Mathematical modelling of ciliary movement mechanism

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The main purpose of the paper was to present a new approach to the mathematical modelling of ciliary movements. This approach is based on the solution of the inverse problem of the dynamics, which is described by Lagrange's equations for the system of successively hinged rigid rods. In this case, as is well known, the generalized forces may be found as the time functions. It is proposed to represent these functions by the functions of generalized coordinates and velocities and also of the model parameters, whose values are determined as a solution of the parametric optimization problem. Besides, a special algorithm of ciliary movement control was elaborated. This algorithm is based on the hypothesis of variation of the equilibrium positions for cilia during one cycle of beating. The numerical results are in a good agreement with the cilia movements observed in *Paramecium multimicronucleatum*.

Key words: cilium, model, movement mechanism, infusorian, movement control, identification

1. Introduction

An investigation into the mechanism of ciliary movement is one of the interesting and actual problems of modern microbiology and medicine. The cilium is a microtubule-based motile organelle of some unicellular organisms (e.g., infusorian *Paramecium multimicronucleatum* [1], [2]). It can be also found in epithelial cells of oviduct and air passage in human organism [3], [4]. Although the main components of ciliary structure and the functions of some elements can be considered as experimentally determined [5], [6], the overall mechanism of the movement remains not perfectly clear.

Despite a variety of ciliary beating patterns, what is common is that each ciliary beat consists of the two phases – *effective* and *recovery* strokes (figure 1). During the effective stroke a cilium, being weakly deformed, performs rapid movement for fluid propulsion. The effective stroke is followed by the recovery stroke, during which the cilium more slowly returns to initial position forming the bend at the base and propagating it to the cilium tip. The whole time of ciliary beat is approximately equal to 0.3–0.7 ms [6].
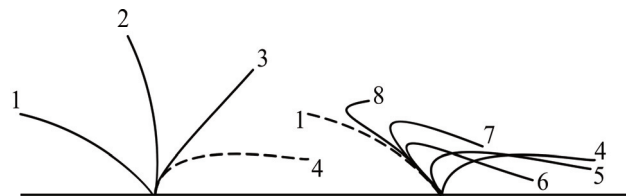

Fig. 1. Movement of cilium: 1–4 – effective stroke,
4–8 – recovery stroke

Many different mechanical models of the cilium were constructed. In a wide range of works, the mechanical model of the cilium is considered as deformable body or as a sequence of the deformable bodies with chain structure. RIKMENSPOEL [1], RIKMENSPOEL and RUDD [2] considered cilium as a nonlinear elastic rod, which performed planar movements. These move-

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ments were initiated by two types of "active" moments for effective and recovery strokes accordingly. The form of the dependence of these moments on the cilium curve length and time is different for the effective and recovery strokes. Dillon and Fauci [3], [7] presented a planar nonlinear finite-element model of the cilium, which consisted of the mechanical models of the elements of the cilium's internal structure called *axoneme*. The control algorithm of model movements was constructed based on the curvature value. This model was applied to computations of surrounding viscous fluid dynamics. Camalet et al. [8], [9] proposed the mechanical model of the organelle consisting of two elastic filaments, arranged parallel to each other with constant intervals between them. The model filaments rigidly attached to the base are not permitted to slide with respect to each other. The bending of the filament pair and local sliding displacement are coupled with geometric constraints. The main mathematical object, which describes the character of the bend, is a functional of free energy. Guirao and Joanny [10] modified this model, including viscoelastic connection between the filaments and base. Besides, filaments are able to slide with respect to each other but not to tilt. The complicated three-dimensional models of the cilium including the elements of internal structure were proposed by Gueron and Levit-Gurevich [11], Holwill et al. [12] and Mitran [13]. The main feature of all the models proposed are the parametrical dependencies of forces and moments, acting on the models, upon coordinates and velocities of the model elements. The method of parametrical identification is based on the solution of the second (direct) problem of the dynamics, which is quite expensive for computational sources.

In the present paper, the new algorithm of the mathematical modelling of ciliary motility is presented. The mechanical model of the cilium is considered as a planar system of successively hinged rigid rods (this mechanical model was presented in [14], [15]). Original mathematical model of the ciliary movement mechanism is discussed. The motion control algorithm is based on the hypothesis for the first time formulated in [16]. According to this hypothesis, the cilium has two positions of its mechano-chemical equilibrium. The first one corresponds to the position from which the cilium starts its recovery stroke. The second one corresponds to the opposite position from which the cilium starts its effective stroke. The process of ciliary motion consists in transitions between these positions. As an example, the results of the computer modelling of *Paramecium multimicronucleatum* movement are considered.

