KEY BIOPHYSICAL AND BIOCHEMICAL CONDITIONS FOR ORGAN CULTIVATION USING INFORMATION TECHNOLOGY

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Annotation. *The donor organ shortage is an acute global problem: many patients are dying waiting for a transplant, and the number of people on waiting lists is growing. Hope comes from regenerative medicine: growing tissues and organs from the patient's own cells. The article describes the key biophysical and biochemical conditions of organ cultivation, as well as the application of information technology.*

Keywords: *organ engineering, 3D-bioprinting, pluripotency induction, regenerative medicine, mehanotransduction, organogenesis in vitro.*

The deterioration of people's health and the destruction of various organs and body parts are some of the most acute and pressing problems of our time. The causes of these problems are multifaceted, and among them we can single out both the consequences of the modern lifestyle and the result of the impact of external factors.

Unhealthy diet and sedentary lifestyle

Many diseases associated with poor diet and physical inactivity primarily include obesity and diabetes. According to the World Health Organization (WHO), in 2020, more than 39% of the world's adult population was overweight, and more than 13% were obese [38]. Obesity can lead to various complications, such as hypertension, heart attacks, strokes, joint problems, and type 2 diabetes. For example, studies show that obese people have a 3 times higher risk of developing type 2 diabetes. One of the unpleasant consequences of obesity is poor circulation, which increases the risk of limb amputation, especially in the case of diabetic angiopathy, which damages the vessels leading to the limbs [31].

Alcohol and nicotine abuse

Alcohol and tobacco are the two main causes of cancer and other serious diseases. According to the WHO, smoking causes over 7 million deaths annually, of which over 1.2 million are due to exposure to tobacco smoke in non-smokers [11]. Smoking is directly associated with lung diseases such as lung cancer, chronic obstructive bronchitis (COPD), and cardiovascular diseases. Alcohol can lead to cirrhosis of the liver, pancreatitis, and esophageal cancer. Research shows that alcoholism increases the risk of developing cirrhosis of the liver by 50-70%. In both cases, serious complications may develop, requiring organ transplantation (liver, lungs) or their partial removal [11].

Formation of stones in organs

An unbalanced diet, including excess fat, salt, and fluid intake, can contribute to the formation of kidney and gallstones. Kidney stones occur in 5-10% of the population during their lifetime. In Russia, about 600,000 new cases of kidney stones are diagnosed annually [2]. Kidney stones can lead to kidney failure, and gallstones often require removal of the organ (cholecystectomy). This complication is associated with metabolic disorders and can lead to serious health consequences.

Injuries and road accidents

The increase in the number of vehicles leads to more road traffic accidents (RTA), which in turn contributes to an increase in the number of people who lose limbs or suffer serious injuries that require amputation. According to statistics, more than 1.35 million deaths occur annually in road traffic accidents worldwide, and about 20 million people suffer injuries that can lead to disability, including loss of limbs [23]. Trauma is one of the leading causes of limb loss, especially in injuries that damage major vessels and nerves.

Uncontrolled use of medications

Uncontrolled use of drugs, especially nonsteroidal anti-inflammatory drugs (NSAIDs), anticoagulants, and some antibiotics and chemotherapeutic drugs, can cause serious damage to organs. For example, NSAIDs can cause ulcers and bleeding in the gastrointestinal tract, and with long-term use, damage to the kidneys and liver. Approximately 25-30% of patients taking NSAIDs for a long time suffer from side effects such as gastritis and ulcers [10].

To address the problem of deteriorating health and loss of vital organs, people need to not only recognize the importance of a healthy lifestyle, but also actively work to change their habits. In recent decades, medicine has made significant strides in the prevention of lifestyle-related diseases and in the treatment of diseases using modern technology. However, not all diseases or conditions can be prevented or cured with simple methods. In such cases, when organ damage becomes irreversible or when amputation is necessary, organ transplantation may be the only chance to save the patient's life.

Organ transplantation is a surgical procedure to replace a damaged organ with a donor organ. It allows you to save the life of a person whose organ has lost its function. However, this method is associated with several serious difficulties:

- Demand for organs exceeds supply. Every year, thousands of people around the world await transplants, but not all receive the help they need [39].
- Even if the transplant is successful, the patient will need lifelong immunosuppressant medication to prevent organ rejection. This increases the risk of infections and other complications [38].
- Issues of donation, organ distribution, consent for posthumous donation - all this requires legislative and moral regulation, especially in a society with a low level of information.

