Published in the Russian Federation
European Journal of Molecular Biotechnology
Has been issued since 2013.
ISSN: 2310-6255
E-ISSN: 2409-1332
Vol. 13, Is. 3, pp. 104-113, 2016

DOI: 10.13187/ejmb.2016.13.104
www.ejournal8.com

Tissue Engineering Constructs for Osteoarthritis Treatment: a Control of Remodeling

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Abstract

Tissue engineering and regenerative medicine technologies (TERM technologies) remarkable progress allowed to use predominantly minimally invasive arthroscopic techniques to treat traumas and chronic joint diseases. The essence of joints tissue engineering is development and manufacturing bioengineering matrices (scaffolds) and their following implantation in cell-free variant, or previously populated by suitable cell pool to recover defects by a full-value 3D-structure. The important challenge here is to make individualized scaffolds, which properties are meet the requirements of person and his cartilage defect. The main objective of the study is to describe tissue engineering system "cartilage – scaffold" using systems biology and biocybernetics approaches. The task is to predict development of considered system through time and investigate the possibility to define and solve the control problem which could open the door for property-oriented scaffolds development. Authors explored the referred tissue engineering system as feedback-controlled system. Then we proposed the system of difference equations, which describe its dynamics. Results of computer simulation and forecasted values of extracellular matrix and cells volume ration are in physiological intervals and on a first approximation correspond with previously obtained experimental ones. The next step is to modify model for inverse solution of developing new generation of tissue engineering implants with predefined and controlled characteristics.

Keywords: tissue engineering, regenerative medicine, articular cartilage, osteoarthritis, biological systems, simulation modeling.

1. Introduction

Tissue engineering and regenerative medicine technologies (TERM technologies) progress in articular cartilage repair determines by well-defined complex of social, economic, medical and biological factors, Firstly, lifespan at developed countries steady increase with the proportion of senior citizens lead an active life. As consequence, joint decease prevalence and demand of high (movement capability in multilevel buildings, car driving, farmland works, tourist trips, etc.) quality of life growth simultaneously. In addition to degenerative changes in joint, specialists point to big joints traumas increase because of technology expansion in all fields of life and, also, extremism (Hunziker, 2009; van Osch et al., 2009). Secondly, remarkable progress of materials and medical technology allowed to use predominantly minimally invasive arthroscopic techniques to treat traumas and chronic joint diseases. At least, the object of treatment – articular cartilage –

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has low regenerative capability, thus in most cases one needs not only to compensate lost structures of articular cartilage and its functions but also to stimulate patient's own cells to remodel zone of cartilage defect replacement into a proper cartilage tissue. (de Isla et al., 2010; Mao, 2015)

The primary function of joint is locomotion – a complex of synchronized motions enables an organism to move. The key component of joint to sustain this function is hyaline cartilage. Low coefficient of contact friction in flexible joint is needed for movements coordination. Such condition is provided by cartilage and synovial liquid, which figures as lubricant. Also, cartilage damps and redistributes loads to keep the subjacent bone intact (McNary et al., 2012; Giorgi et al., 2016).

So, the goal of cartilage as biological system is to reach the state, when: the coefficient of contact friction is in physiological interval (1), and physiological loads damping and redistributing are successful (2). To achieve this goal, the control of cartilage maintains at two levels - central and local ones. The central nervous system controls cartilage through using signals from joint and skin mechanoreceptors. When they signaling the joint malfunction and destruction threat (one suffer pain, for example), organism starts to avoid painful movements. In some cases, one could ignore such signals within certain limitations – when training, for instance. As result, articular cartilage structure will change at the cell and molecular level. Processes at this level are exactly defined the actual joint characteristics and its abilities. That is why we will discuss processes' control at this level only.

The current "gold standard" technique of damaged cartilage recovery is autogenous chondroplasty. This classical approach has several intractable limitations, disadvantages and eventually does not provide adequate restoration of joint function for a long time. Most of specialists in regenerative medicine consider tissue engineering technologies to be a next leader in this area (Getgood et al., 2009; Lu et al., 2013).

