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Information System for Selection of Conditions and Equipment for Mammalian Cell Cultivation

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Abstract: Over the past few decades, animal cell culture technology has advanced significantly. It is now considered a reliable, functional, and relatively well-developed technology. At present, biotherapeutic drugs are synthesized using cell culture techniques by large manufacturing enterprises that produce products for commercial use and clinical research. The reliable implementation of mammalian cell culture technology requires the optimization of a number of variables, including the culture environment and bioreactor conditions, suitable cell lines, operating costs, efficient process management and, most importantly, quality. Successful implementation also requires an appropriate process development strategy, industrial scale, and characteristics, as well as the certification of sustainable procedures that meet the requirements of current regulations. All of this has led to a trend of increasing research in the field of biotechnology and, as a result, to a great accumulation of scientific information which, however, remains fragmentary and non-systematic. The development of information and network technologies allow us to solve this problem. Information system creation allows for implementation of the modern concept of integrating various structured and unstructured data, as well as the collection of information from internal and external sources. We propose and develop an information system which contains the conditions and various parameters of cultivation processes. The associated ranking system is the result of the set of recommendations—both from technological and hardware solutions—which allow for choosing the optimal conditions for the cultivation of mammalian cells at the stage of scientific research, thereby significantly reducing the time and cost of work. The proposed information system allows for the accumulation of experience regarding existing technologies for the cultivation of mammalian cells, along with application to the development of new technologies. The main goal of the present work is to discuss information systems, the organizational support of scientific research in the field of mammalian cell cultivation, and to provide a detailed description of the developed system and its main modules, including the conceptual and logical scheme of the database.

Keywords: cultivation of mammalian cells; information system; biotechnology; digital technologies; regenerative medicine

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1. Introduction

One of the most relevant areas of biotechnology, especially biopharmaceutics development, is the cultivation of mammalian cells, which has found various application in the pharmaceutical industry and medicine. This area requires a comprehensive study on not only the biological and biochemical bases, but also the selection of the necessary equipment and technological conditions. A convenient tool for storing and structuring information related to the process of mammalian cell cultivation is the development of databases and the creation of information systems. Currently, digital data is doubling every two years. The international research and consulting company IDC, which studies the world market of information technologies and telecommunications, firstly predicted that from 2009 to

2020, the volume of world data will increase by 44 times, then by 50 times, now the figure is 55 times [1]. Big Data Analytics (BDA) is becoming one of the most popular tasks in modern business. Frost and Sullivan estimates that in 2021, the total global market for big data analytics will increase by more than 2.5 times compared to 2016 and will amount to USD 67.2 billion, with an annual growth rate (CAGR) of 35.9%. At the same time, the largest market segments will be the manufacturing sector, finance, healthcare, environmental protection (EP) and retail, TAdviser reported in Frost and Sullivan [2–4]. Big data analytics involves analyzing large, complex, and often-unstructured data sets to identify valuable information, accurately identify trends, predict production performance, and optimize costs. At present, there are many databases in various fields; for example, process control [5–7], production [8], medicine [9], biology [10–16], and so on. There are databases in the field of mammalian cell culture; however, they generally contain incomplete data, regarding all components of the process (e.g., process conditions, equipment, matrix) [17,18]. A literature review of the biological sciences database-BIOSIS [19], part of the international database system, STN International, showed that Information systems with structural fields containing information about on both technological parameters and cell culture conditions do not exist. In this regard, an urgent task is to create a system that combines the main elements of the process, including cell line, medium, matrix, and equipment required for carrying out the process. The main purpose of this system is to obtain primary information on the studied cell culture, based on the literature at the design of experiment stage. It should be noted, considering that the originality of this work consist in the development of a unique system for the analysis and selection of conditions for cultivation of mammalian cells. The apllication of this system will allow for reductions of time and cost in research and application, as well as facilitating evaluate of the recommended technological and hardware solutions that help us to understand the importance of cell culture technologies and exploring the differences in the used technologies. The main goal of the present work is to discuss the development of database, creation of information systems, systematization and structuring of scientific research data in the field of cultivation of mammalian cell, and a detailed description of the developed system and its main modules. The structure of this paper as follows. Section 2 reviews of cell culture technology. The main elements of a cell lines, medium, matrices, and equipment are considered. In Section 3, the stages of design and development of the database and information system are described. This is followed by Section 4, the results of the database and information system are presented, the developed modules for searching information in the database and for selecting conditions for cultivation of mammalian cell described in detail. Finally, the conclusions are drawn in Section 5.

2. Data Science: Theoretical Framework

2.1. Overview of Mammalian Cell Culture Technology

Biotechnology studies the ways and methods of changing the natural environment, depending on the needs of the individual. It combines two scientific disciplines: Biology (referring to gene, cellular, and environmental engineering) and technology. As biotechnology has been widely applied in various industries, a special classification of biotechnology—"color"—has been adopted. Mammalian cell cultivation is referred to as "red" biotechnology. There are three main types of cell cultures: primary cultures, which are obtained from any organ and can exist only until the first re-culture; permanent (transplantable) cultures, which can exist for a long time outside the body; and diploid cultures, which are obtained from embryonic tissues. The complete scheme of cell transformation is shown in Figure 1 [20]. There are two major methods for mammalian cell cultivation: Adhesive and suspension cultures. Adhesive cultures provide several advantages, which have secured their wide use in manufacturing [21]:

- The nutrient medium is easily and quickly replaced;
- Any type of cells can be introduced into the monolayer, indicating the flexibility of the system;

- Perfusion equipment can artificially increase cell density; and
- The possibility of changing the "cell–medium" attitude during the experiment, with the help of an instrumental solution.

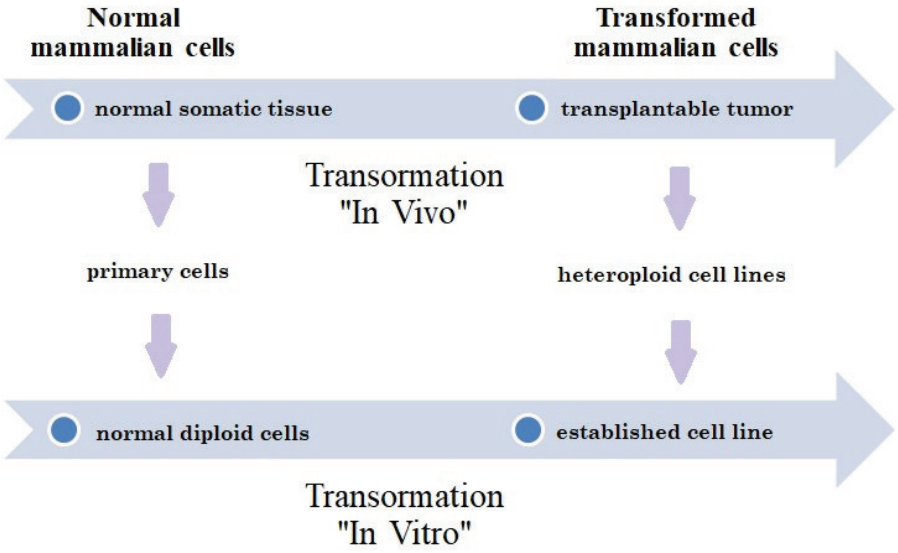

Figure 1. Normal and transformed mammalian cells (from [20]).

