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# Organ Printing as an Information Technology

Rodrigo A. Rezende[a]*, Vladimir Kasyanov[b], Vladimir Mironov[a,c], Jorge Vicente Lopes da Silva[a]

[a]*Division of 3D Technologies, Renato Archer Center for Information Technology, Campinas, SP, Brazil*
[b]*Riga Stradins University and Riga Technological University, Riga, Latvia, European Union*
[c]*DIMAV, InMetro, Xerém, Duque de Caxias, RJ, Brazil*

**Abstract**

Organ printing is defined as a layer by layer additive robotic computer-aided biofabrication of functional 3D organ constructs with using self-assembling tissue spheroids according to digital model. Information technology and computer-aided design softwares are instrumental in the transformation of virtual 3D bioimaging information about human tissue and organs into living biological reality during 3D bioprinting. Information technology enables design blueprints for bioprinting of human organs as well as predictive computer simulation both printing and post-printing processes. 3D bioprinting is now considered as an emerging information technology and the effective application of existing information technology tools and development of new technological platforms such as human tissue and organ informatics, design automation, virtual human organs, virtual organ biofabrication line, mathematical modeling and predictive computer simulations of bioprinted tissue fusion and maturation is an important technological imperative for advancing organ bioprinting.


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*Keywords:* 3D bioprinting; information technology; computer-aided design; computer simulation; organ informatics; organ printing

## 1. Introduction

Organ printing is a biomedical variant of additive manufacturing technology [1-3]. It could be define as a computer-aided layer by layer additive biofabrication of functional 3D tissue and organ constructs based on digital model with using tissue spheroids as self-assembling building blocks [3]. It is obvious (based on this definition) that it is not possible to bioprint functional human organ constructs without correspondent digital model or simply speaking without organ blueprint. Design of digital models of physical objects using computer-aided design (CAD)

* Corresponding author. Tel.: +0-000-000-0000 ; fax: +0-000-000-0000 .
*E-mail address:* rodrigo.rezende@cti.gov.br


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software is a classic example of information technology. In this context it is not a big surprise that 3D bioprinting is considering now as an information technology (Fig. 1) [4]. Organ printing is a rapidly evolving novel biomedical technology on interface of biological and engineering disciplines. The information science and technology is a critically important essential integral component of emerging 3D bioprinting technology.

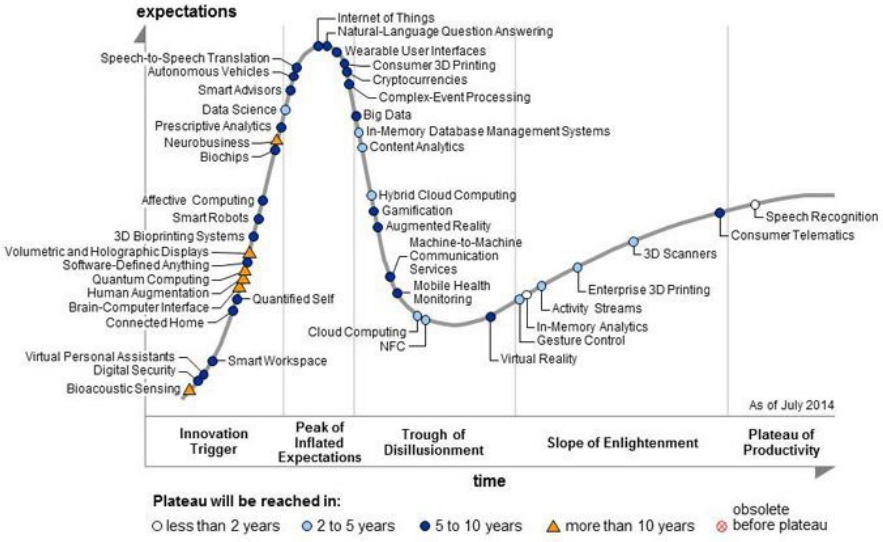


Fig. 1. Gartner report: 3D Bioprinting as an Information Technology [4].

3D bioprinting technology similarly to more established 3D printing or additive manufacturing technology includes both hardware (3D bioprinter) and software (digital model). 3D bioprinter is a robotic dispensing device which precisely place biomaterials and living cells or tissue spheroids and rods in three-dimensional space according to digital model. Software is a part of its operational control which enables robotic bioprinting of 3D tissue and organ constructs. It is logically that at initial stage of development of 3D bioprinting technology the hardware or 3D bioprinter attracted the main attention of researchers and bioengineers. However, we strongly believe that with increasing availability of 3D bioprinters (hardware) the research interest will gradually be more focused on development of software or digital model for bioprinted organs. 3D bioprinters are now commercially available and their price will be only reduced and they eventually became a cheap commodity.