In the context of a shortage of donor organs and the growing number of diseases that lead to their loss, regenerative medicine is becoming increasingly important, especially in the context of growing organs *in in vitro* based on stem cells. This direction is one of the most promising solutions to the problem of transplantation, allowing the creation of functional analogues of organs, minimizing the risk of immune rejection and overcoming the shortage of donor material.

The process of creating an organ *in vitro* involves several key stages:

1. Stem cell production - most commonly used are induced pluripotent stem cells (iPSC) or embryonic stem cells. There are different sources: embryonic SC, adult (e.g. from bone marrow or adipose tissue) and induced pluripotent stem (iPSC) cells. iPSC cells are reprogrammed from somatic cells (e.g. skin) using trans factors Yamanaka (Oct4, Sox2, Klf4, c- Myc). Such cells resemble embryonic ones in their capabilities, but are taken from the patient himself, which reduces the risk of rejection by the body. It has been shown that iPSC cells can be differentiated into the desired cell type for therapy, without the need for lifelong suppression of the immune system. They are capable of differentiating into any type of cell in the body [41].
2. Biophysical and biochemical stimuli - in order for stem cells to transform into cells of a specific organ, it is necessary to apply special growth factors, signaling molecules, as well as mechanical and electrical stimulations that imitate conditions inside the body [24].
3. Use of biomaterials and scaffolds - to direct cell growth and form a three-dimensional structure of the organ, biocompatible scaffolds are used. They can be created using 3D printing technologies, which allow the shape and structure of the future organ to be accurately reproduced [28].
4. Cultivation in bioreactors - the growing process takes place in specially designed bioreactors, where optimal conditions (temperature, pH, gas composition) are maintained and tissue growth and differentiation are monitored [27].

Application and Prospects

To date, scientists have managed to grow a urinary bladder, liver tissue, cardiomyocytes, retina, and even prototypes of lungs and kidneys in laboratory conditions. Although not all organs can be fully transplanted into a patient, progress is obvious: clinical trials are in full swing, and some developments are already being implemented in transplantation practice [17].

In the future, growing organs *in vitro technology* could completely change the approach to treating serious diseases, replacing donor transplantation with personalized restoration.

Continuing to consider the biophysical and biochemical aspects of this process, it is worth noting tissue engineering, an interdisciplinary field aimed at restoring, replacing or regenerating biological tissues and organs. One of its key components is the creation of three-dimensional (3D) scaffolds that serve as analogues of the extracellular matrix (EM), providing structural support, directing cell growth and promoting the formation of functional tissue.

In a living organism, cells are located in the extracellular matrix, which is a network of proteins (including collagen, laminin, fibronectin) and polysaccharides. It not only provides mechanical support, but also participates in the regulation of cell differentiation, proliferation and migration [17].

In order to reproduce these conditions *in vitro,* in laboratory conditions, artificial frameworks (scaffolds) are used. They play the same role as VM, but allow flexible control of the mechanical and biochemical properties of the environment, as well as its geometry.

Frameworks can be created from both natural and synthetic materials. The choice depends on the goals: some materials imitate the biological environment better, others have predictable mechanics and the ability to be destroyed in a controlled manner.

Natural materials:

- Collagen is the main protein of the extracellular matrix, supports cell adhesion and survival, and is actively used in the creation of skin and vascular substitutes [35].
- Alginate is a polysaccharide extracted from brown algae, used in the form of hydrogels, often combined with other substances [43].
- Hyaluronic acid is involved in the regulation of cell migration and is especially effective in the reconstruction of soft tissues [1].
- Decletarianized animal tissues are tissues that have been cleared of cells but retain the VM architecture. They are often used in cardiovascular and liver engineering [37].