Adhesive cultures, however, have some disadvantages as well:

- Difficulty of scaling;
- Lack of informative visual analysis;
- Difficulties in determining and maintaining parameters, such as acidity, O_2 content, and cell homogeneity; and
- A lot of space is required.

To obtain a large volume of cell mass, it is more advantageous to use suspension cultures. The cultivation of suspension cells is carried out in roller bottles or bioreactors, where favorable conditions for continuous mixing of the liquid and gas phases specific to certain cell lines are created. Suspension cultivation can also be carried out in fermenters, where permanent mixing of the medium is performed by magnetic or mechanical stirrers, or in flasks with a high speed of rotation, preventing the attachment of cells to the walls of the vessels. This cultivation method can significantly reduce the cost of the nutrient medium, compared with stationary adhesive cultivation, if the costly enzymes and buffer solutions are completely eliminated [22].

2.2. Equipment for the Cultivation of Mammalian Cells

The development of bioreactors has been associated with the rapidly growing knowledge about cell biology, cultivation technology, and biochemical engineering. Classification systems for bioreactors have been developed, according to the distribution of the biocatalyst, its metabolism and growth type, the bioreactor regime, the configuration, and so on. The classification of commonly used bioreactors for the cultivation of animal cell cultures is shown in Figure 2. The sensitivity of animal cells to damage and air bubbles affects the design of bioreactors, especially the mixing and aeration system, which should not create stressful conditions for cultivation while operating [23].

It can be seen, from the scheme, that the bioreactors are divided into two categories: static (Figure 3) and dynamic (Figure 4).

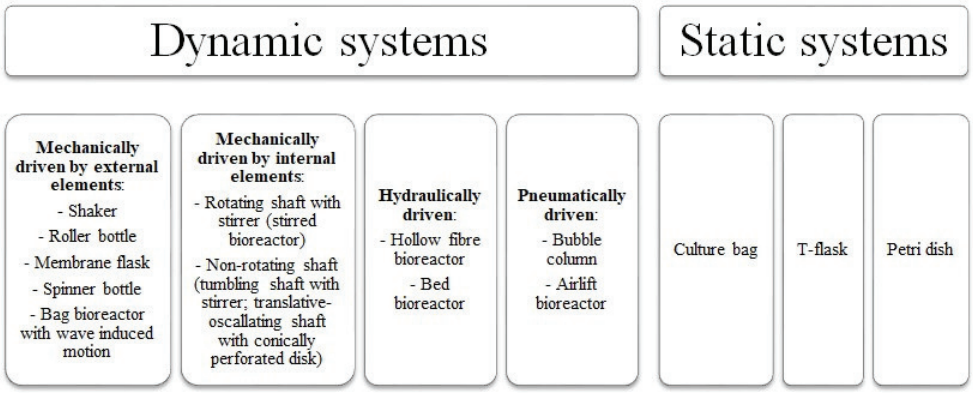

Figure 2. Cell culture bioreactor categorization (from [20]).

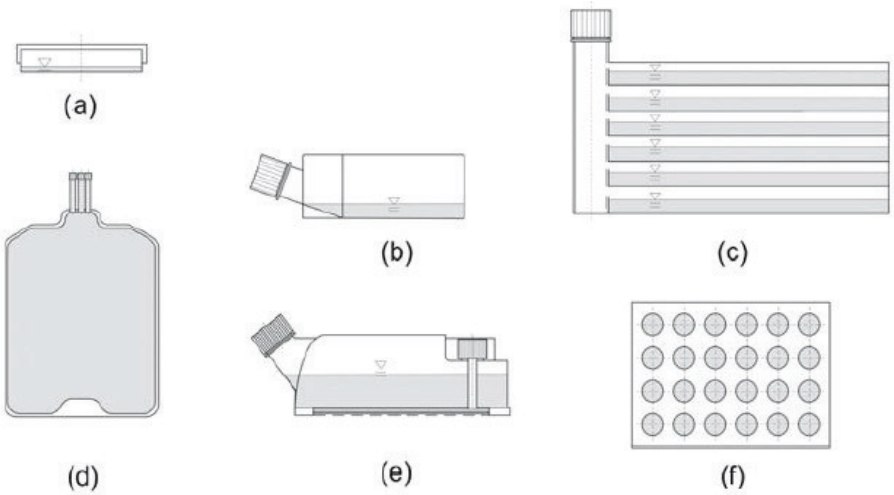

Figure 3. Basic scheme of static cell culture bioreactor: (**a**) Petri dish, (**b**) T-flask, (**c**) Multitray cell culture system, (**d**) Culture bag, (**e**) Static membrane flask bioreactor, and (**f**) Multiwell plate (from [20]).

Modern biotechnological production is generally characterized by technologies that exclude those multistage processes that have negative effects on the physicochemical and mechanical factors of the production cycle. Biological equipment has been optimized and improved, by using bioreactors with disposable vessels for the cultivation of mammalian cells [24]. To date, many companies have offered various strategies for the cultivation of tissue and stem cells, from monolayer processing in CO_2 incubators to suspension cultivation in shaker CO_2 incubators and bioreactors with accurate multidimensional process control. In laboratory studies, the bioreactor capacity is usually 3–10 L, while that in pilot-industrial studies is 100–300 L; meanwhile, for industrial studies, 10–100 kiloliters is common. The various designs of such equipment are used to create optimal technological conditions for the rapid growth and differentiation of cells. In such bioreactors, the composition of the nutrient medium, pH, temperature, oxygen partial pressure, oxidation–reduction, aeration, homogenization of the culture medium, and defoaming are all carefully controlled and maintained [25]. Modern bioreactors are operated using universal control systems, such as USB, Ethernet, analog, and digital inputs/outputs, and can be remotely controlled through a web browser from any PC, smartphone, or tablet. At present, disposable bioreactor systems are in high demand.