2. Method

2.1. Algorithms of modelling ciliary movements

A mathematical model of the cilium may be considered as a system of the equations of motion of the mechanical model with the expressions for forces (or generalized forces) acting on the model. In general case, each force may depend on displacements $\mathbf{r}(t)$, velocities $\dot{\mathbf{r}}(t)$, the set of parameters $\boldsymbol{\gamma}$ and also explicitly on time t. The main problem of the mathematical modelling is to establish the specific kind of this dependence. For this purpose any hypothesis on the expression of forces as the functions of $\mathbf{r}$, $\dot{\mathbf{r}}$, t and parameters $\boldsymbol{\gamma}$ must be formulated and then the values of parameters are determined. This parametric identification presents the main computational problem which is solved upon the process of modelling. The model parameters must be found which allows the model to reproduce the motion laws of the real cilium. These laws can be obtained from the results of experimental observations via approximation of the form of the real cilium by mechanical model and by approximation the values of coordinates of the model elements by smooth function (for example, by smoothing splines).
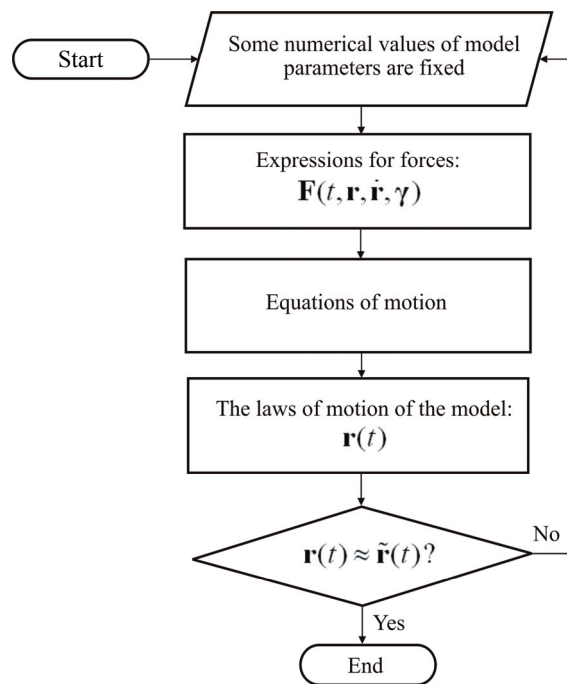

Fig. 2. Block-scheme of the algorithm of the modelling process based on the solution of the second problem of dynamics for parametric identification

The algorithm of mathematical and computer modelling of ciliary movements based on the solution of the second (direct) problem of the dynamics is used in most of previously conducted works. The second (direct) problem of the dynamics lies in determining the motion laws $\mathbf{r}(t)$ of the mechanical model using the dependencies of forces (or generalized forces) $\mathbf{F}$ on coordinates $\mathbf{r}(t)$, velocities $\dot{\mathbf{r}}(t)$ and parameters $\boldsymbol{\gamma}$, which are considered as known. This algorithm of modelling process can be considered as a sequence of several steps (figure 2):

Step 1. Some numerical values of the model parameters $\boldsymbol{\gamma}$ are fixed and inserted into the mathematical expressions for forces $\mathbf{F}(t, \mathbf{r}, \dot{\mathbf{r}}, \boldsymbol{\gamma})$.

Step 2. The expressions for forces (or generalized forces) $\mathbf{F}(t, \mathbf{r}, \dot{\mathbf{r}}, \boldsymbol{\gamma})$ are inserted into the equations of motion.

Step 3. The problem for the equations of motion is solved and the motion laws $\mathbf{r}(t)$ of the model are found.