As example, at least two software companies Autodesk (USA) and Materialise (Belgium) are already trying to position itself as developers and suppliers of software for 3D bioprinters. In this paper we will illustrate that organ printing is indeed an information technology and that application of existing information technology and computational tools as well as the development of new software is an important technological imperative for advancing organ bioprinting.

## 2. Conceptual Framework

Concept of organ printing has been invented already one decade ago [5]. In essence it is a biomedical application of rapid prototyping technology or additive manufacturing. The additive manufacturing enables transforming digital model of object into physical reality. Thus, information technology is an integral part of organ printing. Information is a critically important aspect of 3D bioprinting technology but it still got rather insufficient attention of researchers and engineers. Meantime, computer-aided tissue engineering is gradually evolving and there is even already book on this topic [6]. Unfortunately, up to now computer-aided tissue engineering predominantly has been focused on design of solid scaffolds for tissue engineering construct and in this context could not be even considered as a really revolutional 3D bioprinting technology because BIOprinting is actually missing in this approach. The concept of

organ printing from the another side from its inception is based on using living cells in form of tissue spheroids. Tissue spheroids, however, could be approximated as some sort of droplets and digital unit. The main challenge for application information technology for organ printing using discrete tissue spheroids as building blocks (and not continuous filaments like in the most of computer-aided tissue engineering approach) is an absence of corespondent adequate softwares which will enable the design of blueprints for bioprinting human organ constructs although there are certain attempts to develop such software using function representation approach [7].

Another unsolved problem of application of information technology in organ printing is a design of human organ. The main question is this context – do we really want to bioprint 100% authentic human organs or just more simplified but functional organ constructs. At this stage of development of organ printing technology it is safe to state that we must at first try to design rather simplified but functional version of real human organ. We must learn to look on human organ from the engineering point of view and identify functional components of human organ which enable its most essential main functions and basically ignore some other existing anatomical structures and details. For example, in case of kidney, it is a nephron enabling filtration and reabsorption. Such reductionistic simplified approach can induce certain concerns and even critique. However, history of development prostheses and artificial organs strongly indicates that from clinical point of view it is most important to provide functionality rather them imitate organ anatomy and histology. Vascular and teeth prostheses as well as artificial heart valves are good examples of such approach. The human tissues and organ have different level of complexity. There are certain tissue like cartilage, cornea, heart valves which do not have vascularization which make them first target for 3D bioprinting. Most of complex human organs are highly vascularized and have elaborated intraorgan branched vascular trees which dramatically increase the level of their structural organization and make task of designing corresponding organ blueprint more challenging. There are also stroma and complex hierarchically organized branched ductal systems and, of course, innervation. Classification of human organs based on the level of their complexity from engineering perspective is essential for the selection of the easiest targets for demonstration the feasibility of organ printing. For example, thyroid gland could be such target because as a typical endocrine organ it has no complex ductal system and its structural-functional unit - thyroid follicles are relatively simple structures [8].-

## 3. Previous and ongoing related works

With the ongoing progress in the development of organ printing technology there is a growing demand in digitized version of human anatomy or some sort of organ informatics. In this context great interest represent virtual human projects which allow to reconstruct virtual human organs. The first virtual human was funded by NIH and developed in USA several decades ago [9]. Now there are Chinese, South Korean, Japanese virtual human projects [10-12]. Most advanced attempts in building virtual human and logical extension of this concept have been recently made by group of committed researchers from UK and New Zealand [13-14]. Some of digitized images from virtual humans such as kidney vascular tree or external ear has been already used in 3D printing. It demonstrates that problem of compatibility of CAD software and computational tools used in designing virtual human could be overcome. On histological level one of the first attempt to bring information technology was a concept of tissue informatics. Peter Johnson – a founder and CEO of company with name TISSUE INFORMATICS was a pioneer of digitalization of histological images of normal human tissues for using them as some sort of standards or references for tissue engineering application [16]. For example, TISSUE INFORMATICS developed metrological morphometrical standards for human skin histology.

The interesting attempts have done in application of information technology in the the area of tissue engineered scaffold design. This emerging field of research was named scaffold informatics or scaffoldomics [16-19]. National Institutes of Standard and Technology (USA) even developed a first standard or reference scaffold based on using 3D printing technology [19]. In 2014 the NIH Library offered a free 3D Printing Pilot as an integral part of the opening of the new Technology Sandbox [http://nihlibrary.campusguides.com/3Dprinting]. How useful these rapidly growing database for 3D bioprinting time will show. At least for 3D printing of scaffolds of hard tissues like bone is definitely a valuable resource. However, 3D printing allows to create customized prostheses and scaffolds. Thus, the development of digital libraries and databases of 3D anatomical structures is already well established trend.