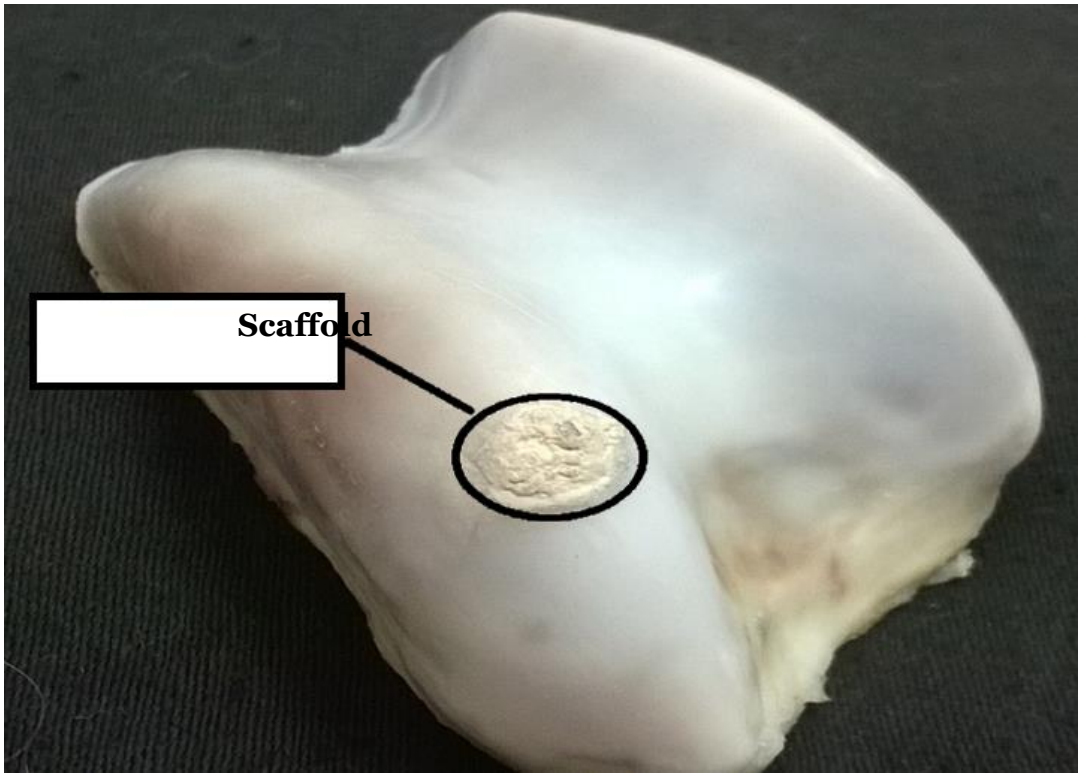

Fig. 1. Chitosan scaffold on bovine cartilage before remodeling differ from surrounding cartilage in its structure and properties.

The essence of joints tissue engineering is development and manufacturing bioengineering matrices (scaffolds) and their following implantation in cell-free variant, or previously populated by suitable cell pool to recover defect and to stimulate damaged tissue 3D-structure. The key

problem is to completely remodel tissue engineering construction to native cartilage. The solution needs to use predictable control of cells population, proliferation, differentiation and adequate phenotypical expression in scaffold's material and future native cartilage matrix. One of key approaches to such of control is planning and manufacturing scaffold with predefined complex of its properties (O'Brien, 2011; Zohreh et al., 2012).

Currently there is a wide spectrum of materials suitable for making scaffolds. Such materials must meet the following prerequisites: cytotoxicity and inflammatory and immune response absence, support of cells adhesion, fixation, proliferation and differentiation, bioresorbtion through common metabolic pathways, ability of self-recovering, structure and characteristics changing in response to environmental factors, including physical stress (Zhang et al., 2009; Correia et al., 2011; Kuo, 2011; Bogatov et al., 2015; Maitz, 2015).

