

# Software for Bioprinting

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**Abstract:** The bioprinting of heterogeneous organs is a crucial issue. To reach the complexity of such organs, there is a need for highly specialized software that will meet all requirements such as accuracy, complexity, and others. The primary objective of this review is to consider various software tools that are used in bioprinting and to reveal their capabilities. The sub-objective was to consider different approaches for the model creation using these software tools. Related articles on this topic were analyzed. Software tools are classified based on control tools, general computer-aided design (CAD) tools, tools to convert medical data to CAD formats, and a few highly specialized research-project tools. Different geometry representations are considered, and their advantages and disadvantages are considered applicable to heterogeneous volume modeling and bioprinting. The primary factor for the analysis is suitability of the software for heterogeneous volume modeling and bioprinting or multimaterial three-dimensional printing due to the commonality of these technologies. A shortage of specialized suitable software tools is revealed. There is a need to develop a new application area such as computer science for bioprinting which can contribute significantly in future research work.

**Keywords:** Bioprinting, Computer and mathematical modeling, Computer science for bioprinting, Digital biofabrication, Function representation approach, Software

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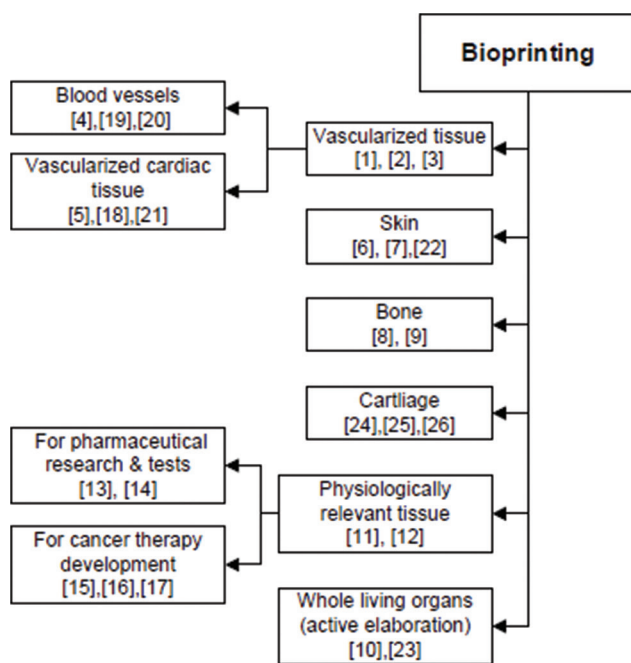
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## 1 Introduction

There are two research fields of bioprinting in a broad sense: Printing of living cells and printing for purposes of a living organism. Printing of living cells includes printing of tissues or whole organs for purposes of medicine, for example, for surgery, pharmaceutical research and tests, transplantation, and others. The printing of multi-material or heterogeneous structures is the main issue in bioprinting nowadays. In the application of living cells printing, the main issue is that the structure of the majority of

human organs is often vascularized and consists of different tissues.

A full description of research and manufacturing fields of bioprinting is illustrated in **Figure 1**<sup>[1-26]</sup>. In the field of bioprinting, the printing of living cells, including vascularized tissues, skin, bones, and cartilages is the most widespread. There is also bioprinting of physiologically relevant tissues for pharmaceutical research and development therapy of cancer treatment. Furthermore, there is also bioprinting of complete living organs which is the subject of active research and elaboration nowadays. While another general field of



**Figure 1.** The schematic diagram of the research and manufacturing fields of the bioprinting <sup>[1-26]</sup>.

manufacturing is the printing of multiple scaffolds for bioprinting and tissue engineering which may be both biodegradable and non-biodegradable, bioprinting of some critical parts for drug delivery systems and tissue reconstruction.

## 2 Living cells printing

There are several fields in the printing of living tissue. Physiologically, relevant tissues are often printed, in addition to other purposes, for pharmaceutical researches. For example, in Peng *et al.*<sup>[12]</sup>, the authors reported that three-dimensional (3D) tissue models could mimic native tissues quite closely. The authors had adopted scaffold-free and scaffold-based approaches to the creation of models and demonstrated that the 3D tissue models could simulate the physiological response of natural tissue to drug.

Scaffold-free 3D models can be generated from cells, often from stem cells which are self-assembled into neotissues through cadherin-mediated adhesion using exogenous scaffold support. Stem cells are suitable option and commonly used because of their pluripotency (opportunity to differentiate into many different

cell types). The ability of stem cells to produce a large number of cells is the second reason for using them<sup>[27,28]</sup>. Scaffold-based 3D models can be generated by seeding cells or embedding cells in a hydrogel matrix or on a prefabricated scaffold. Widely used materials for scaffolds include decellularized extracellular matrix components and many synthetic and natural biomaterials. Bioprinting technologies can be potentially useful for the fabrication of a wide variety of tissues such as composite tissues, vascular tissues, lung, neural, pancreas, brain, bone, cancer, cardiac, cartilage, heart valve, liver, retinal, skin, and others<sup>[1-5,7,8,15,25]</sup>. In addition, there are different goals of using bioprinting in pharmaceutical researches such as developing drugs against cancer and other diseases<sup>[13-17]</sup>.

Vascularization in 3D printed tissues is challenging and is the current subject of active research and it still remains as unsolved problem<sup>[3,12]</sup>. Vascularization plays a crucial role in tissue viability for its survival and growth and for drug delivery. Bioprinting of vascular constructs, such as bioprinting of physiologically relevant tissues, can be performed using scaffold-based or scaffold-free approaches. These approaches produce the same results as in the case of the bioprinting of physiologically relevant tissues<sup>[29]</sup>.

There are two main approaches for arranging cells in 3D patterns: Top-down fabrication or bottom-up fabrication<sup>[30]</sup>. Top-down fabrication means that cells co-arranged with biomimetic scaffolds with tissue maturation in a bioreactor. Bottom-up fabrication means secretion of a matrix by cells themselves instigated by temporary support<sup>[31,32]</sup>.

As an example of the early progress that can be considered, as bioprinting is the first bioprinted skin created in 2009 by Lee *et al.*<sup>[6,30]</sup>. They presented a method of creating multi-layered engineered tissue composites that consist of human skin fibroblasts and keratinocytes, which mimic skin layers. It could be useful for drug testing and modeling of diseases. Another opportunity of using skin in bioprinting is wound healing with the 3D bioprinting of skin<sup>[33]</sup>.