Step 4. If the motion laws of the model $\mathbf{r}(t)$ can be considered as approximately equal (with arbitrarily preset accuracy) to the laws of motion of the real cilium $\widetilde{\mathbf{r}}(t)$, the process of modelling can be finished, otherwise it must be returned to the Step 1.
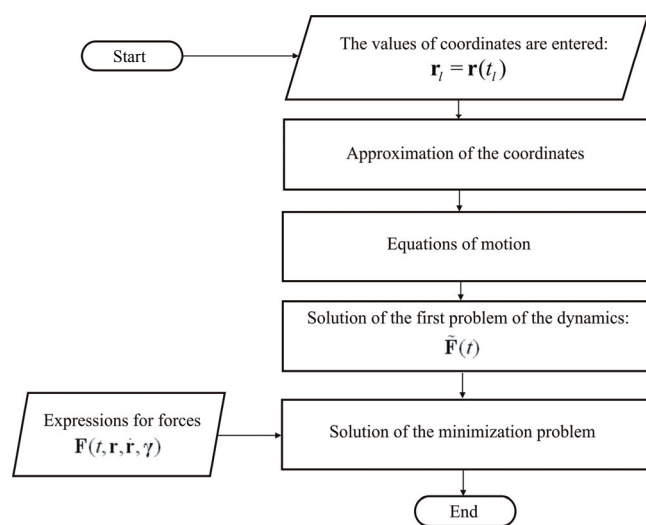

Fig. 3. Block-scheme of the algorithm of the modelling process based on the solution of the first problem of dynamics for parametric identification

This algorithm has the main disadvantage that this method of modelling is quite difficult, expensive and time-consuming. Another disadvantage of this algorithm is that the last moment (finish) of the modelling process is considered as unknown. That is why another algorithm of the modelling process is proposed in this article. Such an algorithm of the modelling

process can be considered as a sequence of the following steps (figure 3):

Step 1. The numerical values $\mathbf{r}_l = \mathbf{r}(t_l)$ of $\mathbf{r}(t)$, obtained from experimental observations and after approximation of the form of the real cilium by mechanical model, are stored.

Step 2. The problem of the approximation of the model coordinates as time functions $\widetilde{\mathbf{r}}(t)$ is solved (for example, using cubic smoothing splines).

Step 3. Approximations of the coordinates $\widetilde{\mathbf{r}}(t)$ are inserted into the equations of motion and the first (inverse) problem of the dynamics is solved. As a result, we obtain the forces (or generalized forces) acting on the model, found as time functions $\widetilde{\mathbf{F}}(t)$.

Step 4. The problem of the parametric identification is solved as a problem of minimization of functional $\Im(\boldsymbol{\gamma}) = \Im(\| \mathbf{F}(t, \mathbf{r}, \dot{\mathbf{r}}, \boldsymbol{\gamma}) - \widetilde{\mathbf{r}}(t) \|)$ ($\inf_{\boldsymbol{\gamma}} \Im(\boldsymbol{\gamma}) = 0$).

After this, the process of modelling must be finished.

2.2. Mechanical model of the cilium

The discrete mechanical model of the cilium is considered as a sequence of successively hinged rods, which can perform planar motions (figure 4). The number of the degrees of freedom of such a model is equal to the number of rods N. The equation of motion can be written in the form of the Lagrange's equation:

$$\frac{d}{dt}\left(\frac{\partial T}{\partial \dot{q}_i}\right) - \frac{\partial T}{\partial q_i} = Q_i, \quad i = \overline{1, N}, \tag{1}$$

where:

t – time,

T – kinetic energy of the mechanical system,

q_i – generalized coordinates,

$\dot{q}_i$ – generalized velocities,
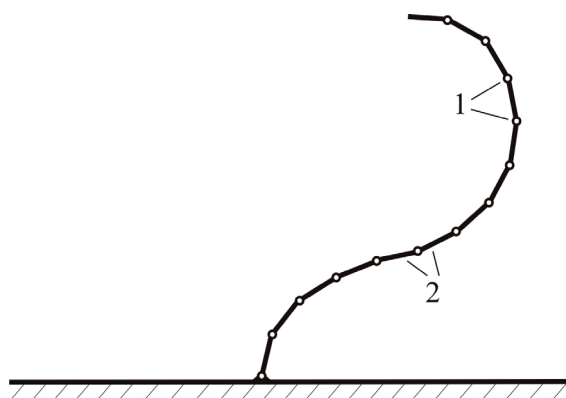
Q_i – generalized forces.