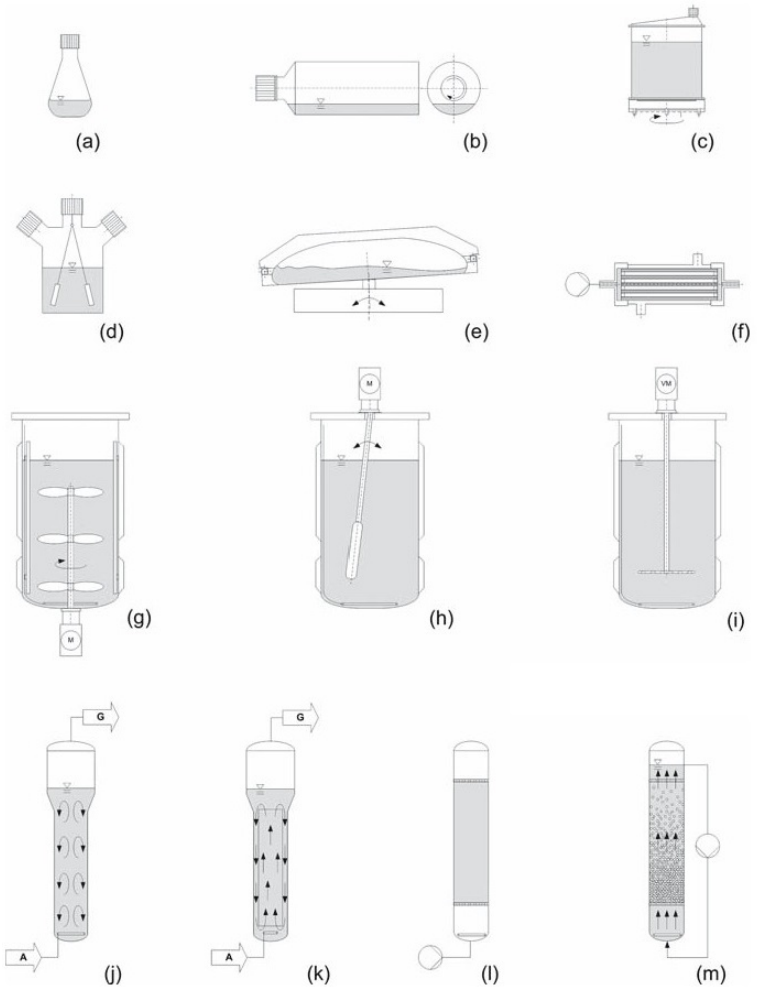

Figure 4. Basic scheme of dynamic cell culture bioreactors: (**a**) Shake flask, (**b**) Roller bottle, (**c**) Rotating membrane flask bioreactor, (**d**) Spinner flask, (**e**) Rocking bag bioreactor with wave induced motion, (**f**) Hollow fiber bioreactor, (**g**) Stirred bioreactor, (**h**) Bioreactor with eccentric motion stirrer, (**i**) Bioreactor with Vibromixer, (**j**) Bubble column, (**k**) Airlift bioreactor, (**l**) Fixed bed bioreactor, and (**m**) Fluidized bed bioreactor (from [20]).

2.3. Matrix for the Cultivation of Mammalian Cells

A matter of key importance in regenerative medicine is the development of special matrices or scaffolds, the functional purpose of which is to create structural supports, as well as optimal conditions for cell metabolism and differentiation, and providing possibilities for the vascularization and remodeling of regenerating tissue. Various materials have been used to manufacture such scaffolds (polymers of synthetic or natural origin), as well as their hybrids [26,27]. The increased interest in synthetic materials is due to the number of their advantageous characteristics; in particular, the simplicity of their manufacture and chemical modification, high versatility, ability to biodegrade, and ability to modulate mechanical properties [28,29]. These scaffolds are three-dimensional porous or fibrous matrices, the main function of which is to provide a mechanical framework for cells [30]. Ideally, the scaffolds should have a number of properties allowing for the formation of a full-fledged tissue, such as the presence of an adhesive surface that promotes cell proliferation and differentiation, biocompatibility and lack of immunological rejection, non-toxicity, biodegradability, and optimal pore size for the spatial distribution of cells, vascularization, as well as for the diffusion of nutrients and removal of waste products [31]. Three main groups of materials used in the manufacture of scaffolds are natural polymers, synthetic polymers, and ceramics [32].

3. Methodology Development

3.1. Design of the Database

The design of a database (DB) starts with developing data schemas, in which the main logical relationships between the tables are established. If the data model suits the requirements of normalization, parameters for maintaining database integrity can be specified in the data schema [33]. Data integrity means that the relationships between records of different tables are comprehensively maintained by supporting the addition, modification, and deletion of records in the linked tables using key fields. After the database structure is formed, all of the necessary information is added to fill in the database [34]. There are a number of methods for developing information-logical models. The Entity–Relationship Diagrams (ERD) methodology is usually used, where the data are presented using "object–relation" characteristics. This model was proposed by Peter Pin Chen Sheng in 1976. Several versions of this technique have been developed, to date, but all of them are based on the graphical diagrams proposed by the original author. These diagrams are constructed from a small number of components. Eventually, such diagrams are implemented as databases. The final result of this stage is the information-logical model, which provides high potential for the development of databases and information systems, as well as improving the quality of software products, supporting a unified and consistent style of work. There are three types of information models representation: Hierarchical, network, and relational. The only difference is how the information about objects and their relations is stored. The hierarchical data model is constructed according to the hierarchy of object types, forming a tree-like structure. The top record is a parent and records at the lower levels of the hierarchy are child nodes. In the hierarchical representation of information, the model of the object is represented by a node containing a set of its attributes. In the network data model, any object can be a parent and/or a child. This means that each object can participate in any number of relationships. Objects and relations in the relational data model are represented using tables. Each table consists of rows and columns. Data entered in a table row is called a data record. Each object in such a model has a primary key, which is a unique identification index of the record in the table. No two table entries can have the same primary key value. The abbreviated primary key is denoted by PK. The objects can have foreign keys, which are used to connect records between different tables. In certain operations, they are used as a primary key or part of it; for non-identity keys, they serve as non-key attributes. In practice, relational databases are the most often used. As the database is implemented and populated with available data, the necessary queries for various forms, modules, and reports have to be developed.