### 3 Scaffolds and bioimplants printing

In the field of biomedicine, there are many important purposes for each component of the created device. The task of finding a material that will satisfy all these needs is a complicated issue. Therefore, creating biomedical devices must be heterogeneous in most cases. According to Shi and Wang<sup>[34]</sup>, current researches on 3D printing technology for biomedical applications in the field of printing of non-living objects can be classified into two main areas: Personalized manufacturing of permanent non-invasive implants and fabrication of local scaffolds, which could be biodegradable or bioactive. The advantage of 3D printing of implants over traditional machine technology is that 3D printing can achieve personalized real-time manufacturing of any sophisticated implant with high-dimensional accuracy and short production cycles. Multi-material 3D printing is a widespread technology in the field of implants manufacturing. For example, in Yan *et al.*<sup>[35]</sup>, a bone prosthesis of 3D hydroxyapatite (HA)-coated porous titanium with osteoconductivity composed of an osteoinductive composite material was successfully created. The new bone successfully grew through it after 24 weeks. The porous Ti, which also acted as an osteoinductor, provided the required mechanical strength.

3D printing technologies could be used for the manufacturing of various scaffolds for the bioprinting of living tissues or whole organs. Scaffolds must satisfy such requirements as biophysicochemical properties, structural features, mechanical properties, and other necessary characteristics. According to Mogali *et al.*<sup>[36]</sup>, these essential characteristics could be a 3D porous interconnected network for cell growth, flow transport of nutrients and metabolic waste; suitable surface chemistry for cell adhesion, proliferation and differentiation; biocompatibility, and matching with the controlled degradation and absorption rate of cell or tissue growth; and properties that match the tissues to be implanted. Scaffolds with high water content, excellent biocompatibility, and controllable biodegradation can be manufactured using different technique such as extrusion-based, inkjet-based, microvalve-based, or laser-assisted

bioprinting. The selected method should be based on the properties of the tissue, for which the scaffold is created. The mechanical properties of scaffolds can be enhanced using various crosslinking technologies.

Ionic crosslinking can be used to deplete mechanical energy. Personalized scaffolds should provide an environment with micro-stress that is equal to the natural habitat for cells. It should maintain structural stability and integrity. It must possess mechanical strength, which matches those of the subchondral bone and adjacent cartilage of the implant location to provide an immediate and long-term load-bearing function<sup>[37]</sup>. Crosslinking technologies were adopted to improve the mechanical properties of widely used gel materials due to their disadvantages such as poor mechanical properties, natural shrinking, and others<sup>[38]</sup>. Considering Hutmacher, Wu *et al.*<sup>[37,38]</sup>, 3D printed bioactive glass scaffolds were manufactured with a hierarchical pore architecture and well-ordered mesopores in various shapes. Then, polyvinyl alcohol as a thermo-crosslinking agent was used to improve the mechanical properties. A combination of materials can be used to resist cracking and fatigue, to obtain desired physicochemical properties, to avoid extra cost, and for antibacterial purposes which is crucial in health care<sup>[39]</sup>.

3D printing technologies can be useful for the creation of high-fidelity clinical organ models for clinical treatments and medical education. Thanks to 3D printing technologies, these models could be created at a lower cost and taking into account of the individual differences among patients. Advantages of 3D printed models are physical dimension and durability, as well as the opportunity to be color- or material-coded by tissue type. Future materials with different elasticity, color, and composition to simulate the appearance of human tissues and organs can be developed<sup>[40]</sup>.

To achieve different functions, scaffolds should integrate different materials, for example, metal with ceramic and polymer can be used to fabricate a porous scaffold to satisfy the implant requirements<sup>[33,41]</sup>. 3D printed smart materials, which can switch their shape or properties under the specific external stimulus, can show high

potential for therapy in clinical application that will be minimally invasive.

Multiple materials usually are integrated into medical biomaterials that are used in 3D printing to achieve complex functions in printed objects. New equipment to guarantee high porosity, dimensional precision, and other useful properties could be developed in the future. There is also a need to study high-performance materials for various medical-oriented 3D printing techniques.

For all applications in the field of 3D bioprinting described above, multi-component compatible materials must be used. A combination of materials should lead to maximum fitness according to specified parameters.

A number of issues in the field of bioprinting are similar to problems that are already solvable by additive technologies and manufacturing. Therefore, it would be a perspective solution to use the experience that was previously gained in the field of multi-material 3D printing with necessary adaptation for the bioprinting. Summarizing all the above, studying multi-material 3D printing and developing new approaches in this research field represent one of the critical elements that will make progress in the field of bioprinting.

Bioprinting research field could be subdivided into the biology, materials, and computer engineering. We will focus our attention on the third subdivision.

In the field of multimaterial printing for both bioprinting and additive technologies, the creation of the mathematical and computational model represents one of the critical tasks. To produce a perfect model in this field, it is necessary to choose or create software that meets all model requirements.

#### 4 Software for bioprinting

The computational model is a crucial point in bioprinting technology. It is the first issue that must be solved when there is a task in creating some living tissue or whole organ using bioprinting. Nonetheless, the software development still lags behind than the advancement of bioprinting<sup>[42]</sup>.

#### 4.1 Printer control software

Most of the current existing software are for the bioprinting process controlling such as graphical user interfaces (GUI)-based control software like Bioscaffolder from GeSim company<sup>[43]</sup>. This software works with StereoLithography (STL) files representing object surface. It has two modules: Scaffold-generator and STL-interface. The Organovo company for their NovoGen MMX Bioprinter developed a general software that only includes essential functions. It has a graphical interface for designing various 3D constructs. It allows a user to choose parameters such as materials, cell types, printing speed, and write and load pre-defined commands for realizing specific movements of the robot and deposition heads. Now, Organovo collaborates with Autodesk to develop controlling software for bioprinters<sup>[44]</sup>. EnvisionTEC company has developed a computer-aided design and computer-aided manufacturing (CAD-CAM) software with a user-friendly graphical interface for its 3D-Biplotter system. This software has been designed to monitor and control the printing process until it is completed. Fujifilm Holdings Corporation Ltd. developed a GUI application software for its Dimatix Materials Printer. This software works with bitmap files by importing them as CAD models and allows the conversion to bitmap format.

CELLINK designed their own software package named HeartOS, DNA Cloud, and DNA Studio to control the bioprinting process. It is for fast droplet layer-by-layer printing, where the model in the G-code or the STL format could be loaded. The software package is user-friendly and does not force users to spend their time on learning the process. The software allows the user to simply adjust parameters such as flow and speed<sup>[45]</sup>. The software enables the user to preview a model before printing, to perform slicing preview to see how each layer setting will affect the results and to use active tools for printing infill.

Allevi developed the Allevi BioPrint Pro control software for bioprinting<sup>[46]</sup>. It runs online, which allows user to work with it from any computer. Allevi BioPrint Pro has built-in-model generation,



project-based workflow, and integrated slicing. Besides, the software supplies cutting-edge visualization features and interface to allow users to view and fix potential problems in their projects before printing.