Fig. 4. Mechanical model of the cilium: 1 – hinges, 2 – rods

The angles between rods and vertical lines φ_i (called absolute coordinates) are used as generalized coordinates for the Lagrange's equation. In addition to this, the angles between rods ψ_i (relative coordinates) are introduced in the following way:

$$\psi_1 = \varphi_1, \quad \psi_i = \varphi_i - \varphi_{i-1}, \quad i = \overline{2, N},$$

$$\varphi_i = \sum_{j=1}^{i} \psi_j, \quad i = \overline{1, N}.$$

Nonlinear equation of motion (1) in dimensionless form can be written as follows:

$$\sum_{j=1}^{N} A_{ij}(\varphi_i(t), \varphi_j(t))\ddot{\varphi}_j(t)$$

$$+ \sum_{j=1}^{N} B_{ij}(\varphi_i(t), \varphi_j(t))\dot{\varphi}_j^2(t) = Q_i, \quad i = \overline{1, N}, \quad (2)$$

where $A_{ij}(\varphi_i(t), \varphi_j(t))$ and $B_{ij}(\varphi_i(t), \varphi_j(t))$ can be expressed by:

$$A_{ij}(\varphi_i(t), \varphi_j(t)) = \begin{cases} \left(\dfrac{1}{2} + N - j\right)\cos(\varphi_i - \varphi_j), & i < j, \\[2mm] \left(\dfrac{1}{3} + N - i\right), & i = j, \\[2mm] A_{ji}, & i > j, \end{cases}$$

$$B_{ij}(\varphi_i(t), \varphi_j(t)) = \begin{cases} \left(\dfrac{1}{2} + N - j\right)\sin(\varphi_i - \varphi_j), & i < j, \\[2mm] 0, & i = j, \\[2mm] -B_{ji}, & i > j, \end{cases}$$

$$i, j = \overline{1, N}.$$

The explaining of the reason of the local bends, which can rotate one part of the cilium model to another, is one of the main purposes of biological and biophysical studies of the cilia. That is why "biological" sense can be given to only relative coordinates ψ_i and generalized forces Q_i^{rel}. The connection between Q_i and Q_i^{rel} can be expressed by:

$$Q_i^{\text{rel}} = \sum_{j=i}^{N} Q_j, \quad i = \overline{1, N},$$

$$Q_i = Q_i^{\text{rel}} - Q_{i+1}^{\text{rel}}, \quad i = \overline{1, N-1}, \quad Q_N = Q_N^{\text{rel}}.$$

2.3. Mathematical model of the mechanism of ciliary motility

The mathematical model of the motility mechanism is based on the rules of changing the model parameters.

It is assumed that generalized forces can be written as the totals of positional and dissipative parts:

$$Q_i^{\text{rel}}(t, \psi_i, \dot{\psi}_i) = Q_i^{\text{rel,pos}}(\psi_i, \mathbf{a}_i(t))$$

$$+ Q_i^{\text{rel,res}}(\dot{\psi}_i), \quad i = \overline{1, N}, \quad (3)$$

where:

$Q_i^{\text{rel,pos}}(\psi_i, \mathbf{a}_i(t))$ – positional parts of generalized forces,

$\mathbf{a}_i(t)$ – vectors of model parameters,

$Q_i^{\text{rel,res}}(\dot{\psi}_i)$ – dissipative parts of generalized forces.

It is assumed that the dissipative parts are the models of energy dissipation process, which can occur until cilium performs effective and recovery strokes. The main reasons for the energy dissipation are the processes in axoneme and the resistance of the surrounding viscous fluid. As an example, the linear relationship between $Q_i^{\text{rel,res}}$ and $\dot{\psi}_i$ is considered:

$$Q_i^{\text{rel,res}}(\dot{\psi}_i) = -b\dot{\psi}_i, \quad i = \overline{1, N}, \quad (4)$$

where $b > 0$ is a constant considered as an input parameter of the model, being introduced by researcher.

The positional parts of generalized forces $Q_i^{\text{rel,pos}}(\psi_i, \mathbf{a}_i(t))$ are assumed as the models of the influence of the active elements of the axoneme, which are the main reason of the ciliary motility. It is assumed that $Q_i^{\text{rel,pos}}$ can be expressed by:

$$Q_i^{\text{rel,pos}}(\psi_i, c_i(t), \psi_i^{(0)}(t)) = -c_i(\psi_i - \psi_i^{(0)}),$$
$$i = \overline{1, N}, \quad (5)$$

where $c_i = c_i(t)$ are the stiffness coefficients of the mechanical model of the cilium. Parameters $c_i(t)$, $\psi_i^{(0)}(t)$ must be found via the process of model identification.