3.2. Design of the Information System

The term "Information System" is often found in many areas of science and system analysis. The main task of such a system is to support intellectual work; in particular, in searching for useful information, management, expert evaluation, decision-making, knowledge accumulation, and so on [35]. To build an information system, two basic approaches are usually applied: Inductive and deductive. The selection of the approach depends on criteria used, nature of the problems, and resources available. If the technology has been comprehensibly studied and the actual problems it can handle have been determined, then the technologically-oriented approach (inductive) is applied. On the other hand, in the case where the problems are identified first, a problem-oriented approach (deductive) is used. Both approaches depend on each other: New technologies alter solutions to problems, while changing the way that problems are solved leads to the development of even more advanced technologies affecting the decision-making process. With the help of information systems (ISs), it is possible to solve various tasks in different areas. The frequent use of such systems has led to the development of numerous systems of different types, differing in terms of construction principles. Information systems can be classified according to a number of different characteristics which depend on the scope of the tasks, the technical data used, and the organization and operation of the information system. To develop the system,

a classical IC design scheme was used (Figure 5), as adapted for a specific task. In the first stage, an expert opinion was assessed and the literature (articles, publications, technical documentation) was studied, which provided the data for the database that was used to develop a logical algorithm for the operation of the IS. The final stage was implementation of the IS in the form of a software application with a graphical, user-friendly interface.

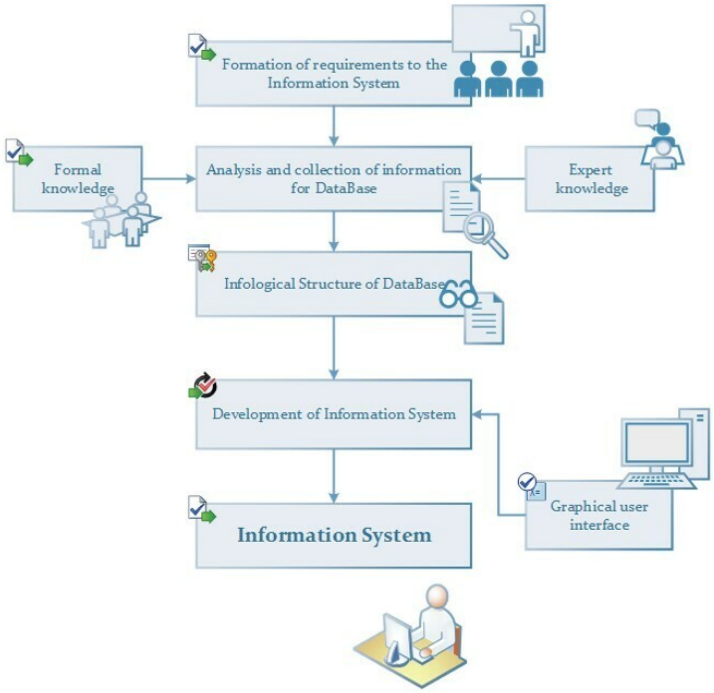

Figure 5. Stages of information system creation.

The main objectives of the developed Figure 6 (IS) are:

- To organize all the data on conditions and equipment for mammalian cell cultivation;
- To provide the most comprehensive information on standard cultivation and choice of matrix. This information system includes a reference part, in the form of a database;
- To select the necessary system for carrying out the cultivation process.

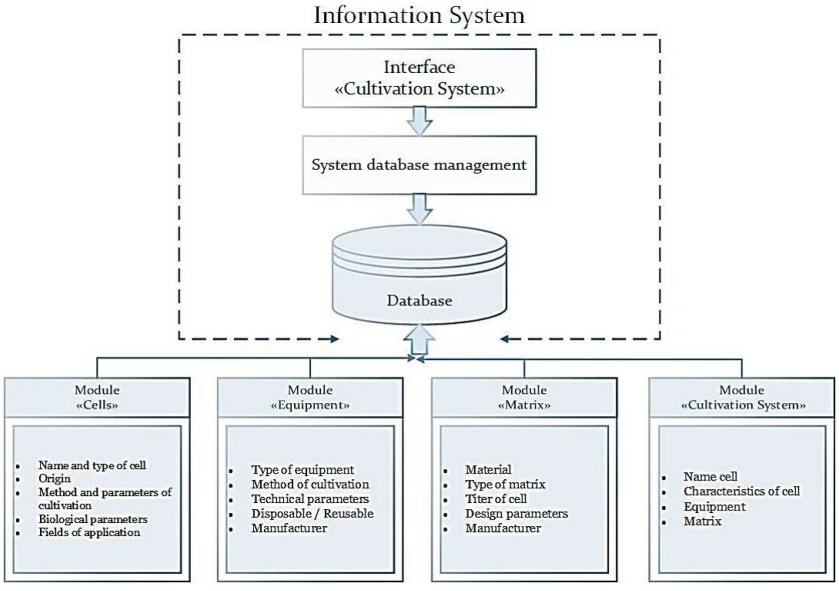

Figure 6. Structure of the information system.

4. Analysis of Results

4.1. Results of the Database Implementation

First, the logical model of the database was constructed, the main tables and their fields were defined, integrity constraints were developed, field types and formats were chosen, and constraints imposed on the values were described [36]. Then, the relationships between different data tables were determined:

- One cell can have various fields of application;
- One cell may have different cultivation systems;
- Different types of cells can be cultivated within one equipment;
- One matrix can be applied to different cells; and
- One method of cultivation can be suitable for different types of cells.

An infologic diagram of the database is shown in Figure 7.

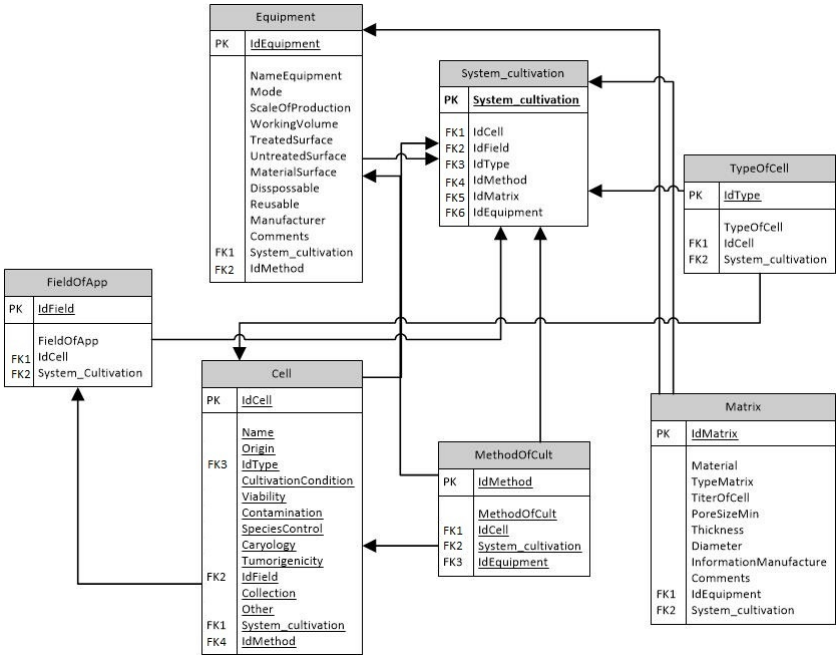

Figure 7. Infological scheme of the database.