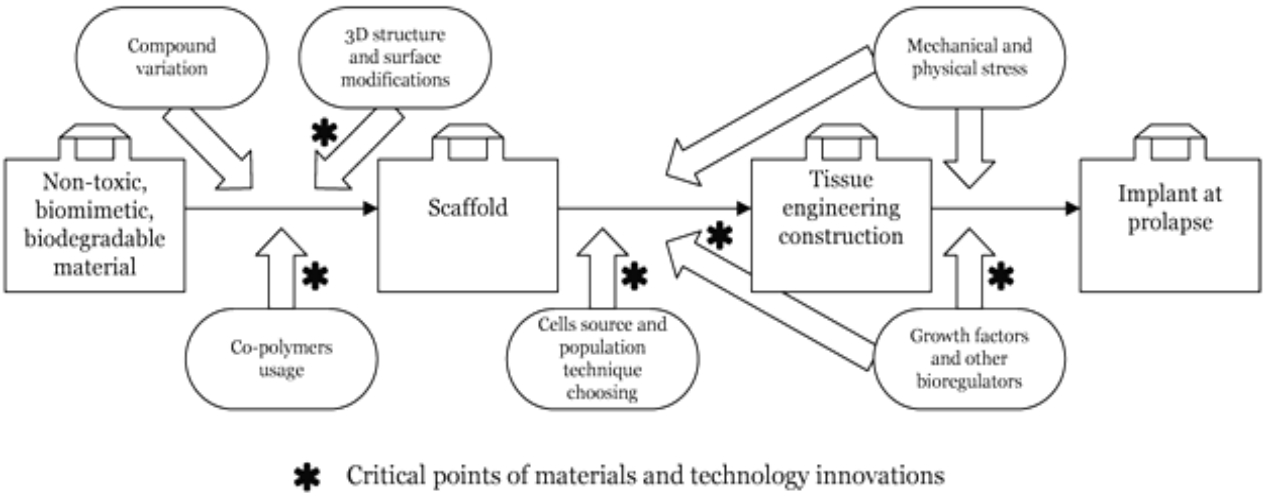

Fig. 2. The schema of crucial processes responsible to quality of scaffold-technologies for articular cartilage repair demonstrates critical point of material and technology innovation.

One of promising approaches applies high hydrostatic pressure (HHP) to treat cartilage for its repair. Cartilage devitalization using HHP demonstrates effective cellular deactivation when tissue structure remains intact. Then chondrocytes and mesenchymal stem cells are successfully cultured on devitalized cartilage (Hiemer et al., 2016).

High ability for chondrogenic differentiation of umbilical cord blood mesenchymal stem cells (UCB-MSCs) demonstrates at this (Gómez-Leduc et al., 2016) study. Authors combined 3D culture in type I/III collagen sponges and chondrogenic factors. Results showed that UCB-MSCs have a high proliferative capacity and that human ones can be a reliable source for cartilage tissue engineering.

The preceding study (Shiroky, 2014) explained the renewal of the articular cartilage in normalcy and osteoarthritis development by principles of mathematical modeling. Such models help to develop advanced methods of prevention, detection and treatment of osteoarthritis including molecular biotechnologies based on tissue engineering conception. We used histological images to perform structural analysis to discover the signs of active system and its states. Received data are useful to develop research protocols in cartilage tissue engineering.

Now the study continues to describe tissue engineering system 'cartilage – scaffold' using systems biology and biocybernetics approaches. The objective is to predict development of considered system through time and investigate the possibility to define and solve the control problem which could open the door for property-oriented scaffolds development.

2. Material and Methods

Role of scaffold' structure and biochemical properties in cartilage remodeling

Articular cartilage unable to regenerate when osteoarthritis (Hunziker, 2009). The common way to treat such a serious degenerative pathology is total articular replacement, which is horribly traumatic operation leads to long rehabilitation period.

A more prospective way is to use tissue engineering constructs – scaffolds. Scaffold is complex three-dimensional biomimetic implant made of customized biopolymer like native cartilage tissue in density and load damping and redistribution ability. And it is not a prosthesis – cartilage cells populate scaffold and then, during 8–12 weeks, remodel it into a native extracellular matrix (ECM). Thus, scaffold disappears leaving behind physiological healthy cartilage (Fitzpatrick, 2015; Ivanov et al., 2015). However, complete remodeling takes quite a long time.

An important characteristic of scaffold is its three-dimensional vesicular structure with specific size of pores and thickness of barriers between them. According to experimental research, suitable porosity for cartilage repair is about 80–85 % with pores diameter in range 150–400 mkm and barriers thickness not less than 50–70 mkm. It is necessary to provide the specific integrity, high cells adhesion ability and, simultaneously, possibility of gases and metabolites transport in newly originating tissues (da Silva et al., 2010; Bhardwaj et al., 2011; O'Brien, 2011). Currently researches focused on modifying scaffold-technologies by varying co-polymers, making nanostructured products and adding growth factors depot.