The mathematical model of the ciliary motion control is defined by the rules of the changing of the parameters $c_i(t)$, $\psi_i^{(0)}(t)$. It is assumed that $c_i(t)$ and $\psi_i^{(0)}(t)$ are piecewise constant time functions:

$$c_i(t) = c_{i,l}, \quad \psi_i^{(0)}(t) = \psi_{i,l}^{(0)},$$
$$t \in [t_{l-1}, t_l), \quad i = \overline{1, N}, \quad l = \overline{1, L}, \quad (6)$$

where $L + 1$ is the number of the nodes of the time mesh: $t_0, t_1, ..., t_L, t_{L+1}$; $t_0 = 0$, $t_{L+1} = 1$.

The algorithm of ciliary motion control is based on the hypothesis on transitions between positions of mechano-chemical equilibrium, proposed in [16]. To make the hypothesis proposed consistent with the mechanical model of the cilium, the model has two positions of equilibrium, position *I* and position *II*. The position *I* corresponds to the position from which cilium starts its recovery stroke, and position *II* corresponds to the position from which cilium comes into effective stroke (figure 5).
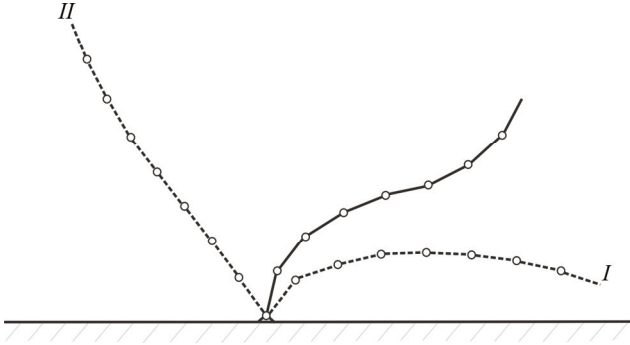

Fig. 5. The positions of equilibrium
of the mechanical model of cilium

The initial moment of the ciliary-like motion arrives when the rod at the base of the model has *maximal* value $\psi_{i,\max}$ of its generalized coordinate $\psi_1(t)$. It is assumed that the stiffness coefficient $c_1(t)$ at this moment has its *minimal* value $c_{1,\min}$. After the changes in t and $\psi_1(t)$ the value of $c_1(t)$ is *not* decreased, but may be increased, and at the moment $\psi_1(t)$ has its *maximal* value again, the value of $c_1(t)$ is decreased to the *minimal*. Another stiffness coefficient $c_i(t)$, $i = \overline{2, N}$ changes in the following way: when generalized coordinates $\psi_i(t)$, $i = \overline{2, N}$ have *maximal* values $\psi_{i,\max}$, $c_i(t)$ have *minimal* values $c_{i,\min}$, in the process of motion their values are *not* decreased, but may be increased, and at the moment $\psi_i(t)$ has its maximal values again, the values of $c_1(t)$ are decreased to the minimum (figure 6). The ciliary-like motions of the model (with recovery and effective strokes) are reproduced owing to this algorithm of the changing of $c_i(t)$, $i = \overline{1, N}$. According to this algorithm, the values of $c_{i,l}$ are restricted by inequalities:

$$0 \leq c_{i,1} \leq C, \quad c_{i,l-1} \leq c_{i,l} \leq C, \quad i = \overline{1, N}, \quad l = \overline{2, L}, \quad (7)$$

where $C > 0$ is a given supremum of the values of $c_{i,l}$ and is considered as an input parameter of mathematical model.
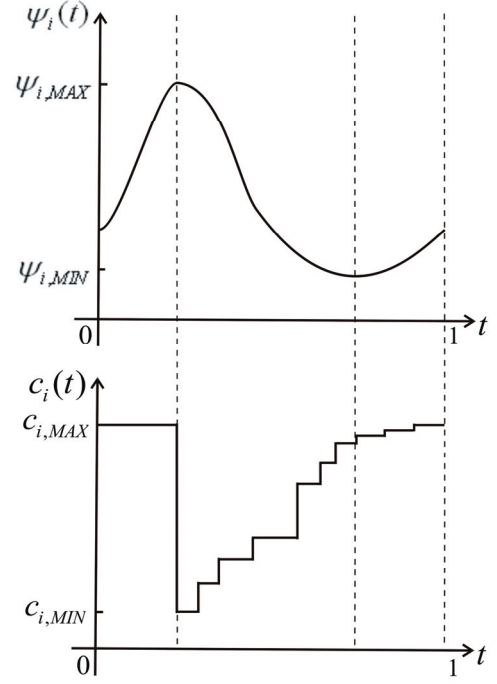

