnostic tools fabricated via selective laser melting. In the selective laser melting (SLM) process or direct selective laser sintering (SLS), metallic powders are melted and fused *via* a high power-density laser at a high resolution (10–100 μm). The SLM process consists of the same series of steps as those in other printing techniques: obtaining CAD data, exporting the data in STL format, slicing the model into layers, and 3D printing. The 3D printing process begins with laying a thin metal powder layer on the building plate and continues with high energy[63] (Fig. 2c). In the metal AM process, laser and electron beams are the most used heat sources to fuse the metal powders to the underlying layer after selectively melting in the bed. Electron beam-based approaches displayed a much higher power density and faster melting rate than laser-based sources.[64]

SLM is a very suitable approach in the medical and dental areas as it allows the production of complex geometries and

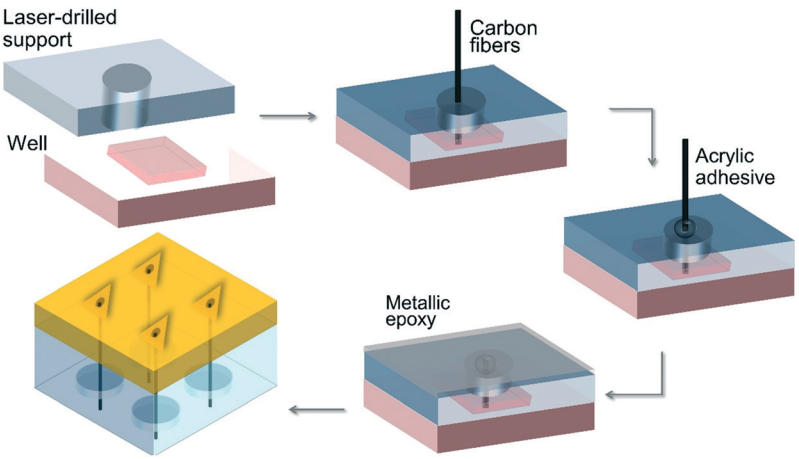

Fig. 3 Schematic illustration of the hybrid microneedle developed by Miller *et al.*[61]

individualized models. Moreover, multiple parts can be fabricated in a single run, enabling mass production.[65] In 2007, Vandenbroucke *et al.*[65] investigated the effect of the SLM parameters (material, surface post-treatment, the thickness of layers, the angle of slope, and the variance between the upper and lower surfaces) on two biocompatible metal alloys: Ti–6Al–4V and Co–Cr–Mo to be used as a dental prostheses. The results confirmed that optimized SLM factors resulted in achieving a part density of up to 99.98% for titanium. The printed parts were shown to have appropriate strength and stiffness, corrosion behavior, and process precision for medical or dental applications.

Kwon *et al.*[66] used the SLS approach to fabricate copper nanoparticle thin films onto a polymer substrate and obtained a flexible, conductive, and transparent material. The method demonstrated that Cu, which normally suffers from severe oxidation, can be sintered rapidly at low annealing temperatures with significant oxidation suppression. Their results suggest that copper-based flexible electronics can be produced onto plastic substrates using the SLS technique.

Table 2 shows a summary of developed diagnosis tools *via* additive manufacturing.

2.1.1.4. Bioprinting. The unique 3D printing fabrication approach, namely 3D bioprinting, has been recently developed in the field of tissue engineering and regenerative medicine, which is a promising substitute for scaffold-based approaches.[68] 3D bioprinting is a layer-by-layer fabrication process capable of precisely positioning cells, biological materials, and biochemicals.[69] Fig. 4 shows the steps of the bioprinting process. The shape, size, internal porosity, and interconnectivity of the fabricated samples can be controlled by the 3D bioprinting technique. Homogeneous pore size and controlled interconnectivity form ideal cell–cell and cell–matrix interaction which affects cell adhesion, proliferation, and differentiation.[70] In the 3D bioprinting approach, bio-ink simulates the target tissue extracellular matrix to provide a physiologically similar environment for cell proliferation and differentiation. Extracellular matrix (ECM)-based materials mimic cellular patterns in terms of composition and structure. Decellularized ECM biomaterials are also frequently used as bio-ink to take advantage of the natural cues of the native ECM.[71] The common bioprinting techniques include inkjet printing, extrusion-based printing, laser-assisted printing, and stereolithography.[69] Besides, special bioprinting technologies have been also presented which are designed for fixed-point deposition of macromolecules like DNA, polycose, and cytokines.[72]

2.1.1.4.1. Bioprinting and biosensors. The basis for the development of applying living cells as bioreceptors is their capability of expressing various molecules (receptors) in various amounts. The cells can provide a quantitative response to a particular activator in a specific condition, and they can analyze over one analyte quantitatively. The development of cell-based probes provides a rapid and facile method to diagnose species that were not determined *via* electrochemical methods.[73] Laser direct writing (LDW) and inkjet printing are promising 3D bioprinting approaches to achieve patterning of surfaces using non-contact deposition methods. This technique allows direct patterning of cells and materials without the need of specific binding chemistry. Patterning provides unique features to biosensors, such as allowing the placement of specific analytes, cells, and materials in defined areas to test specific stimuli simultaneously. 3D bioprinting, therefore, enables rapid screening of multiple analytes in a high throughput manner for diagnostic purposes.[74] Some other features, such as immobilizing thin films of metal nanoparticles or nanowires on a substrate, have been achieved *via* some printing methods, like electrodeposition. Using the electrodeposition approach, thin films of biological materials such as bacterial cells, enzymes, proteins, polysaccharides, and nucleic acids can also be printed.[74] The cell-based biosensors can investigate and track the interactions of drug–ligand complexes, environmental toxicity, bioactive agent impact, *etc.* A wide variety of cells can be applied in biosensor fabrication, including bacteria, yeast, fungi, algae, and eukaryotes such as fish, rat, and human cells. Microbial cells, like bacteria, fungi, yeast, and algae, have been widely applied to evaluate water quality and toxicity.[75] Cui *et al.*[76] demonstrated myotube formation of C_2C1_2 cells when bioprinted onto micro-sized cantilevers at a 300 dpi (85 μm) resolution using a thermal inkjet printer. They reported that the printed cells fused with each other and successfully formed myotubes in 4 days compared to 14 days for randomly deposited cells. The myotubes were shown to respond to electrical stimulation.