Synthetic biodegradable polymers:

- Poly(hydroxyalkanoates) (PHA) is a family of polymers with good biocompatibility and biodegradability. They are used for bone and nerve implants [20].
- Polyglycolic acid (PGA) and polylactic acid (PLA) are the most studied synthetic polymers used to produce fibers, membranes, and scaffolds of varying densities. They have a predictable degradation profile [29].
- PVLA (polyvinyl lactone) is used less frequently, but has high flexibility and controlled porosity, which is important in the regeneration of cartilage tissue [44].

Production technologies

Modern methods such as 3D bioprinting, electrospinning, lithography, freeze-drying and emulsion molding allow precise modeling of the scaffold structure with the required parameters of porosity, strength and biodegradation [40]. This increases the chance of successful cell colonization and subsequent formation of functional tissue.

The physical and mechanical characteristics of the environment in which cells grow play a vital role in their fate, development, and specialization. These parameters not only provide support, but also participate in active mechanobiological regulation, influencing cell behavior through complex molecular mechanisms.

Mechanical stiffness (or matrix stiffness) has a direct effect on stem cell differentiation. This is because cells are able to "sense" the elasticity of their substrate through mechanoreceptors, integrins, and the cytoskeletal network that transmits signals to the nucleus. This process is called mechanotransduction [26].

On soft matrices (elastic modulus < 1 kPa) that imitate adipose tissue, mesenchymal stem cells (MSCs) predominantly differentiate into adipocytes.

On rigid substrates (> 30 kPa), close in rigidity to bone tissue, MSCs transform into osteoblasts – cells that form bone [27].

In addition, flexible bioreactors create cyclic stretching and compression, which is especially important for stimulating the maturation of muscle and vascular tissues. Such loading imitates natural physiological conditions, enhances the expression of specific proteins and promotes cell orientation [28].

Micro- and nanotopography of the surface affects:

- direction of cell migration;
- their attachment (adhesion);
- distribution and differentiation.

Longitudinal nanofibers can orient cardiomyocytes along the fiber axis, creating conditions for the correct formation of muscle bundles similar to heart muscles [4].

Porosity is also important – sufficient pore sizes (from 10 to 300 μm depending on the tissue) ensure the penetration of oxygen and nutrients, as well as the formation of a vascular network [36].

3D bioprinting methods allow us to precisely tune these parameters, creating structures with optimal geometry and microarchitecture.

Within the body, tissues are in constant contact with fluid dynamics:

- blood and intercellular fluid create a shear flow;
- the vessels experience pulsations and pressure;
- fluid movement helps remove metabolites and supply oxygen.

In laboratory conditions, these effects are reproduced using perfusion bioreactors in which the nutrient medium circulates through the cell culture [22].

In addition, the following are used:

- pulsating pumps that simulate the work of the heart;
- rotating bioreactors that create conditions for uniform supply of nutrients and “massage” of growing tissue.

Example: in cartilage tissue culture, intermittent compression increases the synthesis of type II collagen and glycosaminoglycans, key components of the extracellular matrix of cartilage [33].

For proper growth, division and differentiation of stem cells (SC) and tissue cultures, a carefully controlled chemical environment is required. Such conditions imitate the natural microenvironment of the cell and allow its behavior to be directed in the right direction. The main components of this environment include growth factors, elements of the extracellular matrix, genetic modulators and metabolic support.

Growth factors are signaling proteins that activate specific pathways within the cell, influencing its division, migration, apoptosis and differentiation. They are actively used for targeted tissue maturation:

- FGF (fibroblast growth factor) - stimulates proliferation, angiogenesis and bone development.
- VEGF (vascular endothelial growth factor) — activates angiogenesis (formation of blood vessels), especially important when growing tissues with a vascular network.
- TGF-β (transforming growth factor beta) — regulates the synthesis of extracellular matrix (ECM) components and cellular specialization.
- BMP (bone morphogenetic protein) - induces osteogenic and chondrogenic differentiation (bones and cartilage).
- IL- and TNF-families are involved in immunoregulation, inflammatory reactions and support of tissue regeneration [5, 32].

These factors are introduced into the culture medium or applied to scaffolds to trigger the desired signaling pathways in cells.

To simulate the natural environment in which the cells are "embedded", the following are added to the nutrient media:

- Collagen - provides a strong base for attachment, enhances cell survival and guides cell behavior;
- Fibronectin and laminin regulate adhesion, migration and morphogenesis;
- Hyaluronic acid - maintains water balance and promotes cell migration;
- Proteoglycans bind growth factors and regulate the diffusion of signals [8].

