# 3DBIOPRINTING- TRENDS IN FUTURE PHARMACY

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# Introduction

In order to create complex living tissues and organs with the desired 3D cellular architectureandfunctions,3Dbioprintingisa computer-aidedtechnologythatinvolvestherapidprintingof bio functional materials[1] and their supporting components in a layer-by-layer manner on asubstrateor atissueculturedish.Humans have long aspired to the in vitro biomanufacturing of tissues and organs for tworeasons: organ transplantation and precise tissue models. First off, there[2] is a severe lack oforgans available for transplant. In 2016, there were only 16000 people donated organs in USA compared to 160,000 organ transplant recipients. It is now far too hopeful to use 3D bioprinting to alleviate the shortage of organ transplants because human organs are so complicated, as demonstrated by the production of duplicates of delicate structures[3] and the biologically mysterious process of organ growth.Second,traditional approachesusedfordrugmonitoring and medical mechanism analysis, such as two-dimensional (2D) cell culture oranimal experiments, have many drawbacks. The microenvironment [4]Compared to 2D cell culture, where 2D models are used, in vivo is significantly more complex which mayproducethe[5]oppositeoutcomes.Furthermore,theinteriorenvironmentsofanimalsandhumansarevery[6]differentfromoneanother.Theseelementsincreasetheurgencyofthe needformoreprecise[7]invitromodels,which 3D bioprinting is good at. The most ideal method for creating live[8], Now known as 3D bioprinting, which permits spatio-temporal[9] directed manipulation of a range of cells, 3D cell-laden structures in vitro. In a predictable amount of time, 3D bioprinting[10] willundoubtedlyplayabiggerandbigger partwhen making organ models in vitro.

# 3D bioprinting: its history, methodology, and classification

The ability to 3D bioprint (Figure 1) fully functional organs[11] for transplant is currently not veryplausible.Thefactthat bioprinting methods have considerably advanced[12]cannotbedisputed,though. Several pioneers, including Thomas Boland, Gabor Forgacs, and Vladimir Mironov,saw the natural fusion of technologies, including cell patterning, with others, such ascommercial inkjet printing, decades ago in order to construct living structures that might oneday be used in human organ transplantation. The image below shows a chronology of thedevelopmentof bioprintingtechnologyup to thepresent.

Extrusion 3Dprinting technology, also known as fused filament fabrication (FFF), is a popular additive manufacturing process that involves the placement of melted thermoplastic materials are arranged in layers. This technology has gained significant attention due to its ability to fabricate complex geometries, high accuracy, and relatively low cost compared to other 3D printing techniques.Firstly,the fundamental principles of extrusion 3D printing, including the types[14] of thermoplastic materials used, extrusion process, and nozzle geometry, will be discussed, Secondly, the different parameters that affect the quality of printed objects such as layer height, printing speed, and nozzle temperature will be explained. Finally, the applications of extrusion 3D printing technology will be highlighted. This includes its use in prototyping, production of low volume parts, and even in medical applications such as the fabrication of prosthetic and implants. In conclusion extrusion 3D printing technology isa promising technology that has the potential to revolutionize many industries and has already made[15] significant contributions to the field of additiv4 manufacturing.



Figure 1: Development of 3D Printing technique[2]

Stereolithography(SLA)[16],whichCharlesHullcreatedin1984toprint3Dobjects fromdigitaldata, is regarded as the invention that gave rise to 3D printing. In 1988, Klebe usedcytoscribing technology to deposit[17] cells on a surface using a conventional Hewlett-Packard(HP) inkjet printer. In order to assess tissue cohesion, Forgacs and colleagues discovered in1996 that apparent tissue[18] surface tension constituted the macroscopic expression of cellularmolecular adhesion. Odde and Renn used laser assisted bioprinting for the first time in 1999to deposit living cells[19] for creating analogues with intricate anatomical structures. Directprinting of a bladder-shaped scaffold and the seeding of human cells both happened in 2001.Landers et al. described the first extrusion-based bioprinting method in 2002; it was latermarketed as "3D-Bioplotter." By adapting[20] an HP ordinary inkjet printer, Boland and Wilson created the inkjet bioprinter introduced in 2003. A year later, their team used a commercial SLAprinter to achieve cell-loaded bioprinting[21]. The same year, 3D tissue made entirely of cells—without a scaffold—was created. In order to deposit living cells, electrohydrodynamic jettingwas used in 2006. Norotte et al. created[22] scaffold-free vascular tissue in 2009 via bioprinting.Skardal et al. attempted in situ bioprinting[23] in 2012 using mice models. Many otherbioprinting items were introduced in the years that followed[24], including artificial livers andarticularcartilagein2012,tissueintegrationwiththecirculatorysystemin2014,andmore.Gaoetal.usedcoaxialtechnologytocreateatubularframeworkin2015.Rapidcontinuousoptical 3D printing based on DLP was used by Pyo et al. in 2016[25]. The same year, AnthonyAtala's research team used an integrated tissue-organ printer to create a cartilage model(ITOP). Noor and colleagues created a perfusable scale-down heart in 2019[26]. A few monthslater, Lee et al. used the freeform reversible embedding of suspended hydrogels (FRESH)techniquetosuccessfullybioprintcollagenhumanheartsatdifferentscales[27].