The database includes seven main tables describing the main element parameters of the system, as well as the field of application of a particular cell type, in accordance with the chosen cultivation system. The analysis of numerous studies in the field of mammalian cell cultivation showed that each cell line has both its own individual properties and general characteristics, using which sorting and systematization can be carried out. The "Cells" table includes such fields as name and type of cell, origin, method and parameters of cultivation, biological parameters, fields of application, and so on. This table reflects the morphology of cells, principle of cultivation, ability to re-seed, and possible fields of application. The table was filled with the results of analysis of a number of sources, the main one being the catalog of the Russian collection of cell cultures [37,38], as well as experimental data from scientific articles. The "Equipment" table contains the fields "Equipment ID", "Equipment name", "Method of cultivation", "Single used", "Reusable performance", as well as others that cover the information about the main types of equipment used for mammalian cell cultivation [39]. The following geometric and process parameters were distinguished: Equipment operation (dynamic/static), working volume of the machine, and manufacturer [40]. Data on the materials and their features are concentrated in the table "Matrix". In this part of the database of all types of matrices—membranes, microcarriers, and 2D and 3D scaffolds—their geometric parameters, matrix material, presence of pores, and the maximum cell titre were considered [41]. Materials such as gelatin, chitosan,

polylactic, and other various carrier options (made from biomaterial of both natural and synthetic origin) were obtained. The information was sorted using the fields "Matrix ID", "Material name", "Surface type", "Cell titer", "Minimum pore size", "Thickness", "Diameter", and so on. Not only were popular industrial matrices reviewed, but also the variations developed by various researchers. Connection between the cultivation system, cell culture, and equipment tables is carried out using the "Method of cultivation" table. As a result of the cell cultivation process, the main directions of product application are obtained (i.e., tissue and cellular engineering, virology, and biopharmaceutics) and stored in the table "Fields of application". Figure 8 shows the main tables containing data on mammalian cell cultivation.

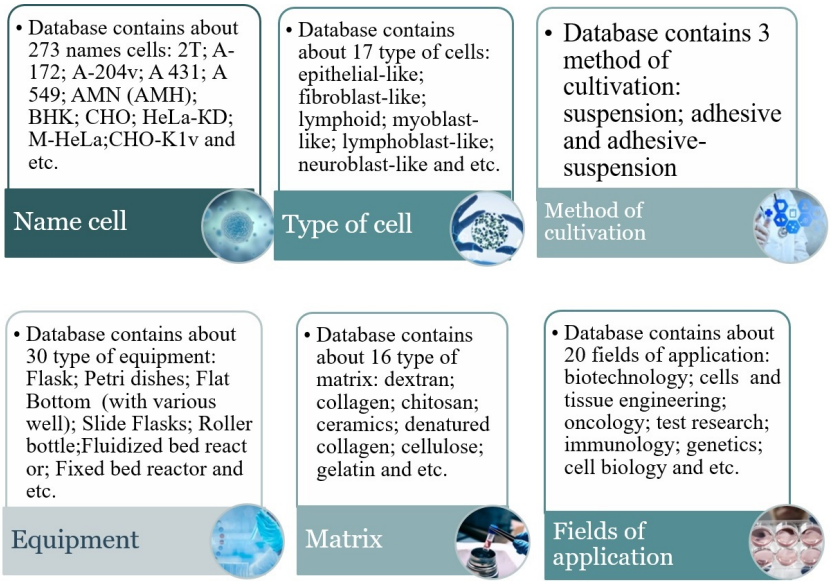

Figure 8. Information contained in the database.

Thus, the developed database allows for sorting and systematizing crucial data for the process of mammalian cell cultivation, depending on the cultivation method, cell type, field of application, and other parameters. This database provides the basis for an information system, which provides recommendations when setting up an experiment or for production design [35].

4.2. Results of the Information System Implementation

In order to perform fast and convenient information retrieval, an application with a user-friendly interface was developed in the Microsoft Visual Studio 2015 software. Figure 9 shows the main IS page.

This application contains the following modules:

- Database module, which handles data manipulation procedures (entering, modifying, deleting);
- Search module, which is used to find the information using various parameters and to sort the results, according to different criteria;
- Ontology module, which contains the ontology of bioreactors (i.e., the structure of selection of the cultivation system); and
- Help module, where the main objectives of the application are described.

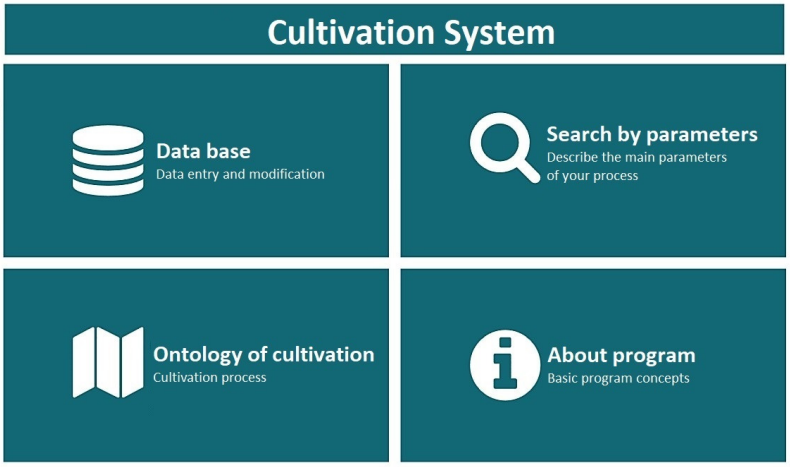

Figure 9. Main page of Information system.

4.2.1. Information Search Module

In order to search by parameters, the technical documentation of manufacturing equipment, matrices, and so on were analysed and the main parameters were identified, such as "Name cell", "Type of cell", "Method of cultivation", "Equipment", "Fields of application", and "Matrix" (Figures 10 and 11).