RegenHU Ltd. is an innovative biomedical company that developed three specialized software for bioprinting which represents as a “bioprinting software suite”<sup>[43,44]</sup>. BIOCAD serves as a user-friendly drawing suite to design scaffolds or tissues within minutes from scratch. BIOCAM is the user-friendly toolpath generator and slicer of STL files for 3D models for RegenHu’s bioprinters. This software allows the user to create multimaterial tissues that are based on digital 3D models obtained from 3D scanners or CAD systems or medical images. BIOCUT is a user-friendly Digital Imaging and Communications in Medicine (DICOM) viewer with analyzation tools integrated into RegenHu’s bioprinting digital workflow. Using this software, complex tissue structures can be created from medical images in the DICOM file format into multi-tissue modeling and multimaterial interface for bioprinting. This software suite had been developed to explore the comprehensive potential of the 3DDiscover Evolution RegenHU’s bioprinter. In summary, the RegenHU’s software suite for bioprinting can works with STL and DICOM file formats and allows user to slice 3D models that are generated in STL. This software suite acts as a bridge between medical and bioprinting field. However, it still works with STL which is time-consuming and difficult approach for complicated multimaterial objects such as heterogeneous living organs. In addition, they had developed two instruments for the bioprinting: BioFactory and 3D Discovery, and the Windows-based Human Machine interface software to control it.

Digilab company has developed CellJet printer and Windows-based control software for the printer. The software is named Axsys, and automates low volume liquid handling applications<sup>[43]</sup>. It is user-friendly and provides a user to program protocols for printing with a graphical format. The nScript company developed printers equipped with the computer-aided biology technology that

was created based on the CAD environment. This software, as many described above, is produced for the fabrication process control. In this software, parameters such as deposition linear speed, toolpath deposition, syringe plunger rate in the displacement heads, and air pressure can be altered flexibly.

## 4.2 Software for pre-processing

### 4.2.1 Software for operations with G-code

According to Gulyas *et al.*<sup>[42]</sup>, specialized software tools to control bioprinter hardware that fulfilled the bioprinting requirements was developed. Typically, it represents a package of open-source software tools that allow the users to specify the machine movements precisely with the help of high-level programming languages. Besides, it enables us to distribute the machine movements easily across the batch of dishes of tissue culture. The software is useful in applications for printing of living cells and printing of extracellular matrices. The software can represent movements of the machine or elements of the gCode with simple functions of a high-level programming language such as C# or Python. It includes gCodeAPI.NET, gCode Editor, and PetriPrintes as a graphic user interface. PetriPrinter allows a user to distribute printer movements into several culture dishes that organized in a grid pattern, which is defined programmatically. As for bath printing, PetriPrinter distributes gCode objects into several dishes of the culture. PetriPrinter represents a gCode generator and provides collision-safe and optimized entry, movement between the dishes, and exit. Furthermore, this application can be adjusted to different hardware platforms using settings such as start height, printing temperature, row, or column distance. Besides PetriPrinter, there is second graphic interface known as gCode Editor. It was developed to visualize gCode from third-party slicer applications such as Cura or Slic3r and allows for manual modification and optimization for utilization in the cell culture. Unlike general slicers that do not offer detailed control over the tool movements, gCode Editor

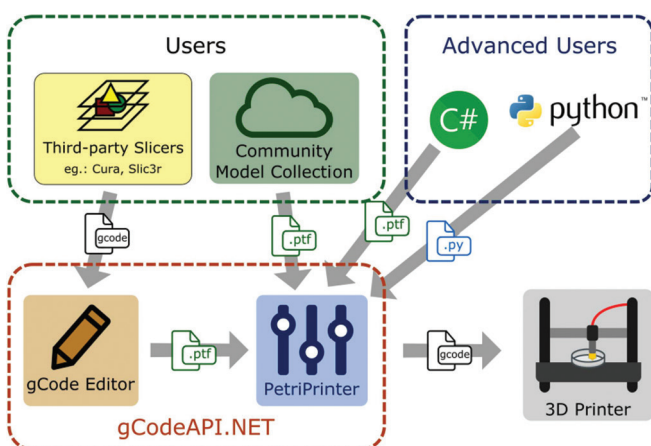
allows us to identify and to replace the problematic head movements, to insert new control points, and to relocate existing points with just a few clicks. Output files of the gCode Editor are compatible with PetriPrinter. The first and the most critical part of these software tools are the gCode API, which can encapsulate gCode commands into high-level programming language functions such as C# or Python<sup>[42]</sup>. GCodeAPI.NET includes such commands as temperature, speed, extrude, line, arc, relative, and absolute position. The scheme of using the gCodeAPI.NET is presented in **Figure 2**. Collectively, these software tools represent a useful and user-friendly software to make gCode analysis easier and less time-consuming. It is a control software for the bioprinting process which can help to make research processes more effective because of the accurate and straightforward prescribing of the machine movements and fast and easy finding some problematic machine movements in the raw gCode.

#### 4.2.2 CAD-based software

The most general approach in model creation for bioprinting is CAD-based software and the STL file format. The most popular commercial software is based on the Boundary Representation modeling principles and Constructive Solid Geometry. Such software are computer-aided 3D interactive application (CATIA) (Dassault Systems), NX (Siemens PLM Software), SolidWorks (Dassault Systems), and Pro/Engineer (PTC)<sup>[43]</sup>. CATIA is a

multi-platform software suite that was developed for CAD. It works with the STL file format and specialized CATIA model formats. NX is a software for design, engineering analysis, and manufacturing. It works with STL, CATIA, STEP, Parasolid, DXF, DWG, 3MF, Initial Graphics Exchange Specification (IGES), ACIS formats, or image, or Virtual Reality Modeling Language data for the import. For the export, it works with all these formats and also PLY, portable document format (PDF), or CSG files. SolidWorks is a CAD and computer-aided engineering (CAE) software that works with the STL file format and widely-used neutral solid modeling formats such as IGES, DXF, DWG, STEP, and ACIS. Pro/Engineer is a software for solid modeling or CAD, CAE, and CAM. It is used to import and export file formats such as ACIS, IGES, and Parasolid formats, which are specialized widely-used general file formats for solid modeling but not for bioprinting. The platform for the CAD system for tissue scaffolds (CASTS) has been developed later based on Pro/Engineer<sup>[47,48]</sup>. For the input model, CASTS uses imaging software such as materialize interactive medical image control system (MIMICS) to convert the patient data from magnetic resonance imaging (MRI) or computer tomography (CT) to the IGES, neutral CAD file format. An output model in this software is saves in the STL file format.