Fig. 6. Changing the generalized coordinate $\psi_i(t)$
and stiffness coefficient $c_i(t)$ in ciliary movement

The values of $\psi_{i,l}^{(0)}$ are restricted by holonomic constraints, which are imposed on the mechanical model:

$$-\frac{\pi}{2} \leq \psi_{1,l}^{(0)} \leq \frac{\pi}{2}, \quad -\pi \leq \psi_{i,l}^{(0)} \leq \pi, \quad i = \overline{2, N}, \quad l = \overline{1, L}. \quad (8)$$

Formulas (2)–(8) represent the mathematical model of the ciliary movement mechanism. The values of the parameters $c_{i,l}$ and $\psi_{i,l}^{(0)}$ are computed by solving the problem of minimization of functional (e.g., functional of weighed least-squares method), which resolves the difference between generalized forces computed by (5) and solutions of the first problem of the dynamics $Q_i^{\text{rel,pos}}(t)$. The values of $c_{i,l}$ and $\psi_{i,l}^{(0)}$ are restricted by inequalities (7)–(8), i.e., the minimization problem is stated as a problem of nonlinear programing [17].

3. Results

The models and algorithms developed above were applied to the problem of modelling ciliary planar movement of infusorian *Paramecium multimicronucleatum*. The length of the cilium of this unicellular organism is 10 μm, and the time of the beat cycle is 40 ms [1].
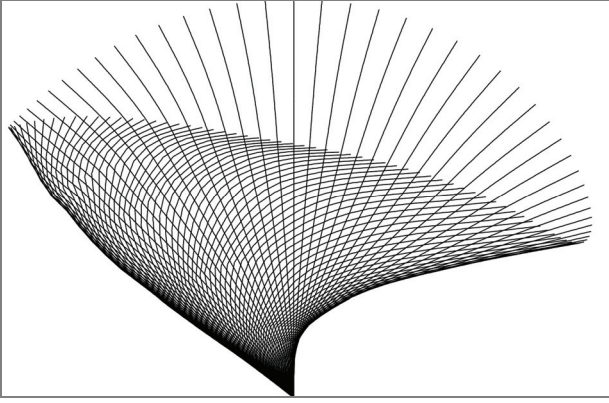
Fig. 7. Movement of *Paramecium multimicronucleatum* infusorian's cilium, reproduced by model at $N = 20$