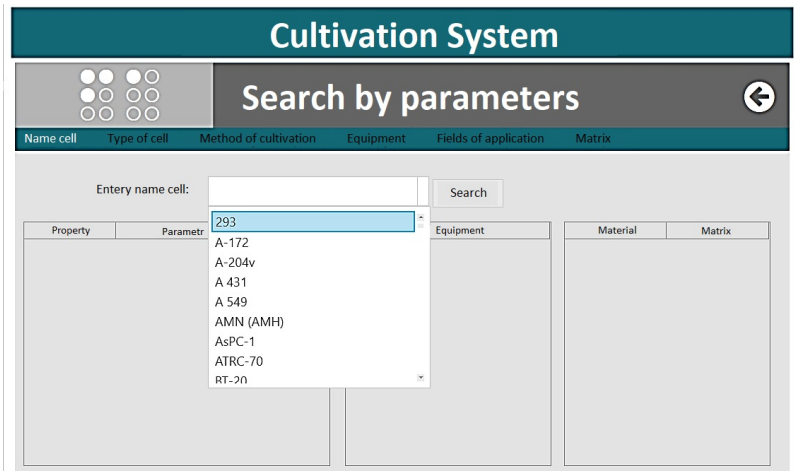

Figure 10. Information search module—query.

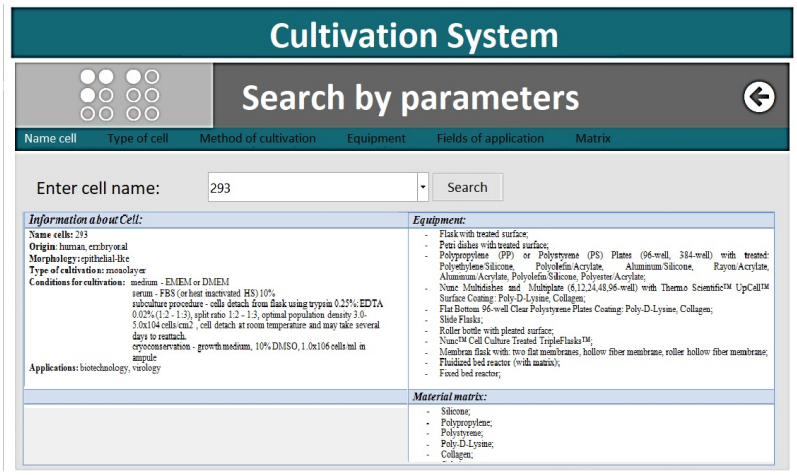

Figure 11. Information search module—result.

When working in this module, the user selects the desired search parameter and, after pressing the "Search" button, the system provides a result that contains information about the name of cell, its origin, and cultivation conditions, as well as equipment and types of matrices suitable for cell cultivation. In the section "Equipment", we consider dynamic and static systems of various types, such as cups, vials, flasks, slide-chambers, culture bags, multi-well plates, culture systems, wave bioreactors, fermenters, and rotor perfusion reactors. The scales of productivity, working volumes, manufacture, and other parameters describing a specific type of equipment are indicated. Thus, the user can obtain general information regarding a particular direction and priority in the mammalian cell cultivation field.

4.2.2. Module "Database": Input–Output (I/O) of Information Data

Using this module, data can be added or modified, through the dialog box shown in Figure 12.

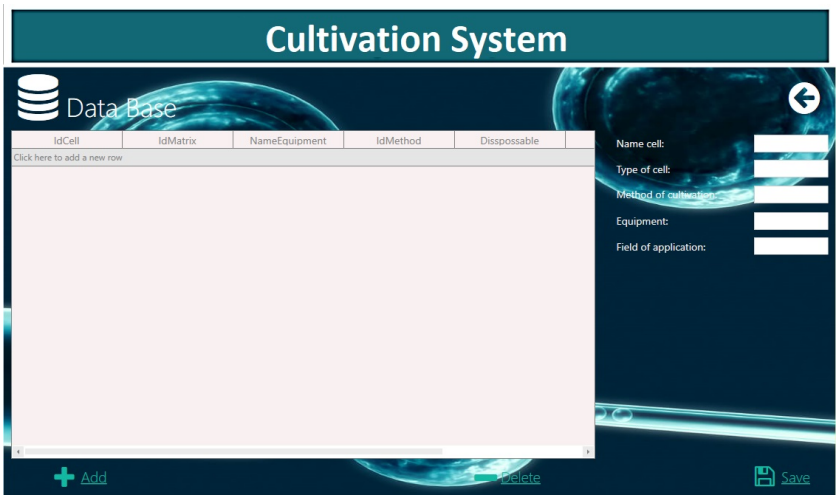

Figure 12. Module of Database "Cultivation system".

The main parameters for filling the information system are "Cell name", "Cell type", "Method of cultivation", "Equipment", and "Field of app". The I/O module provides an option to save all information objects (name of cell, type of cell, equipment, and so on) in a special file that the user has created previously. Such a file can be used later to load all information and to continue previously done work. Thus, entering and storing data through the IS module allows for tracking new changes in the database entered by different users, as well as protecting the IS from loss or incorrect entry of data in the main database file.

4.2.3. Module "Ontology of Cultivation"

The "Ontology of cultivation" module was developed based on system analysis of the subject area (Figure 13).

This module is comprised of an algorithm developed following the recommendations from the technical documentation of various manufacturers of equipment and matrices, for the purpose of selection of cultivation systems. In addition, numerous studies on mammalian cell cultivation were taken into account. According to this algorithm, the cultivation process is selected, according to the required parameters. With such source data as equipment and mammalian cell type, a step-by-step survey of the system takes place. Figure 14 shows the first step: "Select the operating mode of the equipment".

As mentioned earlier, there are two modes of equipment operation—static and dynamic—which have to be selected, depending on the process conditions. At each step, the user can get information describing all the necessary details. In the next step (Figure 15), the system suggests choosing the type of bioreactor. Using the drop-down list,

the user can find the device which is appropriate for their system of interest. In the third step (Figure 16), information about the process of cell cultivation (suspension, adhesive, or mixed adhesive–suspension) must be provided.

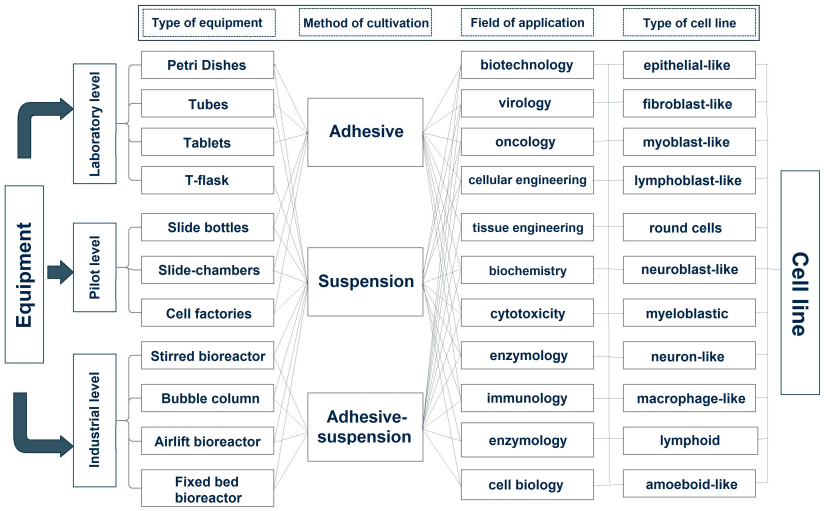

Figure 13. System analysis of the subject area—"Ontology of cultivation".

