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AN UNDERLYING ISSUE OF PUBLIC HEALTHCARE

SUŠTINSKI PROBLEM JAVNOG ZDRAVSTVA

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Abstract

Recently, organ transplantation has seen significant development, largely thanks to France, one of the first countries which successfully performed such procedures with living donors. Despite these medical advancements, the number of patients which require organ transplants is increasing on a yearly level, especially when it comes to kidney transplants. In many cases, this is the only treatment option for patients, hence it is necessary to find solutions for various pathological problems which can occur during the transplantation process. This paper demonstrates some of those solutions, based on 3D printing.

Izvod

Transplantacija organa je u poslednje vreme doživela značajan razvoj, pre svega zahvaljujući Francuskoj, kao jednoj od prvih zemalja u kojoj je izvršena uspešno sa živim donatorom. Uprkos napretku medicine, broj pacijenata kojima su neophodne transplantacije se povećava iz godine u godinu, naročito u slučaju transplantacije bubrega. U mnogim slučajevima je ovo jedina opcija za lečenje pacijenata, i stoga je neophodno naći rešenje za različite patološke probleme koji mogu da se jave pri transplantaciji. U ovom radu će biti prikazana neka od mogućih rešenja, zasnovana na primeni 3D štampe.

INTRODUCTION

France is one of the first countries in the world to have performed an organ transplant with a living donor, making them pioneers in the field of organ transplantations /1/. This scientific milestone enabled significant progress in the field of medicine. For example, in 2019, 3643 kidney transplants were performed in France which is equivalent to approximately 54 people per million inhabitants /1, 2/. However, like with most advancements, it will be shown that other obstacles will inevitably encounter. The following chart indicates a serious problem facing modern society, Fig. 1. For many years in France, a large number of people are on waiting lists for various types of transplants. Most of whom are waiting for a kidney transplant. This tendency is a good illustration of the medical problems associated with various pathologies, such as kidney diseases, that lead to irreversible loss of function of the affected organs. Although certain solutions exist, such as kidney dialysis, they are only temporary and do not lead to a complete cure /3/. Therefore, in many cases, transplants remain the only therapeutic option for treating the diseased organ. Kidney transplants, although steadily increasing, are far from meeting the needs of patients who are piling up on waiting lists.

The growth rate of the number of these patients increases from year to year. In January 2020, 16,180 patients were waiting for a transplant, including 5,269 newly added to the

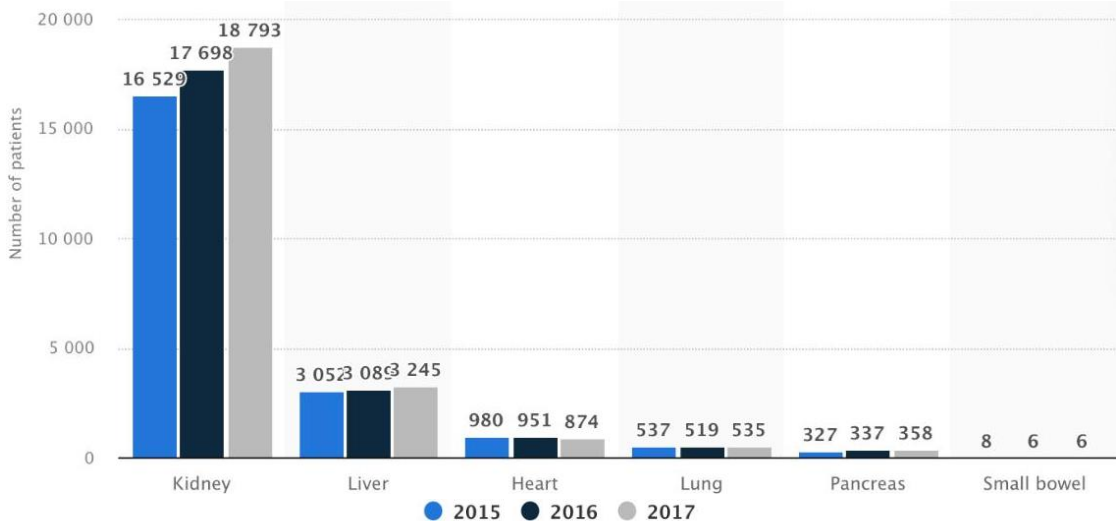

Figure 1. Total number of patients on transplant waiting lists in France from 2015 to 2017, for each individual organ, /2/.