The another very ambitious approach for application of information technology in the biomaterial science was named materiomics. There are already published several reviews and at least two books on this topic [20-21]. The main promise of materiomics to develop high throughput screening assays for rapid testing and screening novel biomaterials. It could be potentially very important for development of bioprintable hydrogels and material for bioprintable solid scaffolds. In recent review it was written ... *materiomics sets the stage for a transformative change in the approach to biomaterials research to enable the design of tailored and functional materials for a variety of properties in fields as diverse as tissue engineering, disease diagnosis and de novo materials design, by combining powerful computational modeling and screening with advanced experimental techniques* [22]. Using large-scale computer simulations to predict materials properties from fundamental molecular principles in combination with experimental work and new mathematical techniques will allow to categorize complex structure-property relationships into a systematic framework [23]. Application of information technology is gradually transforming many fields related to 3D bioprinting (Fig. 2).

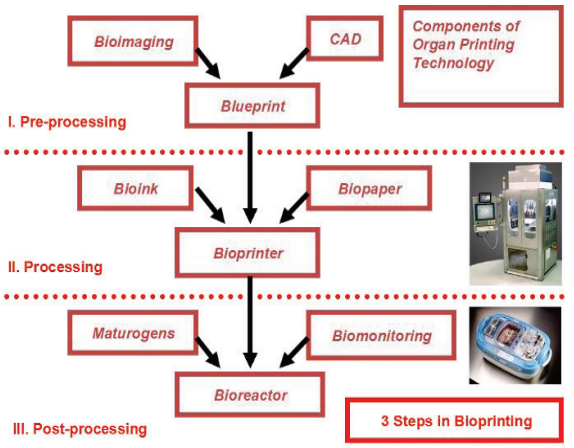


Fig. 2. Scheme of main 3 steps in organ printing technology.

### *3.1. Organ Printing: Pre-Processing*

Before building an organ, we must have a blueprint in the form of a computer-aided design of the designed organ. We might define this as computer compatible precise spatial information about the localization of cells in the 3D organ or, in other words, the "address" of each cellular or extracellular component of the tissue or organ that we want to built. There are several ways in which we can get the information about the anatomy, histological structure, composition and topology of human organs necessary for computer-aided design of printed organs.

Recent progress in clinical bioimaging and ultrasound make it possible for us to discern the gross anatomical characteristics of organs even while they are still inside their owner. The advantage of this approach lies in its the capacity to demonstrate the patient's specific anatomical information as well that of his organs, not to mention the fact that we do not need to remove the individual's organ in order to examine it. However, resolution of this technique has not yet reached the histological and cellular level. More importantly, tissue composition and cell redistribution cannot be precisely identified as yet. In short, this method is not yet refined enough to be utilized in the process of organ printing.

A second approach is based on computer-aided reconstruction of a histological section. This method provides a high level of resolution and information about the size and shape of the organ, as well as details about its composition. The problem inherent in this method lies in the fact that human organs are available for this sort of inspection only after death, and are hence subject to change and distortion. Other limitations of histological approach are that it is enormously labor-intensive, time consuming and is not patient specific. However, considering that organs have a polymeric structure and consist of repeating structural functional units, one can reconstruct only

one typical organ unit and then assemble the whole organ *in silico* by adding a reconstructed unit based on the gross anatomical structure or by filling the available space.

A third approach is based on a mathematical computational anatomical model. For example, by knowing the mathematics of vascular branching it is possible to reconstructed in synthetic materials a very realistic model of the vascular tree found inside the organ. In fact, several commercially available pieces of software permit the creation of a realistic anatomical model from bioimages, and several laboratories around the world have developed virtual cadavers with gross anatomical and microanatomical level resolution, in the public domain and available through the internet. These successes suggest that the computer aided design of printed organs is feasible, although prior to finalizing the task of printing a viable organ, the existing software will need to be upgraded to embody more capacities and greater flexibility.

Thus, it is logical to assume that design of digital model of human organ or blueprint must be based on combination of all above described approaches. Gross anatomical features of patient specific human organ could be derived from clinical imaging. Histological organization of structural functional units or lobules or modules could be derived from computer-aided reconstruction of serial histological sections. Finally, mathematical modeling and computer simulation could be used to put collected macro- and microanatomical structural information together in form of highly desirable digital model of human organ or organ blueprint suitable for 3D bioprinters.