The use of CAD-based software in bioprinting is discussed in detail with concrete CAD systems in this section. The first one is TinkerCAD (AutoDesk, Inc., San Rafael, CA, USA), it is a simple online Web 3D modeling system that does not require any specific and in-depth knowledge from users. Due to its simplicity, experts in bioprinting could exploit it for modeling of basic geometric primitives. Cylindrical primitives modeled in TinkerCAD were used for shape definition of bioprinted samples in works<sup>[49,50]</sup>. The authors of Jeon *et al.*<sup>[51]</sup> printed a cuboid. More complex primitives of TinkerCAD were used in works Lehner *et al.*<sup>[52]</sup> and Jeon *et al.*<sup>[53]</sup>. In the mentioned articles, the authors used letters. More sophisticated models printed from organic materials can be seen in Markstedt *et al.*<sup>[54]</sup>, in which



**Figure 2.** The schematic diagram of using the gCode API<sup>[42]</sup>.

a lattice structure was designed and manufactured. Another example of the printed cellular structures can be found in Faramarzi *et al.*<sup>[55]</sup>, which bioinks were used in this study.

Some researchers used TinkerCAD to print for the printing of necessary equipment needed for biofabrication. For example, it was used for modeling of inserts in papers<sup>[56,57]</sup>. In Ivanov and Grabowska<sup>[58]</sup>, the design of the mold maker was provided with TinkerCAD, the authors of Yang *et al.*<sup>[59]</sup> used it to create a model of a special extruder. Another example of the TinkerCAD application is the modeling of microfluidic chips<sup>[60,61]</sup>.

TinkerCAD is mostly used for modeling of simple geometry or for manipulation with existing meshes. Moreover, in some cases, more advanced specialized software tools like Meshmixer has to be used to postprocess meshes created with TinkerCAD. Meshmixer as a software tool will be considered further.

More sophisticated software can be used for the same purposes. There are few examples of using Blender software for modeling purposes. Blender allows producing more complex geometry based on the skills of the user. In one study, it had demonstrated the use of Blender (Blender Foundation, The Netherlands) for cryogenic 3D printing<sup>[62]</sup>. Built-in Blender primitives also can be used for bioprinting of simple shapes<sup>[63]</sup>. In the study conducted by Mussi *et al.*<sup>[64]</sup>, it was used to prepare an ear model. Some other studies also show the use of Blender's for scaffold generation<sup>[65,66]</sup>. Some papers had also proposed Blender as a tool for vascular modeling<sup>[67-70]</sup>.

However, software tools that were used for modeling the STL format are usually used as a 3D printing standard. An STL file contains triangular mesh, therefore it is necessary to have a powerful tool for mesh processing when working with STL file. Meshmixer (Autodesk, San Rafael, USA) is one of such software tools. Autodesk Meshmixer is the software for editing and modification of the STL mesh. It also allows us to do in filling to build microstructure inside the 3D model. It was used in some above-mentioned researches, such as one study that involves an artery fabrication has applied Meshmixer in their

work<sup>[71]</sup>. Its functionality becomes pretty helpful, when the manufactured geometry is obtained from medical scanning data and mimics natural structures<sup>[72]</sup>. More details on this topic will be discussed further at the software to translate medical data to CAD section.

It should be noted that a short overview above does not mean that the three mentioned software are the most wide spread tools in modeling for bioprinting. Researchers use many other modeling packages. There are others Autodesk products such as Maya, Fusion 360, Inventor Netfabb; SketchUp (Trimble Inc, United States), Rhinoceros (Robert McNeel & Associates, United States), and Voxelizer (ZMorph, Poland).

CAD-based software have a number of lacks for the bioprinting. Some errors of CAD systems acceptable for its direct purposes can lead to serious problems in the development of bioprinting industry. Computer software characterizes commonly as a service, not a product, and its failure leads to legal issues. Clarifying the industry standards could help in the early identification of potential coding defects. However, it could be challenging to predict scenarios that may require legal attention in 3D bioprinting. Therefore, there will be a need to determine what are the essential quality of the 3D bioprinted organ or tissue, including the type of models, biomaterials, methods, or all of these combined. Besides, in software development, there is a need to pay more attention not only to its efficiency but also to the safety of the software. Requirements of the software validation should meet the patient requirements. Hence, there is a need for various validation methods due to the fact that a number of software tools cannot be comprehensively tested only through the source code<sup>[73]</sup>.

There is also another problem arises with using CAD-based software. The software is usually used for modeling of simple shapes or for operating with reconstructed 3D models of organs. In the last case, the interaction is performed under meshes in common such representation lacks functionality essential for bioprinting. For example, it is quite difficult or sometimes impossible to model natural structures with multiple materials. Another problem is difficulties with modeling of multiscale structures.



### 4.2.3 Software for translates medical data to CAD

A standard method for living tissue modeling is using medical scans obtained by CT, optical microscopy, and MRI, ultrasound (US) 3D to create a model based on these images. One of the suitable software for this method is the MIMICS Innovation Suite (MIS) from Materialize<sup>[74]</sup>. It is the specialized software working with medical scans in the DICOM file format and designing 3D models based on the STL file format. Created models could be sliced and exported for 3D printing or 3D bioprinting. Besides, this software suite allows users to analyze the anatomy segments, to make finite elements and other types of 3D analysis. MIS offers a wide range of tools for various clinical applications such as orthopedic, respiratory, and others. Another software for such tasks is BioCAD by Biomedical Modeling Inc.<sup>[75]</sup>. This software was developed for anatomical 3D printing and CAD models for the design of medical devices. It translates medical images obtained by CT and MRI to SolidWorks files. BioCAD allows users to work with mesh and CAD models and to fabricate models for 3D printing. This software is useful to create anatomical models such as bones, blood vessels, heart, and some other internal organs. Developing minimally invasive surgical devices is another purpose for this software usage. There are other options for this purpose in the form of open-source license use such as InVesalius<sup>[76,77]</sup>, a multilingual cross-platform, and 3D Slicer<sup>[78]</sup>. InVesalius is an open-source software tool for visualization and analysis of medical images that works with the DICOM file format. It allows user image segmentation, triangular mesh creation, manual or semiautomatic image segmentation, and volume rendering based on initial medical data obtained by scanning. This software is useful for the reconstruction of a CAD model based on medical scanning data obtained by CT or MRI. InVesalius allows us to import files in the DICOM or analyze format, and to export to the STL, OBJ, and PLY. Besides, InVesalius provides a capability of execution in different operating

systems. 3D Slicer enables user to perform medical image informatics, image processing, and 3D visualization. 3D Slicer is an open-source platform for analysis and visualization of medical images obtained by CT, MRI, US, microscopy, and nuclear medicine. It can be used for analysis and visualization of data includes interactive segmentation and volume rendering.