The beat pattern of the cilium reproduced by a mechanical model at $N = 20$ is shown in figure 7. The representations of the stiffness coefficients $c_i(t)$ obtained via solving the problem of parametric identification at $b = 5000$ and $L = 50$ are shown in figure 8 (the cases of $i = 1, 5, 10, 13, 17, 19$ are shown). From figure 8 it can be observed that in the process of movement, two types of waves are propagated along the cilium length – the wave of an increase in stiffness coefficients (it is called "the wave of stress") and the wave of a decrease in stiffness coefficients (it is called "the wave of relaxation"). The propagation of these waves is coordinated by the algorithm described above.
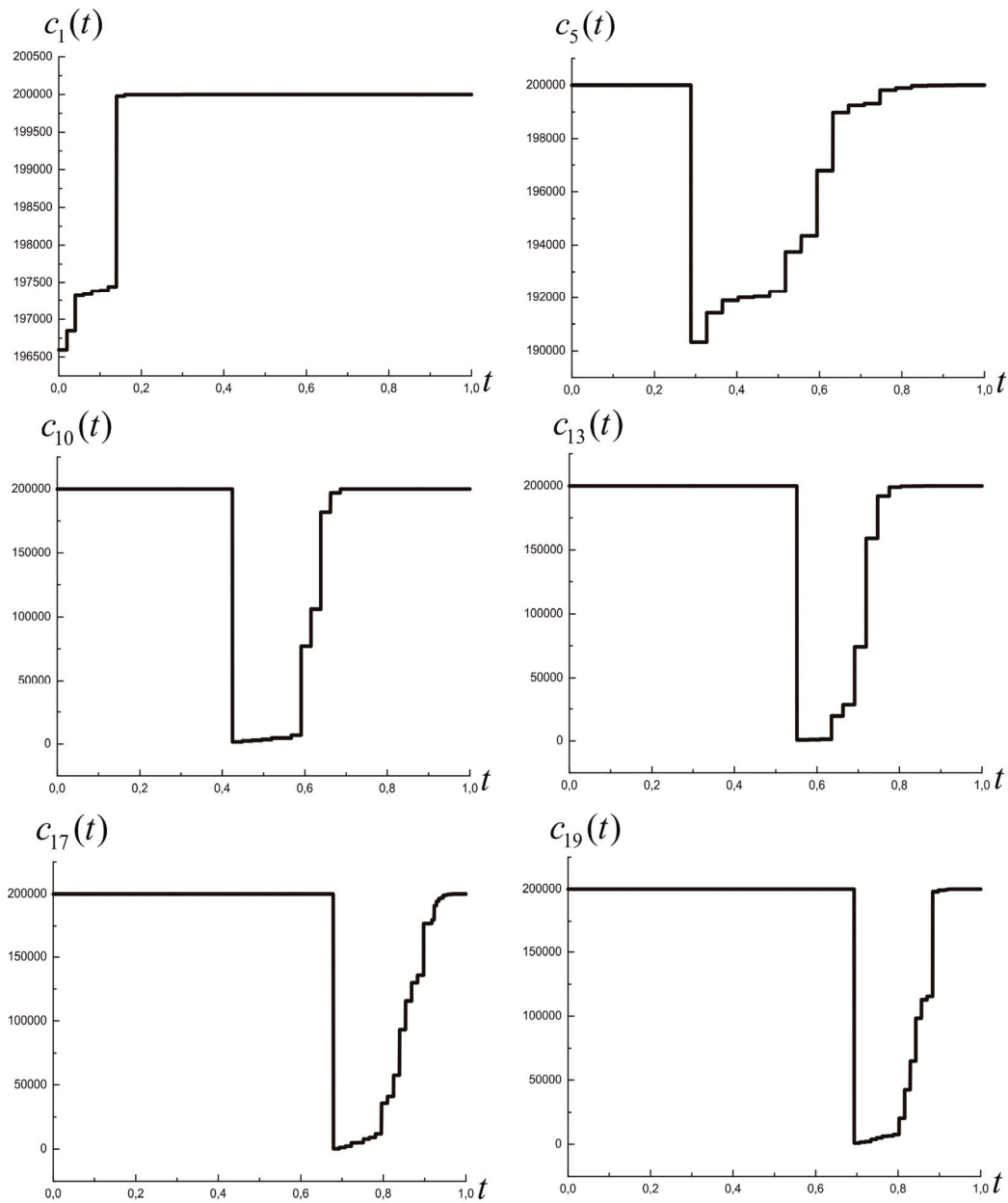