Tissue spheroids are building blocks in organ printing technology. Biofabrication of tissue spheroids of desirable size and composition is an integral part of pre-processing or preparing to actual 3D bioprinting or processing. There are many methods of scalable biofabrication of tissue spheroids which make this approach very attractive from clinical perspective. There are also a lot of published papers about mathematical modeling of tissue spheroids. However, there are practically no mathematical models of tissue spheroids assembly as well as mathematical modeling and computer simulations of changes of tissue spheroids size during tissue compaction.

Using Surface Evolver software we together with original developer of this open source software Dr. Ken Brakke (USA) were able to show that during transition from cell aggregate (where cells are just touching to each other) to much more cohesive tissue spheroid (where cells are densely packed and contact with each other by almost all their membrane surface) the diameter of tissue sphere reduce on 20%. This information provide us important insight on maximal cell packing inside tissue spheroids and bring powerful insight on the processes of tissue compaction which are essential to estimate and understand properly before designing actual bioprinting process.

Mathematical modeling and computer simulation of different modes of tissue spheroid packing is also important because the final shape and size of the bioprinted organ construct is depended on selected mode of tissue spheroid packing. Tissue spheroids packing mode is also essential for survival of bioprinted construct during interstitial perfusion [24].

### *3.2. Organ Printing: Processing*

On of the most comprehensive approach to modeling organ printing technology and application of modern information technology tools is a development of virtual organ biofabrication line (Fig. 3).

The development of virtual organ biofabrication line is another interesting approach and logical and advanced way for industrial and clinical translation of emerging organ printing technology.

Virtual organ biofabrication line must combine all possible visual information about machines, devices and processes through an interactive computer system capable to generate real-time animation and data and also and capable to provide a visit by virtual reality to the organ biofabrication plant as an avatar to visually, observe and virtually interact with all components of organ biofabrication line [25].

The initial step is a computer simulation and virtual representation of major biofabrication equipment such as cell sorters, robotic tissue spheroid biofabricator, robotic bioprinter and perfusion bioreactor. Second step is virtual placing biofabrication equipment into virtual building based according to logics of biofabrication process and restrictions imposed by related regulatory requirement. Finally, sequential steps of bioprocessing and organ bioassembly processes have been simulated on microlevel and seamlessly integrated with correspondent virtual biofabrication equipment. The resulted virtual biofabrication line should be additionally optimized and integrated.

The virtual organ biofabrication line will be a needed step toward development of real organ biofabrication industrial plant. Thus, computer-aided design, computer simulation, mathematical modeling, virtual reality methods and informational technologies are essential tools for developing organ printing technologies and industrial scale biofabrication process engineering [25].

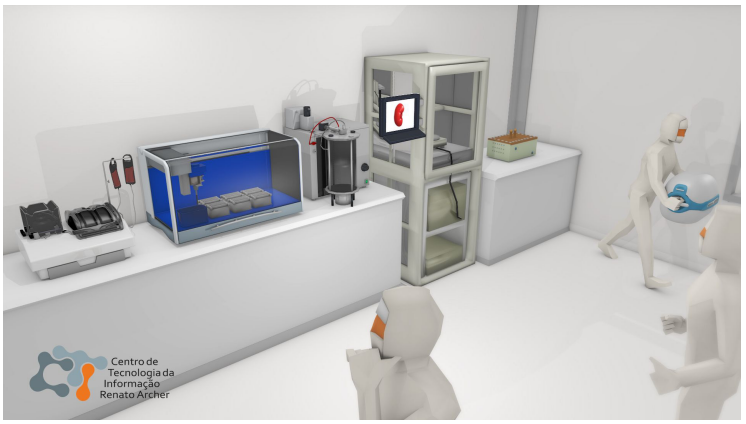


Fig. 3. Virtual organ biofabrication line [25].

### *3.3. Organ Printing: Post-Processing*

Post-processing starts immediately after finishing bioprinting process (processing). The main task of designing post- processing is ensuring viability and survival of 3D bioprinted organ construct, fusion tissue spheroids into integrated constructs and its accelerated maturation. Modeling post-processing will enable non-destructive and non-invasive biomonitoring viability, integration and maturation of bioprinted organ constructs.