Growth factors and other biologically active substances supporting chondrocytes adhesion and proliferation are particularly important to make scaffolds for cartilage repair and remodeling (Elder, 2009; Novochadov, 2013; Almalki, 2016).

It is known that such powerful bioactive substance as insulin causes chondral differentiation. The study (Malafaya et al., 2010) is devoted to chondrogenous differentiation and growth stimulation of cell systems synthesizing biomolecules. For that purpose, various forms of insulin have been added to scaffold as potential model system of cartilage. Insulin dose of 5 % at the system was proven as the most effective to stimulate chondrogenous differentiation.

Therefore, scaffolds are continuously improving by adding growth factors (Novochadov, 2013) and other signal molecules, which stimulates cartilage tissue synthesis and accelerating the remodeling. Unfortunately, these molecules are expensive – therefore two conflicting problems are rising: to minimize the time of complete remodeling (1), and to reduce scaffold cost by minimizing concentrations of signal molecules (2).

There are two main approaches to solve these problems. The first one is to modify structure of scaffold by changing its porosity and three-dimensional configuration. The second approach is to manipulate attitude, concentration and activation time of signal molecules. We discuss the last one here.

The controlling object in considered tissue engineering system is the cell pool of chondrocytes which are remodel the cartilage. The controlling action is signal molecules – growth factors and cytokines (Goldring, 2012). The structural schema of the system is on Fig. 3.

Naturally this system is error-actuated. For example, matrix slowly scuffs when moving and its wear debris enters the synovia. This leads, on the first hand, to rising its viscosity, lowering the friction coefficient and, on the second hand, to activation of phagocytes, absorbing tissue shreds and emitting cytokines, which are accelerating the degradation of ECM (Zhen, 2014).

Definition of control problem

Let us set the $x = (M, C)$, where $M \in [0, 1]$ is volume of native ECM in remodeling zone and $C \in [0, 1]$ is volume of chondrocytes there, is a phase vector describing the system state. The initial state of system corresponds to point $x_o = (M_0, C_0)$, where $M_0=0$ directly after the implantation (native ECM is absent), and $C_0=0{,}01$ (some chondrocytes infiltrate into the implant instantly and their volume estimate is 1 %).

Biologically reasonable constraints to phase variables is:

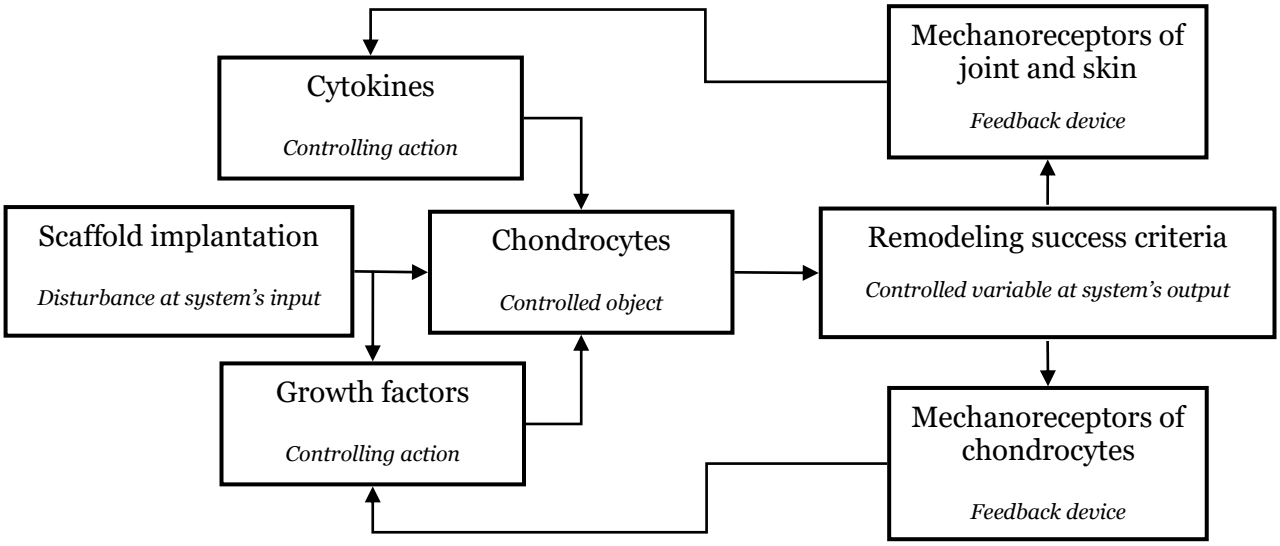

Fig. 3. The structure of the 'Cartilage – Scaffold' controlled system, its components and biological counterparts

