Application of Spatial Mechanisms in Bioreactors: A Design Concept

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***Abstract*—Bioreactors are used in a lot of biological processes. Rotating bioreactor devices are a part of modern biotechnologies used for growth of human cells in vitro. In this paper we suggest and study a mechanism with spatial motion for bioreactors. The authors suggest that the possibility should be investigated to use couplers as carriers of bioreactor chambers with spatial motion. In the traditional literature on the theory of mechanisms and machines, the kinematics and dynamics of spatial motions of coupler links is poorly covered or not mentioned at all. We analyze the possibilities of implementation of spatial mechanisms with one or two degrees of freedom (DoF) with close kinematic chain (CKC), i.e a coupler, in bioreactor devices, which requires an extensive analysis of coupler's spatial motion. Furthermore, the possibility is studied of using the coupler's rotation around its own axis when both of the kinematic pairs (KP) to which it is linked are spherical ones of the 3rd class. Using mechanisms with CKC for bioreactors will reduce the number of motors necessary to drive bioreactor's chamber in 3D space. We have developed prototypes of these types of mechanisms for bioreactors .**

***Index Terms*—design of mechanisms, kinematics, and bioreactors**

I. Introduction

In vitro technologies for growing animal cell and tissue cultures develop rapidly and successfully [1]-[4]. Their wide application in biochemical technologies and medicine [4]-[6] leads to the design of new and precise mechanical systems of mechatronic type with maximum automation, visualization and sensors which are involved in processes control [7]-[8]. With a number of experiments in the space stations it has been proved experimentally [7]-[9] that cell and tissue culture growth is particularly well affected by the conditions of weightlessness which is otherwise difficult to achieve on the earth. It is a proven fact that pseudo-weightlessness may be achieved when the vector of the relative velocity of the cell in a rotating vessel with continuous fluid media constantly changes its orientation, which is perceived by the living cell as lack of acceleration of gravity, i.e. as a kind of weightlessness [7]-[10]. A bioreactor device with two independent rotations is shown on Fig. 1. The leading is with two motors and sophisticated transmissions [11]. In this sense, the mechanical systems with spatial [10], [11] and oscillating [12]-[14] motions provide a good basis for the design of rotating bioreactors of a new generation.

Spatial mechanisms with CKC are most often used for transmission [15]-[17]. The output link performs a rotational motion (rocker or crank). This is the reason why in the traditional literature on the theory of mechanisms and machines [15]-[17], the kinematic and dynamic analysis of spatial motions of coupler links is poorly covered or not mentioned at all. The authors suggest that the possibility should be investigated to use couplers as carriers of bioreactor chambers with spatial motion.

A. Short Review of Existing Devices for Bioreactor Systems

The human body consists of over 200 types of cells which assemble organs such as skin, bones and muscles. In the middle of the last century the molecular biologist Edmund B. Wilson wrote in his book The Cell in Development and Heredity that, the key to every biological problem must finally be solved in the cell". Cells are about five times smaller than the smallest visible particle and they contain all the molecules necessary for an organism to live and reproduce. This fact prevents the scientists from seeing their structure, disclosing their molecular composition and understanding how their various components are functioning. Therefore, the in vivo methods cannot give an answer to these problems. Growth of human cells in vitro outside living organisms allows for the investigation of basic biological and physiological phenomena such as controlling the normal life cycle and many of its mechanisms. The design of three-dimensional cell cultures which are eligible for medical implants is necessary. Numerous experiments have shown that this is impossible using stationary bioreactor systems. It is also difficult to be achieved with the known rotating bioreactors under the conditions on earth. The experiments made in simulated weightlessness achieved by free falling of an airplane are successful to some extent. This study [1] was funded by NASA, as well as those using micro carriers [2] which play the role of skeleton constructions to which the cells are attached. The authors Manley and Lelkes have developed an experimental device to study the motion of cell formations in rotating bioreactors [8], also funded by NASA. The more popular, commercially available rotating bioreactors with natural fluid circulation are

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shown on Fig. 1a and Fig. 1b [9] shows forced-circulation-loop bioreactor.

Figure 1. Rotating bioreactor with natural circulation of fluid [9].

The main disadvantage of the existing rotating bioreactors is the permanent orientation of bioreactor's axis of rotation to the acceleration of gravity. This fact causes the precipitation of cell cultures, their clinging to the bioreactor walls which has fatal ending and inadequate exchange of substances between cells and media.

The dramatic advance in the fields of biochemistry, cell and molecular biology, genetics, medicine, biomedical engineering and material science gave rise to the development of interdisciplinary scientific areas such as tissue engineering and the solution of organ problems by medical implants. To achieve satisfactory results in cell and tissue cultures, bioreactors have to operate under conditions as close as possible to in vivo conditions. The difficulties occurring with the known bioreactors are that they cannot provide a constant and regulated feeding and metabolic bio-products removal. The growth of three-dimensional cell formations requires physical and chemical bonds. The chemical bonds are accomplished mainly through the culture medium components. The physical bonds for the growth of cell and tissue cultures require the use of a bioreactor. The known bioreactors are designed with only one axis of rotation such as on Fig. 1. They put the cell growth under the influence of one force vector only, due to which they provide a physical signal only in the direction of this one force vector. Hence, cells are not inclined to growth of three-dimensional cell cultures.