However, making organ blueprints just based on CT or MRI data is not a comprehensive approach. This approach could be convenient for considering the anatomy of an organ in a big scale. Nevertheless, to avoid errors or to preserve the anatomy of the printed organ as similar to the diseased organ, some small details of the organ such as alveoli in lung or nephrons in the kidney should be reverse engineered. Besides, the creation of a comprehensive functional organ is rather crucial than imitation of organ histology and anatomy<sup>[79]</sup>. The complex structure of organs that include nerves and complex vascular systems makes the task of organ model designing more challenging. According to Dernowsek *et al.*<sup>[79,80]</sup>, tissue composition and cell redistribution cannot be absolutely identified yet by clinical bioimaging because the technology has not reached the cellular and histological level. Therefore, one of the best ways to produce organ blueprint using medical data is to combine bioimaging, CAD modeling or reverse engineering, and mathematical modeling and simulation<sup>[80,81]</sup>.

### 4.3 Software for slicing

There are various software tools for the slicing of the model, which are commercial and open-source. A commercial software simplify 3D is a software that provides model setup, slicing and print file creation, pre-print simulations, customizable support structures, mesh analysis and repair, machine control, and monitoring<sup>[82]</sup>. Simplify 3D supports hundreds of different printers, provides easy switching between multiple machines, has incredibly realistic simulations, identifies issues in advance, and allows access to industry learning resources to improve print quality. In Sahai and Gogoi<sup>[83]</sup>, the 3D printer Tarantula 3D was modified



with syringe paste extruder for the printing of chitosan composite scaffolds. It allows us to use simplify 3D as slicing and preprocessing software for bioprinting. Other professional software such as additive manufacturing “Magics” (Materialize) was used for the preparation and slicing of the 3D model of the biocompatible implant for the patient’s cranial<sup>[84]</sup>. The 3D model was reconstructed from computed tomography and fabricated from titanium. According to Naghieh *et al.*<sup>[85]</sup>, Magics is used for the design and preprocessing of the 3D model of scaffolds, followed by fabrication of the scaffolds from gelatin using 3D bioplotter (EnvisionTEC, Germany). There are also open-source projects for slicing and preprocessing of polygonal 3D models, such as CuraEngine and Slic3r. CuraEngine is a part of a large open-source project Cura. It represents as a console application and provides prepared G-code for a wide range of fused filament fabrication printers<sup>[86,87]</sup>. Cura is an engine for slicing. CAD integration and other powerful features had been developed for 3D printing and could be useful to resolve 3D bioprinting issues.

According to Ariffin *et al.*<sup>[88]</sup>, CuraEngine is the better solution for application that requires increase accuracy using lesser filament. For the production of parts with a hanging structure, the best solution is Slic3r due to excessive material that can act as a support. The Cura software is popular slicing software for the prototyping of 3D bioprinters. It has many features of 3D model preprocessing and supports various motherboards to control the device that is under development. For example, in projects Mielczarek *et al.*<sup>[89]</sup> and Datta *et al.*<sup>[90]</sup>, the Cura software plays a role in the graphical interface with G-code preparation for a prototype of a 3D bioprinter constructed by the authors. These prototypes of 3D bioprinters use syringe pump extruders with different inks. The gelatin methacrylate doped with a photoinitiator as the printing substance was used in the first study and alginate with honey was used in the second study. In other work, Cura and Slic3r are mentioned as “slicer” software and also used for extrusion-based bioprinters<sup>[91]</sup>.

## 4.4 Software for scaffold generation (pre-processing)

### 4.4.1 Software for automatic scaffold generation

Scaffold generation is a crucial task for bioprinting, and there are specific requirements for tissue scaffolds. For the research tasks in the tissue scaffolds engineering, the following parameters are required: Generation of a uniform and non-uniform lattice, changing the size of pores and porosity of the whole construction, setting up of a volume of material to be used for scaffold fabrication, and opportunity to create the continuous tool paths inside and between layers and others.

The uniform lattices with regular continuous patterns can be generated using BioScaffolds PG. It is a specific software for scaffold generation for bioprinting<sup>[92]</sup>. It has the necessary parameters for modeling of a customizable uniform scaffold and the opportunity to export the models for the Fab@Home platform<sup>[93]</sup>. Successful tests with polycaprolactone scaffolds fabrication proven the usability of this software.

The function representation approach (FRep) based on using real continuous functions can be used for the parametrized non-uniform scaffold modeling<sup>[94]</sup>. It gives a certain freedom in the modeling of lattices and microstructures with complicated forms. It allows us to apply any functions, space-mappings, and transformations for the space coordinates to obtain the sophisticated geometrical shapes. The software which implements such an approach are HyperFun<sup>[95]</sup>, Uformia software<sup>[96]</sup>, and FRepCAM<sup>[97]</sup>.

For the scaffolds fabrication for clinical purposes, triply periodic minimal surfaces (TPMS) structures were studied. In some research works, such structures showed good properties of permeability<sup>[98-100]</sup>. The first researcher working on TPMS structures is Schwarz<sup>[101]</sup>, followed by Schoen<sup>[102]</sup> and Karcher<sup>[103]</sup>. An open-source software based on the generation of the TPMS structures around any surface was developed, which is known as POMES (Porous and Modifications for Engineering Surfaces)<sup>[104]</sup>. It allows generation

of different porous and roughness morphology on surfaces using such structures as Schwartz P, Schwartz D, Gyroid, Neovius and others. Such modification of surfaces increases cells migration inside the implants and improves osteoblast adhesion.

nTopology (nTop) is the software for the lattice generation and microstructures using the method of the implicit surfaces<sup>[105]</sup>. This software is also based on the FRep approach.

The Voronoi tessellation is a generative algorithms used for 3D modeling of the bone microstructure<sup>[106]</sup>. The Grasshopper<sup>[107]</sup> is the software with a visual programming language that allows us to build generative algorithms, including Voronoi tessellation

Autodesk Netfabb<sup>[108]</sup> has a module for the lattice generation, which is called “Lattice Commander.” It allows the user to generate microstructures using the unit cell repetition. It has a wide range of the unit cell patterns, including TPMS structures and a variety of beams intersection.