$$(1)\ \begin{cases} 0 \le M \le 0{,}92; \\ 0{,}01 \le C \le 0{,}12; \\ M + C \le 1. \end{cases}$$

Values at the right part of inequalities were obtained during the numerous measurements of articular cartilage.

Implant could contain specific signal molecules with predefined spatial distribution and activation time. Consequently, the controlling action is a distribution and activation function of the specific molecule. In one-dimensional case it is written $u_i(l, t)$, where i is molecule's index, $l \in [0, 1]$ is a distance for scaffold's surface, t is time since the implantation. At that, if t_i^0 is the activations time of i-th molecule at point l_0, then when $t < t_i^0$ $u_i(l_0, t) = 0$, $u_i\left(l_0, t_i^0\right) = \max_t u_i\left(l_0, t\right)$, and when $t > t_i^0$ $u_i(l_0, t)$ is decreasing logarithmically to level of normal concentration.

Let us describe dependencies between coefficients of equations. Consider to system with four controls, corresponding to basic controlling molecules TGF-β, BMP-7, IL-1α/IL-1β, TNF-α. Table 1 contains description of their influence to biological processes in system.

Table 1. Mutual influence of signal molecules to corresponding biological processes flow rate

The control and basic signal molecule		$u_1(l, t)$ TGF-β	$u_2(l, t)$ BMP-7	$u_3(l, t)$ TNF-α	$u_4(l, t)$ IL-1α/IL-1β
Corresponding phase variable and influence direction		$C+$	$M+$	$C-$	$M-$
Additional molecules and their influence	TNF-α	+ +	– –		+ + +
	IL-1	+	–	+ +	

The X signal molecule when present in remodeling zone could influence to flow rate of process, started by Y molecule. At that the coefficient of X influence to Y usually lies in ranges: [1.5; 3.0) (at + / –), [3.0; 10.0) (at + + / – –), [10.0; 30.0] (at + + + / – – –).

Considering the Table 1 we obtain the following set of difference equations:

$$(2)\quad \begin{cases} M(t+\Delta t) = M(t)\left(k_2 u_2(l,t) k_3^2 u_3(l,t) k_4^2 u_4(l,t) - k_3^4 u_3(l,t) k_4 u_4(l,t)\right); \\ C(t+\Delta t) = C(t)\left(k_1 u_1(l,t) k_3^1 \frac{1}{u_3} k_4^1 \frac{1}{u_4} + k_3 u_3(l,t) k_4^3 u_4(l,t) \right). \end{cases}$$

3. Results and discussion

Simulation Results

Values of controls and coefficients of equations set (2) come from published and available for free measurements of growth factors and cytokines influence to vital activity of the cartilage. The article (Asanbaeva et al., 2008) contains made in controlled study design measurements of cells population and collagen amount in young growing cartilage at 0 and at 13-th day since starting simulation of various growth factors. The publication (Riera et al., 2011) contains evidence of pro-inflammatory cytokines influence to cartilage cells proliferation and differentiation.

Consider the simple case, when signal molecules and cartilage cells are uniformly distributed at remodeling zone. We also suppose the linear dependence between molecule concentration and their effect. Then the following rules occur (Table 2):

Table 2. Estimate controlling actions influence to phase variables values

Signal molecule	Concentration at the remodeling zone	Influence to phase variable in a time Δt = 1 week
None (natural growth/loss)	none	$C(t+\Delta t) = C(t) - 0{,}057 \times C(t)$ $M(t+\Delta t) = M(t) + 0{,}13 \times M(t)$
TGF-β	10 ng/ml	$C(t+\Delta t) = C(t) + 0{,}027 \times C(t)$
BMP-7	50 ng/ml	$M(t+\Delta t) = M(t) + 0{,}04 \times M(t)$
TNF-α	10 ng/ml	$C(t+\Delta t) = C(t) - 0{,}23 \times C(t)$
IL-1α/IL-1β	10 ng/ml	$M(t+\Delta t) = M(t) - 0{,}02 \times M(t)$

The Table 3 contains biologically rational values of additional signal molecules influence coefficients to considering processes.