Therearefourstepsthatmakeupthe3Dbioprintingprocess:

* 1. **Data acquisition**: 3D models can be created directly using computer-aideddesign (CAD) software or indirectly by scanning and reconstructing objectsemploying techniques like X-rays, computed tomography (CT), magnetic resonance imaging (MRI), etc. Then, with the aid of specialised software, 2D horizontal slices of the 3D models with customizable size and orientation would be created.Thevariousbioprintingtechniques wouldfurthertransformthesedataintoparticles orfilaments[28].
	2. **Material selection**: Depending on the needs of printed structures andmethodologies, cells, growth agents, hydrogels, and other materials should be carefully chosen.Technically speaking, the concoction of these biomaterials is known as Bioinks.**[29]**, though these are typically just thought of as cell-filled hydrogels.To ensure biocompatibility, printability, and mechanical property, the choice ofbioinks isessential as shownin Figure 2
	3. **Bioprinting:** The proper configuration of printing parameters must be checked prior to bioprinting. Additionally, keeping an eye on the printing process is essential for making adjustments when issues arise.[30].
	4. **Operationalize**:Following printing, the goal is to physically and chemicallystimulatedispersedcellstolinkandproducesomefunctionsofrealtissueororgan.



Figure 2: Process of 3D printing

The bioprinting technique (X-ray (A), CT (B), and MRI(C) machines, respectively) Alginate is(D). Image of GelMA captured with a scanning electron microscope (E) (used withpermission from WILEYVCH Weinheim-based Verlag GmbH & Co. KGaA Copyright 2018), Human umbilical vein endothelial cells are seen in (F) (HUVECs) (copyrighted 2018WILEYVCH Weinheim-based Verlag GmbH & Co. KGaA)[31]; (G) The principle of extrusion-based bioprinting,(H) The fundamentals of piezoelectric inkjet bioprinting,(I) Theory of digital light processing (DLP), (J) Blood vessel cultured with endothelial progenitor[32] cells (copied with permission from Gao et al., Copyright 2017), (K) Rats were used for the cardiac patch implantation in-vivo,made using forward transfer mediated by laser (LIFT)[33] ((Reproduced with permission of Elsevier, Copyright 2011), Biochip for in vitro examinations, modified fromourunpublished research (L)[34].

Extrusion-based, droplet-based, and photocuring-based bioprinting are the three primarymethodologies used in 3D bioprinting[35], which are based on various prototype principles andprintingmaterials.Extrusion-basedbioprintingusescontinuousfilamentsmadeofbioinkstomake structures; droplet-based bioprinting[35] creates discrete droplets to stack into structures;and photocuring-based bioprinting uses photocuring materials to solidify and build 3Dmodels layer by layer[36].

# Extrusion-basedbioprinting:

Because of its adaptability and accessibility, extrusion-based bioprinting, also known asdirect ink writing and derived from inkjet printing, is the most popular method of 3Dbioprinting[37]. Extrusion-based bioprinting creates ongoing filaments with continuous extrusionforce rather than a single droplet. This method can be used to print biomaterials with a widevariety of viscosities and varied cell densities. Extrusion-based bioprinting is preferred byresearcherstocreatetissuearchitectureswithadequatemechanicalproperties.For avarietyofapplications,Extrusion-based bioprinting may also be perfectly compatible with coaxial and multi-material printing.

# Principles:

Theoretically, extrusion-based bioprinting uses mechanical or pneumatic drive to extrudebioink (often from a syringe) via a nozzle to create continuous micro filaments that are thendeposited on a receptive substrate and finally stacked into the required structures. Thesubstratemightbeeithersolid(likeaculturedish),liquid(likeagrowthmedia),orsomethingmade of gel. After configuration[38], software often generates the nozzle's path based on digitalmodels. The final bioprinted structures would be influenced by factors like temperature,nozzlediameter,extrusionpressure,movementspeed,extrusionspeed,routeinterval,etc as shown in Figure 3,4

The three major classifications are pneumatic, piston, and screw-driven of popular extrusion-basedbioprinting,respectively,basedonthevariousactuatingwaysofliquiddispensingsystems[23].

Figure 3: Types of extrusion Printers

# Classificationofextrusion-basedbioprinting:

**Pneumatic-drivenextrusion:**

Compressed air is used by a pneumatically[24] driven extrusion device to achieve liquiddispensing.Typically,It consists of a syringe loaded with bioink and a pipe and adapter connection to an air pump. Because they maintain their filament condition after extrusion,hydrogels with shear-thinning properties function well with pneumatically powered systems.Air from the air pump must be sterilised for pneumatic systems. Therefore, the best strategytoreducecontaminationofthebioprintedconstructionsistouseafilterontheairway.

Additionally, smooth extrusion must be ensured as much as possible, which necessitates theaddition of additional liquid or gel-based medium whenever semi-solid or solid state bioink isencounteredin ordertomaximiseitsviscosity.