waiting list, compared to 4,557 in 2013. Therefore, it can be seen that the demand for organ transplantation has increased tremendously, by 16 % /2/. Furthermore, the average waiting time between registration and transplantation has gradually increased in recent years and has reached more than 22 months /1/. In the case of an emergency, this waiting time becomes unwarranted.

However, the near future hints at new solutions. Biomedical innovations offer new systems to solve this type of problem. The combination of biology and engineering brings us to the concept of 3D printing of human organs.

The aforementioned represents a difficult situation arising from the inability of public healthcare to currently provide reliable solutions to medical problems surrounding pathologies having a destructive effect on the body, such as kidney failure, leaving a large number of patients stuck on transplant lists. In the following, existing solutions will be listed, as well as methods in the development phase of 3D printing.

MODERN TECHNOLOGICAL ACHIEVEMENTS - WHAT IS A THREE-DIMENSIONAL PRINTER ?

As its name implies, it is a system based on the work of a three-dimensional printer, capable of printing body structures. These structures can be artificial or biological, /4/.

In the second case, bio-printing will be described. This topic will be further elaborated later, in more detail, in order to highlight its specificities.

Firstly, it is essential to explain how a three-dimensional printer works. Three-dimensional printing is a manufacturing method in which objects are created by melting and/or applying materials such as plastic, metal, and more, in layers, to produce a three-dimensional object.

Some 3D printers are similar to traditional inkjet 2D printers, but the final product is a three-dimensional object. There are about two dozen 3D printing processes which use different technologies, speeds, printing resolutions, as well as hundreds of different materials. These technologies enable the production of a three-dimensional objects in almost any shape, which are processed in a computer file.

In the basic configuration, the 3D printer first follows the instructions in the digital file to create the base of the object, moving the print head along the ‘x-y’ plane /5/. The printer then moves the print head along the ‘z’ axis to build the object vertically, layer by layer, /6/.

It is important to note that two-dimensional (2D) images, such as X-rays, MRIs, etc., can be converted into 3D digital printable files, allowing the creation of complex and customisable anatomical and medical structures, /6-8/.

Let's take an example of the system from the following illustration, Fig. 2.

In this model, the basic principle is building an object by melting and stacking plastic under three-dimensional control. The model (number 40, pink colour) is printed on a base plate (number 10, dark blue colour) which moves in horizontal (*x*-*y*) directions, while the print head and nozzle (number 2 and 4, orange colour) move in the vertical direction (*z*). The raw material for printing comes out of a plastic tube (number 46, yellow colour), melted by the printing head. The heating process is carefully regulated by a ‘thermoelement’ (electrical heat sensor) connected to the temperature regulator (number 86, purple). The material from the tube is extruded using compressed air from the large tank and compressor on the right (numbers 60 and 62, green in colour) /6/.

In general, 3D printers using synthetic materials as a cartridge can already successfully create anatomical structures. The resulting product, different from tools such as prostheses and implants, may or may not have the same role as the latter. This is one of the first uses of 3D printers to create customisable devices which vary according to each individual patient and their medical problem. An example would be the artificial reconstruction of the patient's skull, so that the surgeon could better prepare his intervention, /6/.

Characteristics of synthetic printing with its biological counterpart will be compared in the following paragraphs.

Bio-printing is a relatively new technique that is being developed, and is mainly used in bio-robotics, regenerative medicine, and biomedical engineering. Its essential application is in the regeneration or restoration of damaged or injured tissues through the production of new tissues and organs compatible with the patient's body. The idea of this biomedical application is to create biological tissues, in the same way our usual printers are used, /9/.