Predictive mathematical modeling and computer simulation of tissue spheroids fusion in bioprinted construct is one of the most interesting problem which already attracted attention of several groups of researchers [26-30]. There are several mathematical approaches starting from field theory and finishing molecular dynamics [26-30]. The scalable mathematical modeling of tissue spheroid fusion in whole bioprinted organ construct is still limited by computer power. Implementing powerful parallel computing is one approach. The second approach based on approximation of tissue spheroid with foam bubbles and using well developed open source software Surface Evolver. In this case modeling post-processed tissue spheroid fusion in large size 3D tissue constructs is possible. In our group, we used Surface Evolver software for modeling fusion of vascular tissue spheroids in bioprinted segment of vascular tree. This approach enables to estimate how many concentric layers of tissue spheroid must be printed in sequential vascular segments in order to get authentic for each vascular segment diameter of vascular wall [31]. One obvious limitation of Surface Evolver which must be optimized is impossibility of changing topological position of tissue spheroids inside 3D construct.

Modeling interstitial interspheroidal perfusion in 3D bioprinted construct during post-processing tissue spheroid fusion process is another important problem which needs systematic investigation.

Mathematical modeling and computer simulation of emerging material properties of bioprinted constructs is still practically untouched area in the ongoing application of information technology tools in 3D bioprinting. The need for accelerated post-printed tissue maturation in 3D bioprinted tissue construct is obvious because it reduces the cost of final product. As we indicated most of the complex human organ are highly vascularized and their integration in pre-existing recipient vascular system required achievement of certain level of material properties of large diameter extraorgan segment of their vascular tree such as, for example, kidney artery and vein in case of kidney.

The first step in modeling tissue maturation is an identification of structural determinants of material properties of tissue and organs. The main structural determinants of material properties of vascular wall in the large diameter blood vessel is an extracellular matrix usually consisted of two load bearing structural extracellular matrix proteins collagen and elastin. The best way to identify the relative contribution of these two proteins is using method of

selection digestions or the observation of co-evolution material properties of with structural-functional parameters. Using this approach, we recently were able to identify concentration of collagen, diameter of collagen microfibrils and level of collagen cross-linking as most essential structural determinants of material properties of heart valve [32]. The application of mathematical modeling for solving so-called ill-posed inverse problems in biology is another potentially perspective direction of application computational tools for predictive description of tissue maturation during post-processing in organ printing technology. Exploring this approach is highly desirable.

## 4. Conclusions and Perspectives

It is not possible to predict the future. However, there are a lot of very interesting lessons in the history of development of software industry which could provide an important and powerful insight although they, of course, do not guarantee the similar development of bioprinting industry. From another side, as Albert Einstein said - ***Intuition is nothing more but the outcome of earlier intellectual experience***. Based on historical analogies and our intuition and/or experience we will try to outline below some perspectives on the future development of organ printing as an information technology.

First of all, we predict that 3D bioprinters (as computers in Bill Gates time) will soon became a hardware commodity and be a lot less interesting for developers of 3D bioprinting technology and the main actions will be in the software. Why it is not happening right now? It is because there is still a lot of room for innovation in the design of 3D bioprinters and because professional software developers are not yet welcomed participants of bioprinting community and both only start to consider 3D bioprinting as an information technology. But we are sure that time will come and we hope this paper hopefully at least partly will contribute to this forcoming transformation. Moreover, the absence of optimal softwares eventually could be even a main impediment for further successful development of organ printing technology. Secondly, development of biomaterials for 3D bioprinting is also booming research area. There is even a new special term for bomaterials used in bioprinting - bioprintable hydrogel (or biopaper using analogy with von Gutenberg book printing technology) [34]. However, design of biomaterial is also became part of information technology. Computer-aided design of bioprintable hydrogel with desirable and predictable specifications is highly probable. Thirdly, recently introduced concept of 4D printing and 4D bioprinting is exploring the idea of programmable self-assembly [34]. Building blocks and biomaterials used in 4D bioprinting must contain design information which will enable their post-printing self-assembly. Computational design of building blocks with propensity for self-assembly is another interesting and exciting direction in the development of 3D bioprinting as an information technology. There is certainly a need in softwares for designing programmable self-assembled materials. However, living tissue spheroids could be also designed for programmable self-assembly into more complex 3D structures. Finally, it it very logical to assume that complex human organ such as kidney will be first bioprinted virtually or in silico. It is obvious that without digital model is not possible to bioprint physical organ but it is not obvious that the same digital model could be used for virtual human organ bioprinting. Moreover, virtual bioprinting in combination with mathematical modeling and computer simulation could serve as a some sort of virtual screening of digital model of bioprinted organ. Virtual testing can identify potential unexpected problems, find better solution and optimize digital model and, thus, facilitate real physical organ printing. Virtual bioprinting could be also moved to another level – the development of comprehensive virtual organ biofabrication line [35]. Using real time design automation and eventually artificial intelligence especially in the case of in situ 3D bioprinting is also foreseeable.

We agree with one of pioneer of information technology Alan Kay that forecasting is cheap and ***the best way to predict future is to invent it.***

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