Table 3. Coefficients of signal molecules mutual influence

Coefficient	Influence	Coefficient value
k_4^2	IL-1α/IL-1β на BMP-7	0,65
k_3^2	TNF-α на BMP-7	0,33
k_4^3	IL-1α/IL-1β на TNF-α	3
k_4^1	IL-1α/IL-1β на TGF-β	1,5
k_3^1	TNF-α на TGF-β	3
k_3^4	TNF-α на IL-1α/IL-1β	10

Consequently, considering values of Table 2 and Table 3, the set of equations (2) turns up at the following form:

$$(3)\begin{cases} M(t+\Delta t) = M(t)(1{,}23 + \dfrac{0{,}00017u_2(t)}{u_3(t)u_4(t)} - 0{,}02u_3(t)u_4(t)); \\ C(t+\Delta t) = C(t)(0{,}943 + 0{,}012u_1(t)u_3(t)u_4(t) - 0{,}069u_3(t)u_4(t)). \end{cases}$$

Now we attempt to use this set of equations to predict the state of considering tissue engineering system. Consider the following initial conditions: 1) scaffold remodeling into native matrix completed at 50 %; 2) chondrocytes volume ratio is 2 %. At the time t^0 there are activations of TGF-β in concentration of 30 ng/ml and BMP-7 in concentration of 3 mkg/ml. Cytokines concentration is near the physiological standard (suppose it is 2,56 ng/ml). Then there is the following cartilage state forecast:

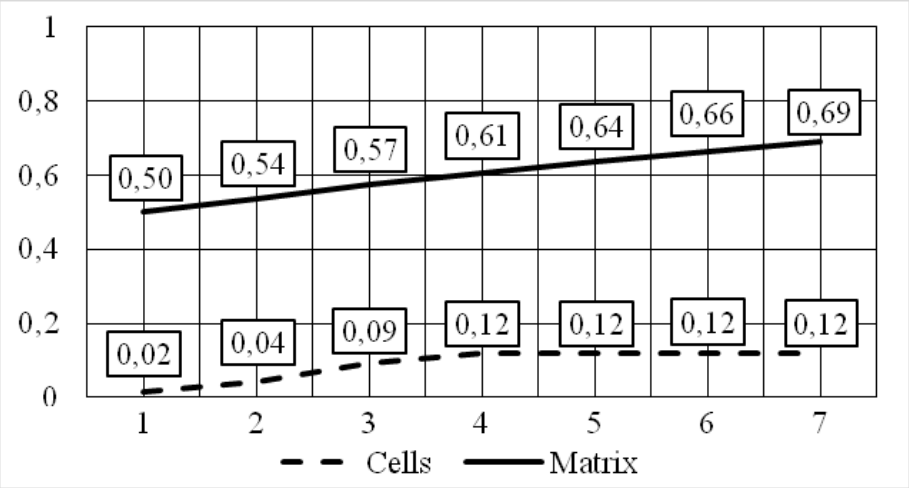

Fig. 4. Scaffold remodeling forecast (weeks 1–6)

It is apparent that TGF emission boosts chondrocytes proliferation and differentiation – in 4 weeks after its activation their volume ratio at the remodeling zone reaches the physiological limit 12 %. So, they also boost extracellular matrix synthesis. In 12 weeks, signal molecules concentrations return to normal and the system shifts to stationary state.