The bio-printer uses cells and bio-materials instead of traditional metals and plastics to create three-dimensional

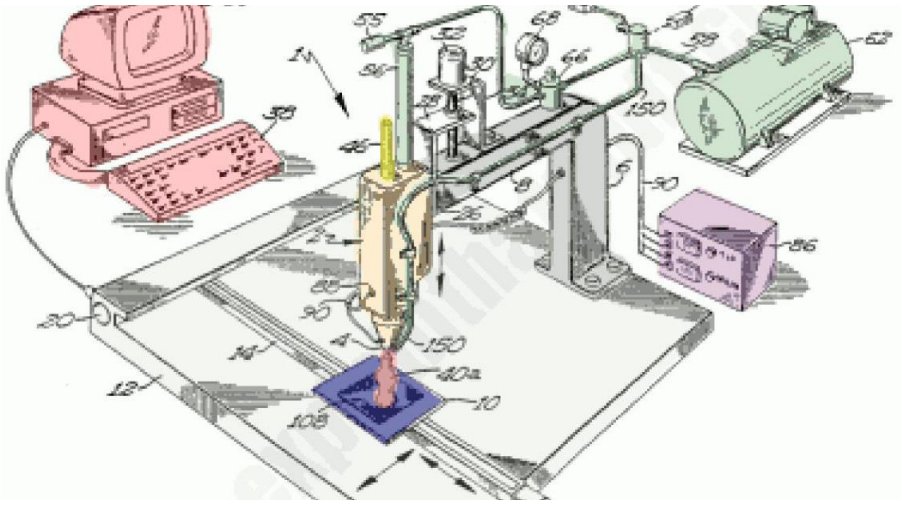

Figure 2. One of the first three-dimensional FDM /6/ printers in the world, developed by S. Scott Crump in the 1980s, /7/.

structures. These materials enable microscopic control of changes in the cellular environment and macroscopic control of the geometry of the construct. This is important because cells in the human body operate in a fully three-dimensional environment. Recreating this environment allows working with more physiologically relevant living tissue models /7/. During the bio-printing process, a solution of bio-materials, or a mixture of several bio-materials in the form of hydrogels (water-soluble polymers), generally creating a coherent community of the desired cell types, also called a bio-cartridge, Fig. 3 is used to create a tissue construct. This bio-ink can be cross-linked or stabilised during, or immediately after bio-printing to generate the shape, structure, and final architecture of the engineered construct. Bio-cartridges can be made from natural or synthetic materials, or from a combination of the two, as a hybrid material. In some cases, cell aggregates without additional bio-materials can be adopted. Ideally, it should possess the mechanical, rheological, and biological properties of the target tissues, which are necessary to guarantee good functionality of the resulting tissues and organs. Some examples of their composition include: 'Polymers of natural origin widely used for tissue engineering include collagen, fibrin, gelatine, alginate, hyaluronic acid, chitosan, etc...' /4/.

Bio-printing exists in various forms. In the case of a thermal inkjet printer, the printhead is electrically heated to produce pulses of air pressure that push the droplets out of the nozzle (whereas acoustic printers use pulses formed by piezoelectric or ultrasonic pressure). Micro-extrusion printers use pneumatic (or mechanical) systems to deliver continuous extruded pellets of material, made up of cells mixed with hydrogels. This bio-ink is fed into the printing chamber and pushed through a round nozzle attached to the print head (filament diameter is about 400 μm), Fig. 4. Laser printers use lasers aimed at an absorbent substrate, thereby creating pressure that ejects the desired cells onto the final substrate. It implies the use of pulsed laser beams and tape, which contains a layer of biological material and a receiving surface facing the final surface or the patient, /11/.