Modern technologies make it possible to modify frames with the addition of these substances to create a more physiological environment.

An innovative approach to cell fate control – genetic programming and transfection:

- mRNA vaccines (eg, encoding VEGF or TGF-β) are used to transiently express desired proteins without altering the DNA;
- miRNAs are regulatory molecules that suppress the expression of certain genes, thereby directing cellular differentiation;
- Plasmids and gene cassettes allow the delivery of synthetic genes or signal chains into cells [47].

Such technologies are becoming especially important for the creation of functional tissues without the use of viral vectors.

For normal metabolism, cells require:

- amino acids, glucose, vitamins, salts, ions;
- strictly controlled pH values (usually 7.2–7.4), maintained by buffers (hydrocarbonates, HEPES);
- optimal levels of O_2 and CO_2 - most cultures require 5% CO_2 and 2% to 20% oxygen depending on the tissue type (some cells grow better in hypoxic conditions);
- removal of metabolites and ensuring circulation of the medium is achieved using perfusion bioreactors [32].

Changes in these parameters can slow growth, disrupt protein synthesis, and even cause apoptosis.

Before organ cultivation or 3D bioprinting begins, precise 3D models of the organ are created using CAD (computer-aided design) systems. design) or BIM (building information modeling). These models:

- based on the patient's CT/MRI data;
- allow you to precisely adjust the anatomical shape to a specific recipient;
- provide layer-by-layer slicing for 3D bioprinting, including vascular structures, cavities and porosity [15,45].

This type of design is especially important when creating complex structures: liver, kidneys, heart, where it is necessary to take into account the precise placement of cells and nutrient channels.

A digital twin is an accurate computer model of a biological process, such as cell differentiation, vascular growth, or cartilage maturation. It is used to:

- virtual testing of parameters: temperature, environment composition, mechanical loads;
- predicting the results of an experiment;
- optimization of time and resources.

In the future, digital twins will allow personalization of the bioprinting process, predicting transplant rejection and adaptation [25].

AI and machine learning are actively used:

- when analyzing the results of cell cultivation;
- for selection of combinations of growth factors, matrix and environment;

• in the development of new bio -inks for fabric printing.

Software algorithms process large amounts of data (big data), learning from failed and successful experiments. They are able to recommend ideal conditions for different cell lines. This speeds up the path from idea to clinical application [7].

Bioreactors of the future operate in the Internet of Things (IoT) system: special sensors monitor in real time:

• pH, temperature, oxygen level, glucose and other environmental parameters;

• fluid movement and pressure in perfusion systems.

All data is automatically sent to cloud storage and analyzed. This ensures automatic adjustment of parameters. In addition, blockchain is used to verify the origin of cell lines and track the entire history of the sample - from biopsy to transplantation [34].

Virtual and augmented reality systems are used:

• in virtual modeling of organ transplantation;

• in training surgeons to work with printed transplants;

• when managing bioprinters, where you can "test" the process in advance in a virtual environment.

For example, using AR, it is possible to "try on" a grown organ on a 3D model of the patient's body, specifying the anatomical dimensions, position of vessels and joints [16].

Thus, information technologies are becoming an integral part of modern organ bioengineering, significantly expanding the capabilities of "wet" laboratory methods. They not only simplify the design and planning stage, but also provide control over the tissue growing process, and analyze the results based on big data and machine learning algorithms. Today, software platforms already exist that combine 3D design, printer and bioreactor control, environmental monitoring, and cellular activity analysis [26].

Growing organs from stem cells is becoming an increasingly realistic strategy for solving the global problem of donor shortage. By combining biophysical stimuli (rigidity, mechanical load, porosity), biochemical signals (growth factors, cytokines, extracellular matrices) and information approaches, scientists achieve the formation of functional tissues. Organoids of the liver, kidneys, intestines, cartilage and skin tissue have already been obtained and are being tested on animals [46].

According to experts, fully-fledged bioprinted organs suitable for human transplantation may appear within 10–15 years [18]. However, the most important principles are already being implemented: the first clinical trials of designs in the field of skin plastic surgery and cartilage tissue are proceeding successfully. A number of biotechnological startups have already demonstrated working samples of vascular and respiratory structures created using 3D bioprinting [14].