Table 2 Summary of developed diagnosis tools *via* additive manufacturing

Year	Scientist	Material	Method	Application	Reference
2007	Vandenbroucke	Ti–6Al–4V/Co–Cr–Mo	SLM	Medical application	65
2017	Gaal	PLA	FDM	e-Tongue	50
2017	Arango	Metal and metal-oxide ink	—	Engineered inks for AM	67
2018	Zacharian	Silver-based inks	3DP	Flexible electronic substrates	57
2018	Palenzuela	PLA/G	FDM	Electrochemical sensor	51
2019	Frizziero	—	FDM	Orthopedic device	54
2019	Kuo	PEG	SL	Microfluidic device	60
2011	Miller	Inorganic–organic hybrid materials	SL	Transdermal bio sensor	61
2019	Narayanan	Au NPs/W/colloidal Pt	SL	Electrochemical bio sensor	62
2020	Marzo	PLA/G	FDM	Enzymatic biosensor	52
2020	Cardosoa	PLA/G	FDM	Electrodes	53
2021	Kwon	Cu nanoparticles/polyethylene naphthalate	SLS	Flexible touch panel applications	66

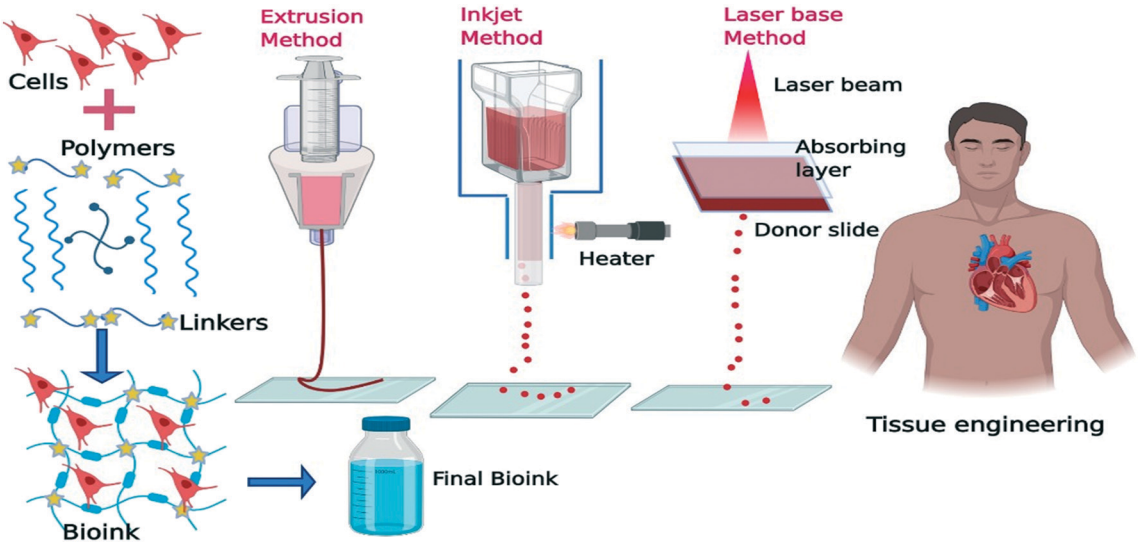

Fig. 4 Schematic illustration of the bio-printing process in tissue engineering applications (created with BioRender).

Chemical stimulation responses were also achieved upon integrating a BIO-MEMS device which demonstrates the feasibility of the developed system as a functional biosensor. In another study, Jiang *et al.*[77] developed a biomimetic 'intestinal microvillus' biosensor using a stereolithography 3D bioprinting approach to detect food allergens such as wheat gliadin. For this purpose, a conductive GelMA bioink was prepared to mix with flower-like copper oxide nanoparticles and hydrazide-functionalized multi-walled carbon nanotubes. After the bioprinting process, basophilic leukemia cells were immobilized onto the structure, and wheat gliadin was sensitively detected at a 0.1–0.8 ng mL^{-1} linear detection range with a 0.036 ng mL^{-1} detection limit showing the stability and the reproducibility of the 3D bioprinting technology.

3. Conclusion

The stage of diagnosis is an essential part of treatment, and the development of diagnostic tools is highly crucial. Additive manufacturing has been recognized as an efficient approach in manufacturing diagnostic tools that are readily available, cheap, sensitive, multifunctional, and miniaturized. 3D printing technology offers many approaches, such as FDM, SLA, polyjet, and SLM printing. Each printing technique yields a unique product as the parameters such as the build orientation, thickness of the layers, raster width and angle, air gap, and feed rate change from one method to another. 3D printing enables the development of multifunctional diagnostic devices that can perform several functions simultaneously and more complex tools yet to be developed in the near future that cannot be readily produced with average bioanalytical tools without 3D printers.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors would like to acknowledge technical support and valuable assistance of the Institutes for NanoBiomedical Research, Rutgers University. We are especially grateful to anonymous reviewers for their valuable and constructive comments.

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