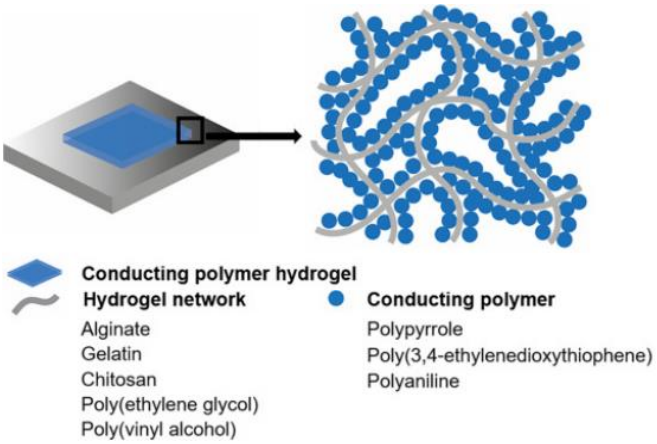

Figure 3. Example of material used as a bio-cartridge, /10/.

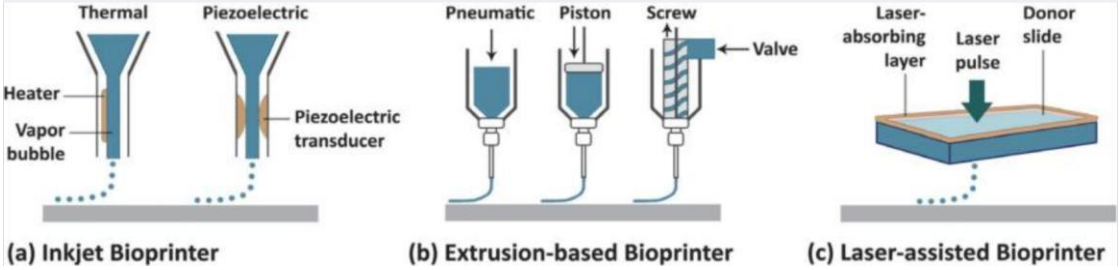

Figure 4. Representation of the main technologies of 3D bio-printing: a) inkjet/droplet bio-printing; b) extrusion bio-printing; c) bio-printing with the help of a laser, /11/.

Medical uses of 3D printing can be classified into several categories, including among others tissue production, creation of custom anatomical models and organs. Such products would have the function of replacing prostheses, implants and the need of animals used in pharmaceutical research, whether for testing, drug administration, or assisting in new potential medicine discovery, /7/. The main specificity in bio-printing is the introduction of the third phase. As stated earlier, attempts were made to ensure that an environment close to that in which the printed material will normally be found is maintained. In the same way, when the material is printed, it is optimal, and in some cases essential, to keep the printed object in an environment suitable for conservation. One of the tools often used are incubators which can imitate the essential characteristics of the human organism (oxygen percentage, temperature, etc.). When possible, tissue development acceleration is also applied. The methods used differ depending on the structure and composition of the printed material in question, /12/.

As shown above, two types of three-dimensional printing are used in medicine: synthetic printing and bio-printing. These two methods exist in different forms. They are mainly carried out in the following three phases, /1/, Fig. 5.

The first phase, also called 'pre-bio-printing', has three stages: 3D imaging (by scanning the target tissue with an MRT (magnetic resonance tomography), to obtain accurate dimensions), followed by 3D modelling (a model developed using one of the CAD software, such as AutoCAD, and finally, the preparation of bio-ink (bio-material cells are carefully selected according to the tissue to be printed).

The second phase is: printing (digital information directs the placement of layers on a flat surface in case the material is immediately solidified or in a liquid container, to hold the structure in place until it stabilises).

The final and third phase is: ripening (the layer, which is in the form of a viscous liquid, solidifies to retain its shape. Certain chemicals, as well as UV light (ultraviolet radiation), or even an incubator, may be used to facilitate this final step). After maturation, in some cases, such as during 'in

vitro' printing, tissue structures are used either for implantation or for 'in vitro' tests. An imprint is considered to be successfully made when the resulting cells begin to signal to each other, exchange nutrients, and reproduce. This means that the obtained tissue is really alive.