#### 4.4.2 Software for post-processing issues

Developing the software for bioprinting is the most anticipated subject of research currently. SIMMMC is the specialized application for predicting post-printing structure formation in bioprinted construct, generating 3D models of various types of bioprinted constructs, and simulating its evolution. The application has been extended for bioprinting purposes, such as modeling and simulation of the evolution of bioprinted tissue constructs composed of living cells, hydrogels, and cell culture medium<sup>[109]</sup>. The metropolis Monte Carlo algorithm (MMC) is the base of this development. Besides, the specialized module that can generate 3D models of fabricated tissue constructs automatically after loading an XYZ file has been created. The XYZ files are used for the purposes of biological systems graphical visualization using visual molecular dynamics<sup>[110]</sup>. According to Robu *et al.*<sup>[109]</sup>, many architectures of bioprinted tissue constructs could be integrated into this platform. SIMMMC for bioprinting was implemented in the Visual Studio.Net 2015 using the Visual C#.Net language. SIMMMC for

scaffold-based approach allows user to create the 3D model of a particular type of biological system that includes living cells and biomaterials and simulates the evolution of the multicellular system in the vicinity of biomaterials using the MMC algorithm<sup>[111]</sup>. SIMMMC for bioprinting as an extension of the initial SIMMMC which allows a user to load different geometry of tissue construct that was obtained by post-printing. Besides, it enables user to simulate shape changes of the uploaded bioprinted construct that includes living cells, biomaterial, hydrogel, and cellular medium with the help of the MMC algorithm. SIMMMC for bioprinting had been validated by procedural bioprinting of the vessel<sup>[109]</sup>. Collectively, SIMMMC for bioprinting represents an useful software tool to produce computer simulations of a large variety of 3D models for predicting post-printing structure formation.

At present, the software tool CompuCell3D is used for *in silico* tissue engineering<sup>[112-114]</sup>. It is based on the Glazier-Graner-Hogeweg model and is an open-source software that was developed especially for simulating the evolution of bioprinted constructs<sup>[112]</sup>. The Surface Evolver software has been invented to predict simulation of directed self-assembly in multicellular systems which considering each single cell as a bubble<sup>[115,116]</sup>. It is based on the Finite Element Method. In the field of bioprinting, Surface Evolver could be used for modeling fusion of vascular tissue spheroids in bioprinted segment of a vascular tree<sup>[117]</sup>. This approach allows us an estimation of the quantity of tissue spheroids concentric layers. These layers must be printed in sequential vascular segments to keep accuracy of each diameter of the vascular section of vascular wall<sup>[117,118]</sup>. However, the software tools that are provided in the Surface Evolver could not allow the comprehensive modeling and simulation in the field of bioprinting, because they can only solve highly-specialized issues. Besides, these software tools are meant for biological simulation, not primarily for bioprinting. There is currently no available software to simulate all aspects of bioprinting or formation of the bioprinted tissue structures with  $10^6$ – $10^9$  cells. However, developing

of control software tools for bioprinting is more widespread nowadays, in comparison with software tools for providing the information of shape changes during the process. In the future, new bioprinters are preferred to have an integrated computational framework that should include software modules for modeling and simulation of pre-printing and post-printing stages, and are compatible with medical image data<sup>[118]</sup>. Therefore, to prevent existing bioprinting software becoming hurdles in their research field, it is necessary to develop new software tools that are specialized and able to meet all bioprinting requirements.

The next step after printing of the organ is a crucial stage where maturation of the organs takes place in bioreactor. At this step, the growth and maturation of the bioproduct occurs. Bioreactors are necessary for the acceleration of the tissue maturation which controls the mechanical, electrical, and biochemical conditions<sup>[119]</sup>. Bioreactors act as a crucial environment in maintaining of the viability of the engineered tissue. Besides, bioreactors are useful for experiments and cells maturation processes monitoring. Although the bioprinting and bioproduct maturation steps are separated steps, it is worth mentioning some of the bioreactors control software. In the future, bioprinting and bioreactor may be able to integrate as one complicated device, but it still remains a task for future development<sup>[79]</sup>.

According to the Burdge and Libourel<sup>[120]</sup>, there is an open-source software based on LabVIEW that was developed for the sophisticated control of environments of the culture. This software uses Python for protocols and allows user to control parameters of the process. LabVIEW also provides an interface for monitoring the process, logging of data, and creating a protocol to execute user-defined protocols. ILS automation provides a bioreactor control system that includes specialized bioreactors integrated with control systems for cell culture systems, fermentation systems, biofuel systems, and two separate software tools as system integration and control software tools<sup>[121]</sup>.

Ignition Scada Integrator is a system integration software tool. It is an all-in-one software solution that provides user with unparalleled data

integration, analysis, control, and visualization. The general control software tools are represented as Real-time Web-based SCADA Software: Batch Expert+. It allows user to manage all bioreactors in one place to get intelligent alarming, store live and historical data together in history, and improve process, yield, and production.

LAMBDA laboratory provides two control software tools, FNet and SIAM, for the control of cell cultures and fermentation in MINIFOR fermentor and bioreactor<sup>[122,123]</sup>. FNet can control common cultures and up to 6 MINIFOR bioreactors with limited options. SIAM has better functions, including able to control up to 99 bioreactors and offers extended functions. Both software tools provide graphical visualization.

BioProcess by Eppendorf Inc provides three BioCommand software packages for fermentors and bioreactors<sup>[124]</sup>. BioCommand provides tools needed for research, optimization, and security trials. BioCommand Track and Trend is useful for essential laboratory management and offers full monitoring and historical record-keeping capabilities with control of set-points and trends visualization. BioCommand Batch Control includes all features of the previous one but also allows us to perform equipment lock-out, programming capability, and has a customize synoptic display. It is useful for optimization and control for the process. BioCommand Batch Control Plus adds three levels of security, including operator, supervisor, and administrator. It provides event logs, audit trails, and a database structure. Besides, this software allows user to have powerful control capabilities.

According to Dernowsek *et al.*<sup>[79]</sup>, omics technologies in integration with data science, machine learning, and other intelligent tools will contribute to a new field known as “computational biology in the 4.0 industry.” Integration platforms that consist of these fields are known as biofabrication lines. Biofabrication line consists of a set of devices that could produce all necessary types of models: mathematical, physical, and biological, keeping the necessary spatial distribution. It is presumed that biofabrication lines will be common in the future<sup>[79]</sup>. The current computational biology

includes analysis of biological data such as cell populations, genetic sequences, or others to make new prediction. There are researches about genome data analysis and computational biology algorithms<sup>[125]</sup>, development of some pattern-based system prototypes<sup>[90]</sup>, and also hierarchical modeling with supporting composite modeling<sup>[126]</sup>. The progress in computation biology could be also accelerated by integrating with machine learning and other research fields, which are traditionally related to data science<sup>[127]</sup>. As for computational approaches for biofabrication, computational fluid dynamics software packages are widely used to calculate flow fields, shear stresses, and mass transport with and around 3D bioconstructs and bioreactor environments<sup>[119]</sup>.

Nonetheless, the most crucial tools in the field of computational biology for the 3D bioprinting are computational methods such as analytical methods, mathematical modeling, and simulation on all 3D bioprinting stages such as pre-processing, processing, and post-processing.