Figure 4: Types of Extrusion Based Printers[6]

# Piston-drivenextrusion:

Using mechanically driven liquid dispensing devices, biomaterials with a high viscosity, such as man-made or naturally occurring high-molecular polymers, can be extruded more successfully.Piston-driven extrusion is one of them, and the market is flooded with related goods likemicro-infusion pumps. The piston and motor are connected in this configuration by a guidingscrew.Whenthe motorturnson,thepiston[26]convertsthespinningmotionoftheguidingscrewintolinearmotion, whichpushesthebioink outof thenozzletoproducefilaments.

# Screw-drivenextrusion:

Screw-driven devices, a different kind of mechanically[25] driven liquid dispensing system, offermore volumetric control and aid in the extrusion of biomaterials with higher viscosities. Theoperation of a screw-driven system is similar to that of a piston-driven system, with theexceptionthatascrewattachedtothemotorisuseddirectlyforextrusionratherthanapiston.Screw-driven devices, however, may inadvertently harm the cell loaded with bioink whilealso providing increased pressure. Consequently, it is vital to design the screw piecescautiously.There have also been studies that combine screw- and piston-driven systems.Polycaprolactone (PCL) was originally[21] printed by Visser et al. using a screw-driven method,andlaterhydrogelwasprintedonPCLusingapiston-drivenmethod.Insummary,pistonandscrew-driven systems offer greater printability and higher resolution with semi-solid- orsolid-state biomaterials than pneumatic-driven methods do (For instance, cell aggregates). Contrarily,gadgets using these two techniques have restricted volume, are more difficult to clean anddisinfect(especially for screw-driven devices) and cost more.

Using extrusion to create bioprints dependable method for creating biomaterials when the rightbioinksareused,notably for the production of hydrogels[18] that are capable of shear-thinning and rapid crosslinking. The final bioprinted formation will be influenced by the extrusion pressure, substrate surface properties, nozzle diameter, bioink viscosity, nozzle movement speed, bioink extrusion speed, and other variables.

Extrusion-basedbioprinting ispopularamongacademicsworldwidebecauseofitsversatility,affordability,andability toprintporous materials.

# TRIALS:

Thefirstlab-grownbladderwassuccessfullytransplantedintodogs.Inthelab,bladdercellswere seeded into a mould fashioned like a bladder, where they multiplied and eventuallyformed an organ. Synthetic bladders typically don't work since they aren't compatible withbodily tissue. Utilizing the urothelial cells that line the inside of the bladder as well as thesmoothmusclecells thatlinethebladder's exterior,bladder[19]was growninlab.A synthetic human bladder was developed as the first human organ in 1999. Cells from sevenspinabifidapatients weretakenfromWakeForestUniversitySchoolofMedicineinWinston-Salem,NorthCarolina,andusedto generateslender sacsof tissue.Anartificial scaffoldofahumanbladderwascreatedbyscientistsusingbuildingblocks,anditwasthencoveredinhumanbladdercells,whichmultipliedto constructanewbladder.Theyusedthepatient's cellsinorder topreventrejectionby thebody.The bladder is the only organ(Figure 5) that has been 3D printed[17] and successfully transplanted into ahuman so far. Luke Massella received it in 2004 to replace his damaged bladder, and sincethen, there have been no issues related to the transplant. Luke Massella's bladder's cells andtiny scraps were removed by surgeon Anthony Atala at the Boston Children's Hospital to startthe process. Atala was able to build a new bladder in a lab using these samples. Later, a 14-hourmedicalprocedurewas performedonAtalatoimplanttheartificialbladder.



Figure 5: Trials and applications of 3D printing[7]

# Applications

The four types of bioprinting applications include cytobiology, drug discovery, tumourmodels, and regenerative medicine. Cytobiology includes research on fundamental questionsregarding cell proliferation, intercellular relationships, and transgenosis. It also encompassesthe creation of single cells or multicellular combinations. Pharmacokinetics, drug screening,and auxiliary drug development are all components of drug research. The major goals of atumour model are the construction of various tumour pathology models, the study ofcarcinogenesis mechanisms, targeted therapy, and other related activities. Regenerativemedicine, which is more closely related to bioprinting[38], entails the production of artificialtissues and organs, including the fabrication of neuronal, cardioid, liver, and other organtissues, as well as scaled-up tissue vascularization and cell therapy. As we previouslyindicated, these use cases cover 3D bioprinting broadly as well as in depth.

![-Examples of applications of 3D printing in pharmaceutical sector. (A) Images of PVA filament (left) and fluorescein-loaded filament (right) under UV light (Reproduced with permission from [11] . Copyright 2014 Elsevier B.V.); (B) design and printed tablets of different geometrical shapes using FDM technology (Reproduced with permission from [43] . Copyright 2015 Elsevier B.V.); (C) multicompartment capsular device printed using FDM technology (Reproduced with permission from [48] . Copyright 2015 Elsevier B.V.); (D) dual-nozzle FDM (Reproduced with permission from [50] . Copyright 2018 Elsevier B.V.); (E) channeled tablets (front and side view with channel sizes) (Reproduced with permission from [57] . Copyright 2017 Elsevier B.V.).]()

Figure 6: applications of 3D printing in pharmaceutical sector[10]

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