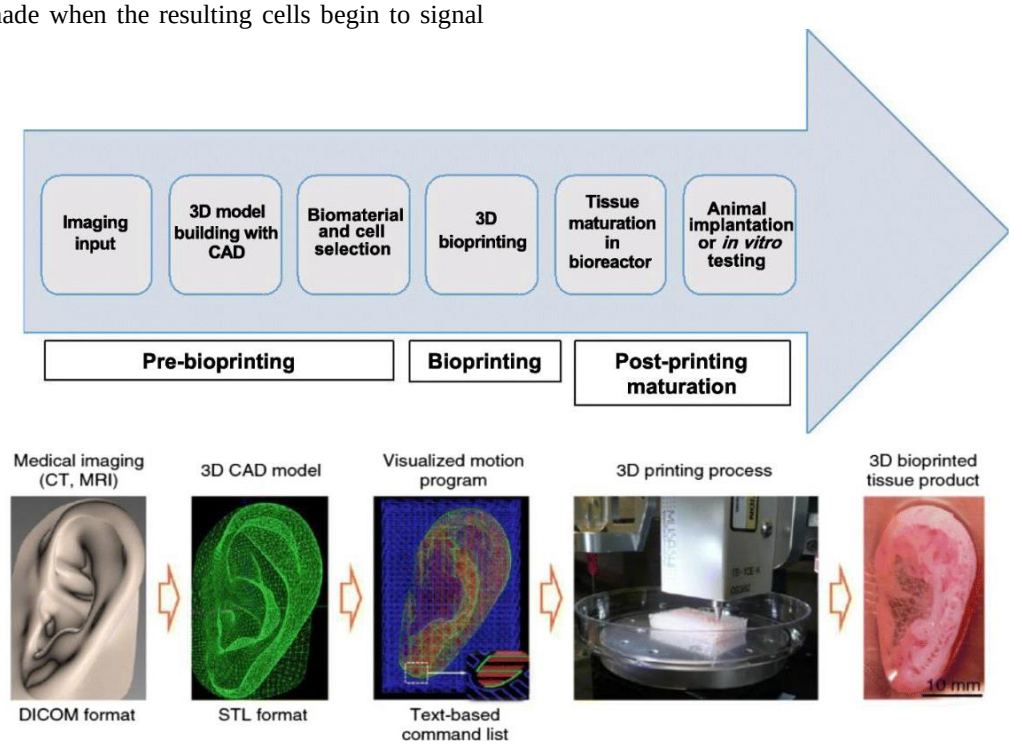

Figure 5. The bio-printing procedure algorithm and stages.

It is important to note that today organ bio-printing is used mainly for skin transplantation in reconstructive surgery and bladder transplantation has recently been successfully performed. The patient's health condition is monitored rigorously. In this way doctors control the patient's body does not reject the transplanted bio-printed organ. As for more complex organs as the heart, pancreas, and kidney, working miniature versions are already developed, but are nowhere near being used as potential transplants, /13/.

PERSPECTIVES AND SUGGESTIONS

First of all, it is necessary to explain why bio-printing and transplantation of organs such as kidneys and hearts are not yet fully developed, in order to help the many patients waiting for a transplant.

There used to be three main problems in 3D bio-printing of human organs. The first two problems have now been solved thanks to the discovery and extensive studies in the field of stem cells and bio-cartridges, which can support three-dimensional structures during printing. Stem cells make it possible to obtain a large number of cell types that were previously unavailable. However, the main obstacle today regarding 3D bio-printing of human organs is the inability to vascularise the printed organ. In order for an organ as large and powerful as the heart to be able to do its job of pumping blood and ensuring that it spreads to the rest of the body, its vascularisation is necessary, bearing in mind that it must constantly perform its role. All of this points to the difficulties associated with this type of organ, as they are expected to perform their job from the moment they are printed. The organ needs to stay in this state throughout the whole transplantation process, /14/.