#### 4.5 Approaches for future development

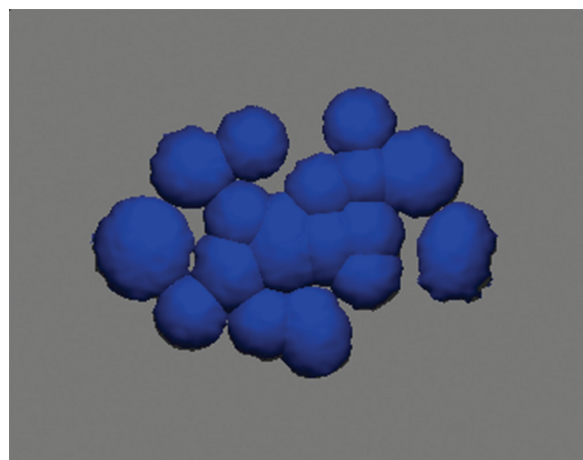
According to Robu *et al.*<sup>[109]</sup>, the software that controls the bioprinter and, in general, includes of CAD or CAM software now should include a module for simulation to predict the evolution of the printed construct. However, nowadays, bioprinting software usually can offer either only control or only simulation. Besides, the software for simulation in bioprinting is not so widespread. The solution of this problem could be developing such software that will include ability to work on all necessary stages. It should be able to provide control of the bioprinting process. Besides, it should have a module for simulation, and a slicer that can work with model file formats that are suitable for heterogeneous volume modeling in bioprinting. FRep has shown appropriate method to solve this issue<sup>[128-130]</sup>. FRep can define an object by a continuous function

$$f(x_1, x_2, \dots, x_n) \quad (1)$$

where  $f$  is a real continuous function defined on  $n$ -dimensional Euclidean space  $E^n$  that must have positive values inside the object, negative values outside, and zero on the surface<sup>[130,131]</sup>. In the 3D

space, the object boundary is named “implicit surface.” Any algorithm or function can be used until it can return a real value. Functions in the FRep approach form a system where different materials and other parameters can be described. The FRep approach is a suitable method to provide a heterogeneous representation of objects with any complexity. Besides, a mammalian cell colony was simulated using the FRep approach<sup>[132]</sup>. The colony was modeled as a set of deformable particles, which are contacting with each other. A new particles pair, which models the process of cell division, can substitute an existed before particle. This simulation has specific features such as real functions that define arbitrary shapes of particles and particular rules of particles’ behavior. A collision detection algorithm was used to define communication between particles. To solve of the packing problem, a genetic algorithm was used. Changing the particle shape, size, and orientation was used for the simulation of a deformable particle. One of the figures of the simulation is presented in **Figure 3**<sup>[132]</sup>.

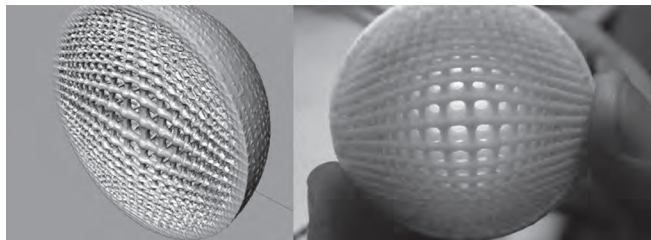
Therefore, the FRep approach represents a method that could help to solve such crucial issues in bioprinting as the heterogeneous volume modeling of living tissues and whole organs. Besides in the living objects modeling, the FRep approach allows us to model various cellular structures that are very important for implants modeling. The example of the cellular structure, developed with the FRep approach, is presented in



**Figure 3.** Simulated with the help of function representation approach mammalian cell colony<sup>[132]</sup>.



**Figure 4**<sup>[128]</sup>. Software tools utilizes this approach are Hyperfun, FRepCAM, nTop, and Uformia that were mentioned above. There is also software such as Curv<sup>[133]</sup> and libfive<sup>[134]</sup>, but not noticeable in the field of bioprinting and biofabrication yet.



**Figure 4.** Digitally fabricated non-uniform microstructure developed with the help of the function representation approach<sup>[128]</sup>.

Summarizing all the above, the overview of properties of the leading software tools and applications are listed in **Table 1**. The current most popular software for the model generation in the field of bioprinting is CAD-based software. Usually, in this kind of software, users can generate STL-file models only and then slice them. This approach is the most common approach, but it is slightly outdated. STL files allow us to work exclusively with surfaces that are good for homogeneous models but are not suitable for heterogeneous models. In addition, using the STL file format leads to some problems. This file format does not allow us to use any colors and textures because these options are not a part of the STL standard.

**Table 1.** An overview of the software tools and applications for bioprinting.

The software name	Supported file formats	Distribution	Purpose	References
GeSim	STL	Commercial	Control	[43]
Novogen	STL	Commercial	Control	[43]
BIOCAD (RegenHU)	STL	Commercial	3D models design	[44]
BIOCUT	DICOM, STL	Commercial	Convert DICOM data to STL, make slices	[44]
BIOCAM	STL	Commercial	Generate the STL and slice it	[44]
No name software from Fujifilm Holdings Corporation Ltd.	Bitmap	Commercial	Control	[43]
Axsys	Graphical formats	Commercial	Allows a user to program printing protocols	[43]
CATIA	IGES, DXF, DWG, STEP, STL, CATPart, CATProduct, CATDrawing, cgr, 3dxml	Commercial	CAD-based	[43]
NX	STL, CATIA, STEP, Parasolid, DXF, DWG, 3MF, IGES, ACIS formats, PLY (export only), image, VRML data	Commercial	CAD-based	[43]
SolidWorks	STL and general solid modeling formats	Commercial	CAD-based	[43]
Pro/Engineer	STL and neutral formats	Commercial	CAD-based	[43]
CASTS	DICOM to IGES to STL	Commercial	Based on Pro/Engineer for tissue scaffolds	[46,48]
MIMICS	DICOM to STL	Commercial	Translate medical data from MRI and CT output files to SolidWorks files + slicer	[43,74]
Biocad (Biomedical Modeling Inc.)	DICOM, SolidWorks files	Commercial	Translate DICOM to SolidWorks files, allows a user to work with the mesh and generates CAD models	[75]

(Contd...)