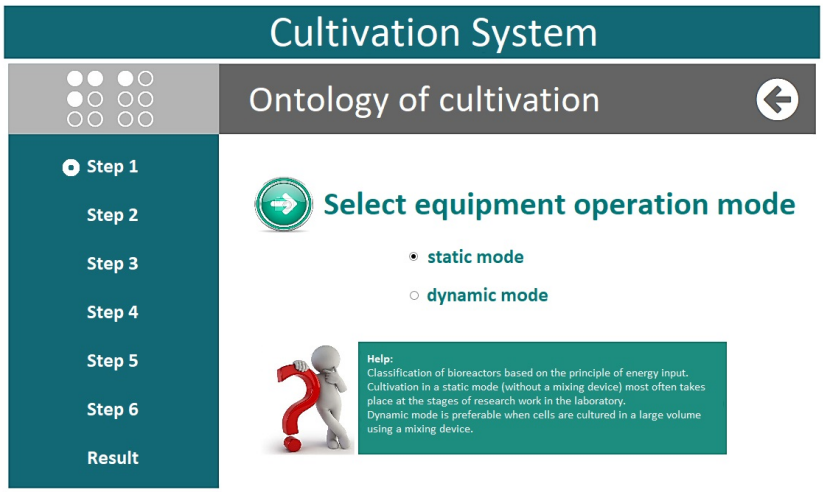

Figure 14. Module for selecting the cultivation system—step №1.

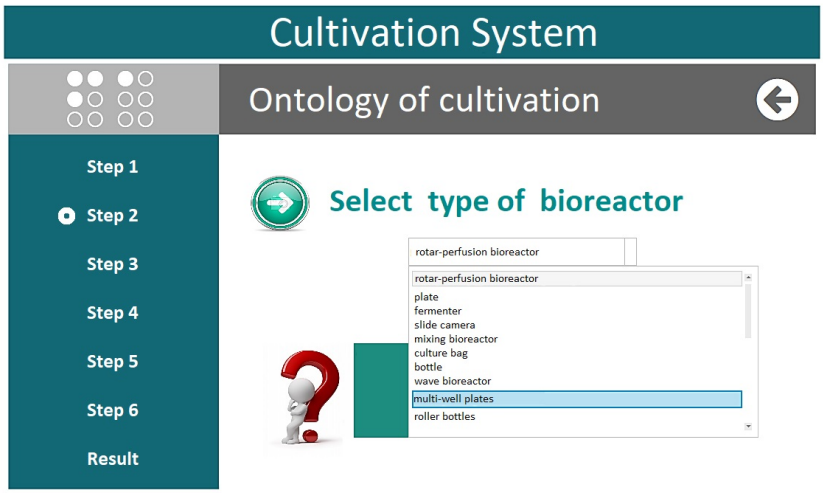

Figure 15. Module for selecting the cultivation system—step №2.

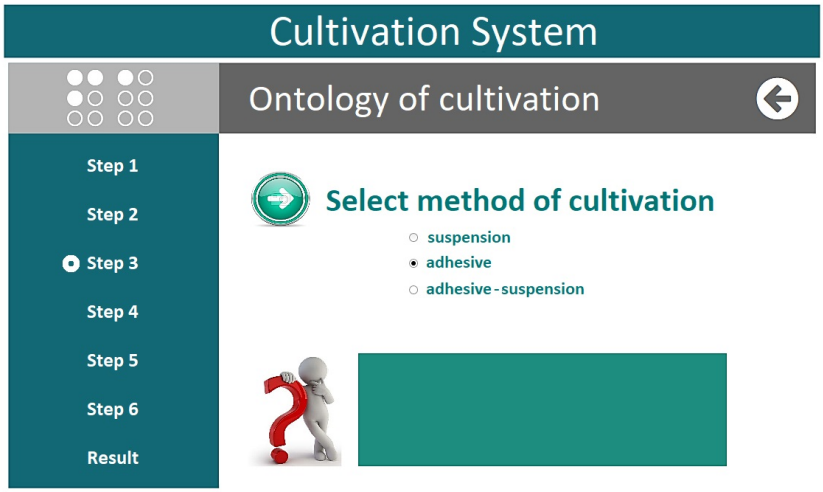

Figure 16. Module for selecting the cultivation system—step №3.

The next step is to specify the field of cell application (Figure 17). The following areas are available: tissue and genetic engineering, biotechnology, virology, carcinogenesis, cellular biology, and so on. The choice of cell line type is carried out in the fifth step (Figure 18). Different cell types can be selected: epithelio-like, fibroblast-like, lymphoblastopodic, rounded, glial, and so on. In Figure 19, the result of the ontological selection is presented.

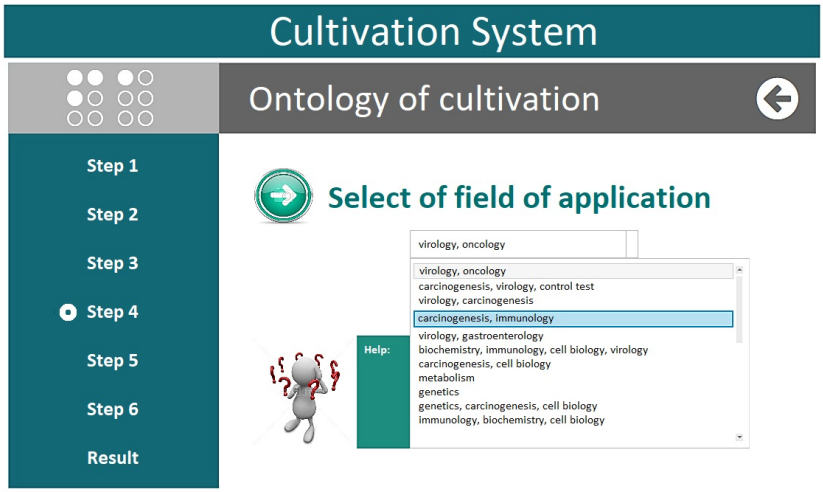

Figure 17. Module for selecting the cultivation system—step №4.