B. Synthesis, Modeling and Design of Mechanisms for Bioreactor Systems

The present paper analyses an innovative proposal for which patent applications have been filed. This is as follows:

A type of spatial four-link mechanisms with one degree of freedom (DoF) is proposed with spherical and spatial motion of the output link, i.e. a coupler to which the bioreactor vessel system is fixed;

A kinematic analysis of mechanisms is made, and more in particular, of the spherical and spatial motion of the bioreactor vessel, as well as of the variation in the location of the instantaneous axis of rotation (IAR) depending on the input parameter of motion, and of the functional relations for the Cartesian components of angular velocity, and of the influence of the constructive parameters of mechanisms.

In particular, the studies refer to two original solutions [15], [16] of a mechanic system driven by a controlled motor with a spatial rotation of one of the bioreactor chambers and pulsing rotation around a fixed axis of the second bioreactor chamber. Underlying these mechanical systems is the modified Hooke's joint, also known as Cardan joint, and a spatial four-bar linkage.

II. A MODIFIED HOOK'S JOINT

This mechanism is named after Geronimo Cardano (1501–1576), a doctor, engineer and mathematician from Milan, who described it in his works [15]-[16]. It was his idea that, what sets a thing in motion must necessarily touch it". This thought is a precursor of the definition of a kinematic pair.

A. Synthesis of Mechanisms for Bioreactors

Fig. 2 shows a kinematic scheme of a Cardan's mechanism. The basic elements 1 and 2, called couplers /connecting rods/ are retained as well as the bearing of all links in kinematic pairs (KP) of the 5th class. The crosshead is replaced with an appropriate bioreactor chamber. The chamber may be cylindrical or spherical. It is known that the crosshead, or chamber 3, respectively, performs a spherical motion. The fixed point O coincides with the point of intersection of the axes of the two couplers. The instantaneous axis of rotation (IAR) passes through this point and constantly changes its orientation towards the coordinate system Oxyz. This means that the mutual position of the IAR and the acceleration of gravity g changes. The trajectories of points B and C of couplers 1 and 2 are circles onto the planes Oxy and Oy, respectively.

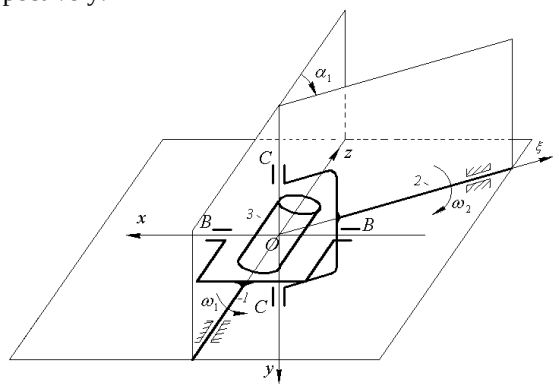

Figure 2. Kinematical scheme of a Cardan's mechanism.

The two axes intersect under the angle α which can be changed by appropriate fixing of the bearings of shaft 2 to the plane of the base β. The axes of the joints A and B make an angle of 90°, and also the angles between the said axes and those of their respective shafts. The actuating shaft 2 performs a rotating motion with periodically changing velocity. This allows for its connection to a second bioreactor chamber. The two bioreactors may be used together or separately. In the research laboratories, experiments may be conducted in order to establish the optimum kinematic parameters for the growth of 3D cultures considering that the velocity ω_1 of shaft 1 may be changed by actuator control. Dependent on this velocity are the periodic velocity changes of both chambers. The bioreactor system is equipped with visual, thermo and other sensors which are not a subject of this paper.

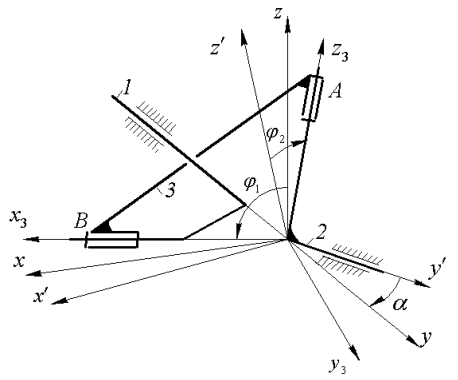

Figure 3. The simple scheme of the mechanism.