However, on April 24, 2022, the Wyss Institute and the Harvard SEAS team announced that they had discovered a customisable 3D bio-printing method for building a broad vascularised tissue structure consisting of human stem cells, collective matrix, and blood vessel endothelial cells, /15/. Their work paves the way for the advancement of tissue replacement and tissue engineering techniques. Since this is recent information, it should be taken with a certain amount of caution and reserve. Therefore, it is not possible to precisely predict how long it will be before printing of vital organs becomes reality, but we can safely hope that it will happen in the near future.

Knowing the limitations of bio-printing, it would be interesting to compare it now with synthetic printing to finally understand what differentiates them. It is important to understand that these two methods serve to obtain two different types of products. They do not have the same function. Synthetic printing which is cheaper to produce, has more available necessary materials (such as plastic and others) and has a simpler and faster implementation. It is also easier to maintain because it does not work with living tissue. Its role is to help the human body, not to replace it.

Its limitations compared to bio-printing are that bio-cartridge-based printing can, theoretically, take the place of a diseased organ and guarantee identical function. This also solves the big problem of organ rejection, because the printed organ originates from the same cells as the body in which it should be implanted. Moreover, if the body accepts it successfully, it will also allow the patient to avoid the use of immunosuppressants, which have significant side effects. Thus, bio-printed organs will be much more durable and could solve the pressing problem of an enormous number of

patients on the transplant waiting list, but they still remain an extremely expensive and more complicated alternative (preservation of the printed organ, cell culture that was previously necessary, etc.), /4/.

Of course, there is also the question of ethics. Ideally, this practice will be available to everyone, but always under the supervision of medical staff. In reality, since the practice of bio-printing, used for existing body parts (skin graft, bone, etc.), is already used mainly by the wealthier strata of society, it could be a sign of even more pronounced inequality in the level of access to healthcare. There is also the question of availability and private use of bio-printing.

Today, synthetic three-dimensional printers are already very popular and widely used. If everyone had access to a machine that could create living cells, would it be ethical or could it endanger our safety? Therefore, if the development of this invention continues to grow at this rate, it is very important to ask the right questions in order to establish rules that ensure our safety and optimal use of these scientific inventions.

Finally, suggestions can be made about the benefits that 3D bio-printing could potentially bring beyond the transplant and reconstructive surgery sectors. Bio-printing could help us understand how to develop better stem cell micro-environments to direct stem cell differentiation into multiple subpopulations of different lineages, /12/.

Bio-printed tissue models, based on human cells, can also completely eliminate the need for animal testing in drug discovery, as well as reduce the cost of preclinical trials. However, this will not completely replace clinical trials, as the drugs would still need to be tested on volunteer patients to determine the observable effects on the whole body by comparing different individuals. Isolating individual cases would not be pertinent enough.

Bio-printed ‘in vitro’ tumour models based on human cancer cells can accurately reproduce the characteristics of human cancer tissue, enabling the study of complex interactions, such as cancer cell dynamics during vascularisation, or cancer cell metastasis. In the future, bio-printed tumour models created from a patient's own cancer cells may also enable the customisation and refinement of cancer drugs. However, upon gaining the ability to isolate and study a disease so easily, knowing what effects it could potentially have on human bodies, this could bring us back to the issue of security and jurisdiction over who would have access to this technology.

CONCLUSIONS

We have been presented with an acute problem that top specialists have been dealing with for many years: trying to cure patients from diseases that have a destructive effect on the body. It was found that the need for transplants is becoming too great to be able to help everyone optimally. Next, the functions of a biomedical innovation that could potentially solve this crisis, are proposed, and explained, but unfortunately, 3D bio-printing does not currently offer a solution to this public health issue. However, it remains very promising with rapid development and all recent discoveries that have motivated its success, bio-printing already offers solutions for non-vascularised graphs such as alternatives for skin and bladder transplants, curing the patients in question and reducing waiting times on transplant lists.

This bibliographic work was concluded by reemphasising very important topics, ones that might often be overlooked. As researchers and engineers, it is always our duty to question and try to foresee everything that these innovations could potentially bring into our healthcare system, to ensure safety and collective well-being first and foremost. With effort, patience, and a little imagination, we can open doors that will lead us to a more prosperous, safer, and healthier future.

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