The prospect of a patient receiving an organ grown from their own cells, free from the risk of immune rejection, is getting closer. Of course, there are still unsolved technical problems: ensuring vascularization, scalability of the technology, standardization of protocols. However, progress in the synthesis of biological, engineering and IT sciences gives every reason to expect that in the coming decades regenerative medicine will move from prototypes to widespread clinical practice [21].

Glossary:

Stem cells are immature cells that are capable of self-renewal and differentiation into various types of specialized cells in the body.

Induced pluripotent stem cells (iPSCs) are adult cells that have been genetically reprogrammed to act like embryonic stem cells.

Tissue biophysics is the science of the physical properties of body tissues (rigidity, elasticity, tension) and their influence on cellular processes.

Biochemical signals are molecules that transmit information between cells to regulate their growth, division, migration and specialization.

3D bioprinting is a technology for creating three-dimensional biological structures, including tissues and organs, using layer-by-layer application of cells and biomaterials.

Bioreactors are special devices that provide optimal conditions (temperature, nutrition, gas exchange) for the growth and differentiation of cell cultures.

Mechanotransduction is the process by which cells convert mechanical signals from the environment into biochemical responses.

Organogenesis in in vitro — the formation of organs outside the body, in laboratory conditions, from stem or other cells.

Hematopoietic stem cells are bone marrow cells that give rise to all blood cells.

The extracellular matrix is a network of proteins and molecules that surrounds cells and provides mechanical support and signaling.

Personalized medicine is an approach to treatment that takes into account the individual characteristics of the patient: genetic, molecular and physiological.

Cell therapy is the use of living cells to restore, replace, or improve the function of damaged tissues and organs.

Biocompatibility is the ability of a material or structure not to cause toxic, immune or other negative reactions in the body.

Scaffolds are artificial three- dimensional structures that support the growth and organization of cells when growing tissues or organs.

Hemodynamics is the science of blood flow through blood vessels, including blood flow parameters, pressure and resistance.

Endothelial cells are cells that line the inner surface of blood vessels and play a key role in regulating blood flow and vascular permeability.

REFERENCES

1. Abramov N.I., Tsvetkova T.V. Hyaluronic acid: properties and application in biomedicine. - M.: Medicine, 2020.
2. Antipov A.V. Modern approaches to the treatment of kidney and urinary tract diseases. - M.: GEOTAR-Media, 2021.
3. Antipov A.V. *Modern approaches to the treatment of kidney and urinary tract diseases.* - M.: GEOTAR-Media, 2021.
4. Artamonov K.D. Nanofibers and microstructures in cell growth management. - Ekaterinburg: UrFU, 2020.
5. Baranov A.I., Mikhailova T.V. Growth factors in regenerative medicine. - M.: Nauka, 2021.
6. Baranov P.A., Kutuzov S.S. Mechanotransduction and cellular differentiation: biophysical foundations. - M.: Nauka, 2020.
7. Chen Y., Wang L. *AI-driven tissue engineering: deep learning for cell culture optimization.* – Trends in Biotechnology, 2022.
8. Chesnokova A.N., Kalinina M.A. Biomolecules of the extracellular matrix and their role in tissue engineering. - M.: GEOTAR-Media, 2019.
9. Chernyshev I.M., Drozdova E.N. Flexible bioreactors in tissue engineering. - M.: GEOTAR-Media, 2022.
10. Dashkevich P.A., Prokofiev V.E. Medical toxicology. - M.: Medicine, 2017.
11. Demidova N.M. Lung cancer: a modern view of the problem. - M.: Peoples' Friendship University of Russia, 2020.
12. Gavrilov L.A., Dmitriev A.V. Microarchitecture of the extracellular matrix and its role in tissue regeneration. – M.: Binom, 2020.

13. Golubev A.V. Mechanics of biomaterials: the role of rigidity in the fate of stem cells. - St. Petersburg: Biomedizdat, 2021.