Fig. 3 shows a simplified kinematic scheme of the mechanism for bioreactors. The following coordinate systems are used: Oxyz – fixed, where the axis Oy coincides with the axis of shaft 1; Ox'y'z' – where the axis Oy' coincides with the axis of shaft 2; and $Ox_3y_3z_3$, where the axes Ox_3 and Oy_3 coincide with the axes of the joint pairs of the crosshead 3, and of the container, respectively, wherein the bioreactor chamber is mounted. The angle of rotation of shaft 1 to axis Oy is indicated with α_1, and the angle of rotation of shaft 2 to axis Oz' is indicated with α_2. Applying the methods of vector mechanics, the components of the angular velocity of chamber 3 and the variable velocity of shaft 2 are found, namely

$$\begin{aligned}\omega_x &= \dot{\varphi}_1 \\ \omega_y &= \frac{\sin\varphi_2}{\sin\alpha\sin\varphi_2}\left(\dot{\varphi}_2+\dot{\varphi}_1\cos\alpha\right)=\frac{1}{\sin\alpha}\left(\dot{\varphi}_2+\dot{\varphi}_1\cos\alpha\right) \\ \omega_z &= -\frac{1}{\tan\alpha\tan\varphi_2}\left(\frac{\dot{\varphi}_1}{\cos\alpha}+\frac{\dot{\varphi}_2}{\sin\varphi_1}\right)\end{aligned} \quad (1)$$

$$\tan\varphi_2 = -\frac{\cos\varphi_1}{\cos\alpha\sin\varphi_1} = -\frac{1}{\cos\alpha\tan\varphi_1} \quad (2)$$

$$\dot{\varphi}_2 = \frac{1}{\cos\alpha}\frac{\dot{\varphi}_1\cos^2\varphi_2}{\cos^2\varphi_1\tan^2\varphi_1} = \frac{\dot{\varphi}_1\cos\alpha}{\cos^2\alpha\sin^2\varphi_1+\cos^2\varphi_1} \quad (3)$$

Having considered (2) for (1) the following relations are obtained (4)

$$\begin{aligned}\omega_x &= \frac{\dot{\varphi}_1}{\tan\alpha}\left(\frac{1}{\cos^2\alpha\sin^2\varphi_1+\cos^2\varphi_1}+1\right) \\ \omega_z &= \frac{\dot{\varphi}_1}{\tan\alpha}\left(\tan\varphi_1+\frac{\cos^2\alpha}{\cos\varphi_1\left(\cos^2\alpha\sin^2\varphi_1+\cos^2\varphi_1\right)}+1\right)\end{aligned} \quad (4)$$

From the obtained kinematic relations (1 and 4) follows that

The angular velocity towards the axis Oy coincides with that of the input shaft, which can be also an angular velocity towards the central axis of the bioreactor chamber;

The other two components of the angular velocity vector are periodic functions of angle φ1 of rotation of the input shaft;

The values of the amplitudes of ω depend on the angle α between the axis of the two shafts, due to which a device for the angle regulation is provided.

B. Desing and Development of Mechanisms for Bioreactors

We have developed prototypes of bioreactors based on the theoretical results mentioned above. We intend to use spatial motion Hook's joint mechanisms. On Fig. 4 is shown a scheme of the proposed mechanism for bioreactors. A standard bioreactor's chamber will be attached to the Hook's mechanism. The main parts of the designed bioreactor are denoted on Fig. 4: *1- base, 2 - DC motor, 3 - front plate, 4 – back plate and 5- chamber*. Our aim is to develop a simple bioreactor construction performing spatial motion. The control of the robot is not difficult because only one DC motor has to be driven with non-constant speed with accordance to the motion law. Generally, the chamber has to perform less than 10 revolutions per minute. After experiments, we will define the magnitude of the speed more precisely as well as the number of the revolutions per minute in accordance with cultivated biological culture.

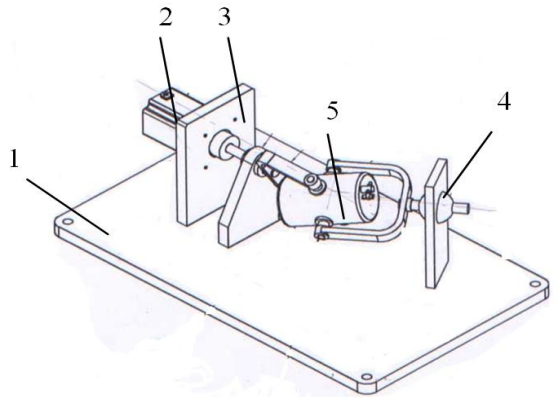

Figure 4. A scheme of the suggested mechanism for bioreactor.

III. CONCLUSIONS

The innovative solutions in this study are:

1) The use of spherical motion of the coupler from the traditional Cardan mechanism as an output link and in particular, as a bioreactor chamber;

2) The use of Cardan mechanism with two axes and two DoF, wherein the full rotation of the coupler or the bioreactor chamber, respectively, is performed around its own axis. The module of the bioreactor chamber with the motor is connected to the coupler of the mechanism through a fixed connection;
3) With reference to these solutions, detailed kinematic analyses are made of the spherical motion of the Cardan mechanism coupler, which is not available in the traditional literature on the theory of mechanisms and machines, because of the use of these mechanisms for transmission between the two links with elementary rotating motions.
4) A design concept for the development of a bioreactor having 3D motion driven by one motor is worked out. Only a standard bioreactor chamber will be used.

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