**Table 1.** (Continued)

The software name	Supported file formats	Distribution	Purpose	References
CELLINK software	GCode, STL	Commercial	Control, preview, slicing	[45]
Allevi BioPrint Pro	-	Commercial	Control from any place (runs online)	[46]
SIMMMC	Visual C#, XYZ	Research project, by request	Simulation	[109-111]
GCodeAPI.NET (PetriPrinter)	GCode, C#, Python	Research project, by request	Convert gCode to functions on C# or Python	[42]
CompuCell3D	XML	Research project, by request	Simulation of the shape changes	[113,114]
Surface Evolver	C	Research project, by request	Simulation of the shape changes considering each cell as a bubble	[116,117]
In Vesalius	Import: DICOM, Analyze Export: STL, PLY, OBJ	Open-source, free	Reconstruction of volume models based of medical scanning data	[76,77]
3D Slicer	DICOM	Open-source, free	Analysis and visualization of medical data	[78]
Simplify 3D	STL, OBJ, PLY, AMF, OFF, 3MF, MIX	Commercial	Pre-processing of the 3D model, slicing, G-code generation	[82]
Materialize Magics	STL, OBJ, PLY, AMF, OFF, 3MF, MIX	Commercial	Pre-processing of the 3D model, slicing, G-code generation	[74,135]
Cura, CuraEngine	STL, OBJ, PLY, AMF, OFF, 3MF, MIX	Open-source, free	Pre-processing of the 3D model, slicing, G-code generation	[86,87]
TinkerCAD	STL, OBJ	Free	CAD	[136]
Autodesk Meshmixer	STL, OBJ, PLY, AMF, OFF, 3MF, MIX	Free	Mesh editing and repair	[137]
Blender	OBJ, FBX, 3DS, PLY, STL	Free	CAD	[138]
BioScaffolds PG	-	Research project, by request	Scaffolds generation	[92]
HyperFun	HF, TXT	Open-source, free	Modeling by Function Representation (FRep)	[95]
Uformia	OBJ, STL	Comercial	FRep modeling	[96]
FRepCAM	C++	Research project, by request	FRep modeling	[97]
POMES	-	Research project, open-source, free	Scaffold generation	[104,139]
nTopology	STL, OBJ, PLY, OFF, X_B, STEP, CAT PART, SLDPRT, etc	Commercial	Building models and slicing (CLI)	[140]
Grasshopper	-	Commercial	Scaffold generation	[107]
Autodesk Netfabb	3DM, CATPART, CGR, FBX, IGES, IGS, JT, MODEL, NEU, PRT, XPR, CLI, SLI, STL, OBJ, PLY, AMF, 3MF, etc.	Commercial	CAM	[141]

(Contd...)

**Table 1.** (Continued)

The software name	Supported file formats	Distribution	Purpose	References
SCADA	-	Commercial	Bioreactor control software, also provides analysis and visualization	[121]
LabVIEW	-	Commercial	Bioreactor control software, allows a user to load Python protocols	[120]
FNet	-	Commercial	Bioreactor control software and graphical visualization	[122,123]
SIAM	-	Commercial	Bioreactor control software and graphical visualization	[122,123]
BioCommand	-	Commercial	Bioreactor control software, visualization	[124]
Curv	Export meshes to STL, OBJ, and X3	Open-source, free	FRep modeling	[133]
libfive	-	Open-source, free	FRep modeling	[134]

CAD: Computer-aided design, 3D: Three-dimensional, STL: StereoLithography, DICOM: Digital imaging and communications in medicine, CATIA: Computer-aided three-dimensional interactive application, PDF: Portable document format, VRML: Virtual reality modeling language

Only one-material surfaces are available. There is no material definition in the STL, thus complex geometry may have given errors. Typical types of errors with the STL standard are missing facets and redundant data, such as unremoved coincident surfaces or traversals, which are not crossed by coincident surfaces that will lead to weakness in the creation. Microstructures such as porosity must be in geometry thus will lead to substantial model files. Communication with build setup is an issue which may leads to issue in the orientation in printer also. Besides all the disadvantages described above, cracks and self-intersections can occur in STL files, and editing in this standard is difficult. Hence, there is a need to develop a specialized software for the heterogeneous modeling in bioprinting based on the FRep approach, which will allow us to work with suitable model file formats for this bioprinting.

## 5 Conclusions

Modeling for biomedicine purposes, especially for bioprinting, needs to transmit and convert biological and medical data as accurately as possible. Such a model must meet a number of special requirements, not only about the accuracy of data converting, but also others, depending on the model and printer specifics.

There are printing of vascularized tissue, skin, bones, cartilage, physiologically relevant tissue and whole living organs. Printer control drivers exist and can process a correctly created model.

Therefore, the created software must be highly specialized. A number of various widespread nowadays software tools, in the focus of using for bioprinting technologies, were reviewed and analyzed. Properties that act as advantages and disadvantages of these software tools were considered applicable to issues of digital bioprinting, especially of the bioprinting of heterogeneous tissues and organs. The authors' approach to systematization and generalization is proposed taking into account the complexity of such a process as creating a model of a complex heterogeneous structure. This paper identifies the main, most important components, through the prism of which the review of studies is conducted. It seems that our review can be regarded as a road map and have an impact on the further development of science in this field of knowledge. It should be noted that the authors have not found such a review, which claims to be comprehensive, either in domestic or foreign literature, which emphasizes its relevance and scientific novelty. The authors reviewed a number of properties of existing software tools for different issues

in the field of digital bioprinting. The direction of development of software tools that will meet critical requirements comprehensively in this field was revealed. A shortage of specialized suitable software tools was revealed with the classification as control tools, general CAD tools, tools to convert medical data to CAD formats, and a few highly specialized research-project tools. All considered software tools were sub-divided on three groups: software tools for pre-processing, for processing, and for post-processing. A number of existing software tools, especially modeling software tools, were considered in the focus of requirements of bioprinting process that they meet and stages of the bioprinting process that they allow us to describe. Comparative analysis of these software tools was carried out, and, based on it, the direction to the future development in this field was obtained. Every kind of bioprinting have specific requirements for modeling software. Programs developed for another applications are widely used. Software for operations with G-code can be used for printing of models with simple geometry. It allows us to print with very high accuracy. But it is difficult to operate with huge and complex geometry on G-code level. The accepted solution is to use standard CAD systems and software that can process meshes in STL-like format. On the other hand, these systems bring their problems strongly linked with boundary representation: cracks, holes, self-intersection in the geometry. Moreover, the size of models that were reconstructed from scans are extremely huge. Some cases of complex geometry can be captured by specific software like the software for scaffold generation. Nevertheless, a general solution for robust modeling in different scales doesn't exist. Recommendations for using of suitable software is given in Table 1.

On the authors opinion the most promising modeling systems for bioprinting are FRep based systems. They allow to operate with compact and accurate models applicable for bioprinting.

To reach progress in modeling methods, the FRep approach represents a suitable method to solve the heterogeneous volume modeling for the digital bioprinting issue. Hence, the possible

solution to the crucial problems in bioprinting is to adapt the FRep approach to the bioprinting problems and to develop a new application area such as computer science for bioprinting that represents a significant future work.

### Conflicts of interest

The authors declare no conflict of interest.

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