14. Hughes CS, Bayat A. 3D Bioprinting for Soft Tissue and Organs. – Bioprinting, 2022.

15. Ivanov AA *Digital design and 3D modeling in tissue engineering.* – Moscow: TechBio, 2021.

16. Karimov AG *Augmented and virtual reality in surgery and biofabrication.* – MedTechnika, 2023.

17. Khaitovich I.E. The future of transplantology: organogenesis and regeneration prospects. - M.: Medical book, 2023.

18. Kolesnikova E. V. The Future of Transplantation: Possibilities of 3D Organ Bioprinting. – Chemistry and Life, 2023.

19. Komarov V.P. Traumatology and orthopedics. - M.: Medicine, 2016.

20. Kozlov D.V. Biodegradable polyesters in regenerative medicine. - M.: GEOTAR-Media, 2021.

21. López CM, Tanaka M. Engineering vascularized tissues: Current strategies and future directions. – Trends in Biotechnology, 2023.

22. Matveev I.V., Tikhonov E.S. Perfusion systems in laboratory biotechnology. - St. Petersburg: Lan, 2021.

23. Meshcheryakov A.I. Prevention of injuries in road traffic accidents. - M.: Rosmedkniga, 2022.

24. Morozov P.A., Ilyin A.V. Tissue bioengineering: biochemistry and biophysics of regeneration processes. - St. Petersburg: Nauka, 2020.

25. Müller V. et al. *Digital twins in regenerative medicine: applications and challenges.* – Front. Bioeng. Biotechnol., 2023.

26. Petrova M. I. Integration of information systems in tissue engineering. – Journal "Bioinformatics and Medicine", 2023.

27. Pogodin D.A. Bioreactors for tissue and organ cultivation. – Ekaterinburg: UrFU, 2018.

28. Rakhimov A.Kh. 3D bioprinting in regenerative medicine. - M.: Medicine of the Future, 2021.

29. Romanova N.S. Polylactide and polyglycolide: synthesis, properties, application. - St. Petersburg: Chemistry, 2022.

30. Saveliev V.A. Diseases of the liver and pancreas. - St. Petersburg: Foliant, 2018.

31. Serov V.G., Benashvili N.N. Clinic of Internal Medicine. - M.: GEOTAR-Media, 2020.

32. Sergeev N.B. Cytokines and tissue morphogenesis: biological significance and application. - St. Petersburg: Biomedizdat, 2020.

33. Sharova T.M. Regeneration of cartilage tissue: the role of mechanical loads. - Kazan: KazSMU, 2023.

34. Sidorova EV *Internet of Things and blockchain in laboratory biomedicine.* – Biomedical Engineering Journal, 2022.

35. Smirnova E.S., Korneev D.Yu. Collagen as a basis for biocompatible matrices. - St. Petersburg: Nauka, 2021.

36. Soloviev R.N. Porous structures in tissue engineering: from design to application. – M.: Binom, 2019.

37. Tyurin V.N. Biomaterials from decellularized tissues: methodology and clinical application. – Kazan: KazSMU, 2018.

38. Vader M.A. Obesity and diabetes: what you need to know. - M.: Eksmo, 2019.

39. Vader M.A. *Obesity and diabetes: what you need to know.* – M.: Eksmo, 2019.

40. Vlasov I.G. Technologies for creating 3D scaffolds for targeted tissue formation. - M.: Institute of Biophysics RAS, 2021.

41. Yudin B.G., Zharov A.V. Fundamentals of cell engineering and stem technologies. - M.: GEOTAR-Media, 2019.

42. Yurchenko I.A., Levin V.P. Microenvironment for culturing stem cells: composition and bioreactors. - St. Petersburg: Lan, 2021.

43. Yushkova E.V. Alginates in tissue engineering and biomedicine. - M.: Logos, 2019.

44. Zakharov P.L. Modern polymers in tissue engineering. - Ekaterinburg: UrFU, 2023.

45. Zakharova N.V., Levchenko D.S. Artificial intelligence in medicine: from data analysis to organ design. - M.: Tekhnosfera, 2022.

46. Zhang B. et al. Stem-cell derived organoids: From models to transplantable tissues. – Nature Reviews Molecular Cell Biology, 2022.

47. Zinovieva I.L., Tokarev A.V. Genetic engineering in cell culture: tools and methods. - Kazan: KazSMU, 2022.