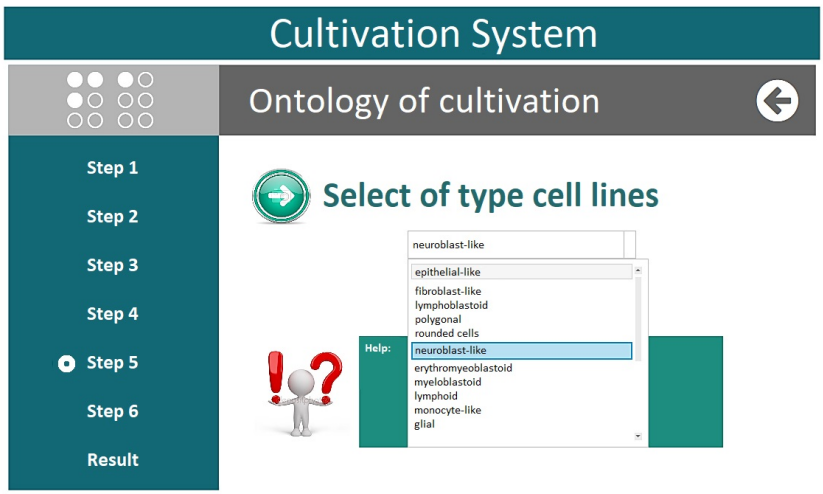

Figure 18. Module for selecting the cultivation system—step №5.

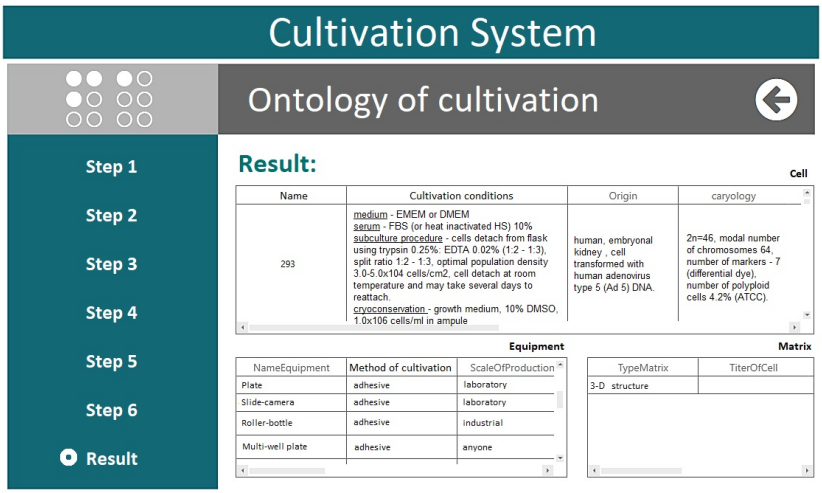

Figure 19. Module for selecting the cultivation system—Result.

Logical questions contained in this algorithm are selected in such way that, when moving to a new step, the system sorts the data from the database; as a result of which, the user receives reliable information about the process of cell cultivation. If there is no data on the process in the final result, it means that, for such parameters, cell cultivation is impossible and the user needs to change the search parameters or add missing data.

5. Discussion

In this paper, we focused on developing of an information system that will allow us to select the necessary conditions for process of mammalian cells cultivation. The literature review (Section 1) showed that the existing databases and information systems [5–10] do not contain all the necessary data for the cultivation process. The databases "The Protein Mutant Database" [12], "MuteinDB" [14] and "The cytochrome P450 engineering database" [15] do not meet the required parameters for cultivation of mammalian cells. In our results, the interesting conclusion that we received was the importance of the fact that there are no similar information systems with the similar algorithm for selecting the conditions for the cultivation process. The structure of the developed Information System was developed based on the recommendations of specialists in this field and it is based on technical documentation of equipment and matrix developers. Furthermore, our Information System was presented at various conferences and scientific seminars, where it received the highest number of positive comments and proposals for cooperation to expand the database. This can be explained by the fact that the research has been actively conducted, in recent years, and researchers need to register their experiments in this area. For the involvement and dissemination of the developed information system, we plan to organize remote access to the system with the possibility of registering and entering experimental data for researchers in the field of cellular technologies. Furthermore, our results emphasize that it is possible to use experimental data from all the world, and based on them, researchers can planning experiments and get reliable results. In this paper, we have demonstrated that information system development is a new direction of digital communication of the 21st century for researchers in the field of cellular technologies.

6. Conclusions

The active development of the field of biotechnology leads to the accumulation of a lot of experimental data all the world [3,4]. With the development of new technologies and new digital communication processes, it is imperative to enhance the current understanding of the possibilities offered by experimental data for analyzing the process of cultivation of mammalian cells of in the field of biotechnology. In order to structure and systematize information, the development of the Information system in the field of cultivation of

mammalian cells was relevant. With the help of modern software products, the information system was developed, which allows to collect, storage, and analyze data about cultivation of mammalian cells. The problem of the preliminary cultivation process optimization was solved by using an algorithm for selecting mammalian cell growth conditions, which was developed using the recommendations provided in the technical documentation of various manufacturers for equipment and matrices. The proposed information system is able to search for the necessary conditions for the given process, select solutions from the known experimental data, and support design work for cultivation of mammalian cells. According to our results, the system has functional completeness, that is, within a specific subject area, it ensures that the user's requirements are met, and it also allows for the accumulation and processing of information in comparison with existing databases [5–10]. Our results have important theoretical implications. First, a systematic analysis of experimental data in the field of cultivation of mammalian cells was carried out and the structure of relationships between the objects of the process, such as: cell line, equipment, matrix, was developed. Secondly, the main strategy of the decision-making methodology is to maximize the use of experimental data about cultivation of cell culture. It is important to note that the main decision should be made by an expert in this field; the information system plays an auxiliary role. Third, in this study, we developed a unique algorithm for selecting the conditions for the cultivation of mammalian cells. In the future, the methodological approach proposed in this paper can be used in further research on data analysis in the field of biotechnology. Finally, our results provide meaningful practical insights for professionals. The proposed information system is the result of the set of recommendations—both technological and hardware solutions—which allow for choosing the optimal conditions for the cultivation of mammalian cells at the stage of scientific research, thereby significantly reducing the time and cost of work.

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Abbreviations

The following abbreviations are used in this manuscript:

DB	Database
IS	Information system
STN	Scientific technical information network
PC	Personal computer
PK	Primary key
I/O	Input/output

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