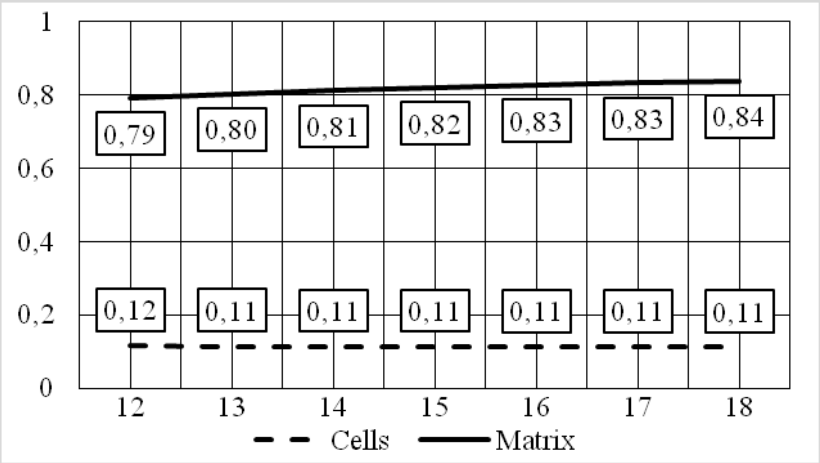

Fig. 5. The stationary state of system "Cartilage – Scaffold" (weeks 12–18)

4. Conclusion

The proposed model contains a lot of assumptions and simplifications. It does not consider structural and functional characteristics of cartilage at surface and at the deep zone, at stressed and non-stressed areas. The set of controlling actions does not contain at least four molecules which

have proven influence to considering processes. The fact that processes flow rate depends from concentrations of corresponding signal molecules non-linearly also left out of consideration.

Nevertheless, forecasted values obtained during the simulation are in physiological intervals. It indicates that the proposed approach is promising and it is reasonable to refine the model by replacing constant coefficients with functions describing dynamics of actual biological processes. As the result, we expect to obtain a model suitable not only for forecast, but also for inverse solution, which will open door to development new generation of tissue engineering implants with predefined and controlled characteristics. Such implants can be produced using various bioprinting technology, which allows scaffolds to meet the defect-specific requirements (Li et al., 2016).

Bioprinting technology shows potential in tissue engineering for the fabrication of scaffolds, cells, tissues and organs reproducibly and with high accuracy. Bioprinting technologies are mainly divided into three categories, inkjet-based bioprinting, pressure-assisted bioprinting and laser-assisted bioprinting, based on their underlying printing principles. These various printing technologies have their advantages and limitations. Bioprinting utilizes biomaterials, cells or cell factors as a "bioink" to fabricate prospective tissue structures. Biomaterial parameters such as biocompatibility, cell viability and the cellular microenvironment strongly influence the printed product. Various printing technologies have been investigated, and great progress has been made in printing various types of tissue, including vasculature, heart, bone, cartilage, skin and liver. This review introduces basic principles and key aspects of some frequently used printing technologies. We focus on recent advances in three-dimentional printing applications, current challenges and future directions (Li et al., 2016).

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Управление ремоделированием тканеинженерных конструкций, применяемых для лечения остеоартроза

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Аннотация. Значительный прогресс технологий тканевой инженерии и регенеративной медицины технологии (TERM-технологий) в настоящее время связывается с использованием высокоточных, преимущественно малоинвазивных методов лечения травм и хронических заболеваний суставов. Сущность тканевой инженерии суставов состоит в разработке и производстве биоинженерных матриц (скаффолдов) и последующей их имплантации в бесклеточном варианте, или предварительно заселенных подходящим пулом клеток для восстановления дефектов полноценно трехмерно-организованной тканью. Важной задачей при этом подходе является определенная индивидуализация свойств скаффолда, которая на настоящий момент практически не реализуется в направлении соответствия свойствам хряща конкретного пациента.

Основной целью исследования является описание тканеинженерной системы “хрящ – скаффолд” с использованием системной биологии и биокибернетического подхода. Задача состоит в том, чтобы спрогнозировать развитие рассматриваемой системы во времени и исследовать возможности этой системы и решить проблему управления, которая может создать возможности для создания скаффолдов с заранее заданными свойствами. Авторы рассмотрели упомянутые тканеинженерные системы как системы с управляемой обратной связью и предложили систему разностных уравнений, описывающих ее динамику.

Результаты компьютерного моделирования и прогнозные значения соотношения объема клеток и внеклеточного матрикса в физиологический промежуток времени, необходимого для ремоделирования скаффолда, в первом приближении совпадают с полученными ранее экспериментальными данными. Следующий шаг состоит в изменении модели для решения обратной задачи – разработки нового поколения тканеинженерных имплантатов с заранее заданными и контролируемыми свойствами.

Ключевые слова: математическое моделирование, биологические системы, суставной хрящ, остеоартроз, тканевая инженерия, регенеративная медицина.

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