Fig. 8. Stiffness coefficients as time functions at $b = 5000$ and $L = 50$
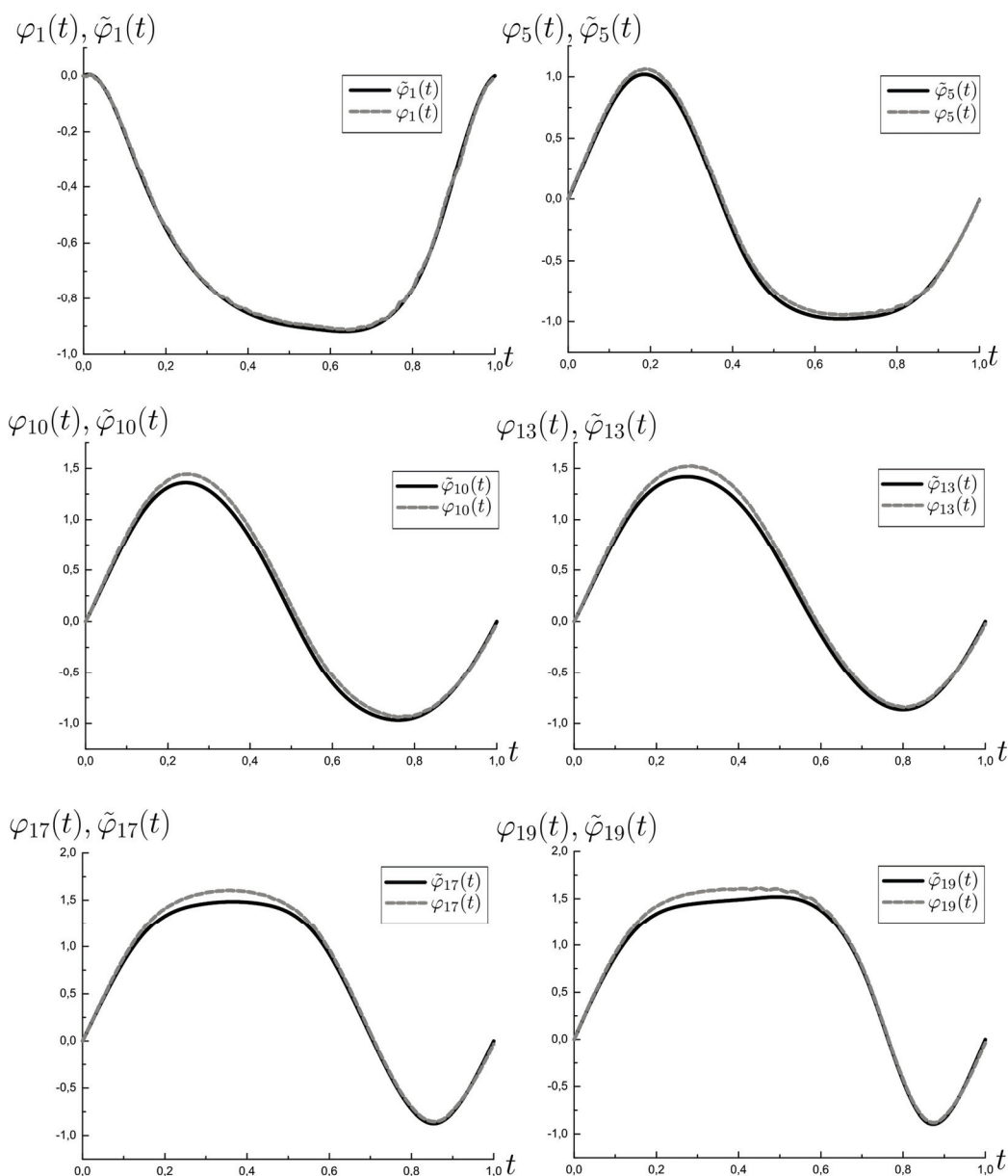
Fig. 9. Solutions of the Cauchy problem $\varphi_i(t)$ and approximations of the experimental observation results $\tilde{\varphi}_i(t)$

Table. The values of K_i obtained for *Paramecium multimicronucleatum* movement
at $b = 5000$, $L = 50$ and $L = 250$

L	K_1	K_5	K_{10}	K_{13}	K_{17}	K_{19}
50	$8.49 \cdot 10^{-5}$	$1.22 \cdot 10^{-3}$	$3.76 \cdot 10^{-3}$	$4.12 \cdot 10^{-3}$	$4.31 \cdot 10^{-3}$	$4.40 \cdot 10^{-3}$
250	$6.69 \cdot 10^{-5}$	$1.13 \cdot 10^{-3}$	$3.08 \cdot 10^{-3}$	$3.69 \cdot 10^{-3}$	$3.98 \cdot 10^{-3}$	$3.97 \cdot 10^{-3}$

After solving the problem of parametric identification of $c_{i,l}$ and $\psi_{i,l}^{(0)}$, the second problem of dynamics for the system (2) with the values of $c_{i,l}$ and $\psi_{i,l}^{(0)}$ must be solved to verify the correctness of solving a parametric identification problem. The second problem of the dynamics is stated as the Cauchy problem for the system (2). This prob-

lem was solved by multistep method of the 3rd order based on backward differentiation scheme [18].

The differences between numerical solutions of the Cauchy problem $\varphi_i(t)$, $i = \overline{1, N}$ and approximations of the cilium laws of motion $\tilde{\varphi}_i(t)$, $i = \overline{1, N}$ are defined based on the integral criterion K_i:

$$K_i = \int\limits_0^1 (\varphi_i(t) - \widetilde{\varphi}_i(t))^2 \, dt, \quad i = \overline{1, N}.$$

The values of K_i for i = 1, 5, 10, 13, 17, 19 in the cases of b = 5000 and L = 50, 250 are represented in the table. The graphs of $\varphi_i(t)$ and $\widetilde{\varphi}_i(t)$ are shown in figure 9 for b = 5000, L = 50.

4. Discussion

Some remarks concerning the mechanical and mathematical models proposed can be made:

1. The mechanical model has a great advantage of approximating the form of the bend of the real organelle with the arbitrarily preset accuracy due to the simple chain structure of this model. For example, the linear elastic models of the cilium proposed in [8]–[10] can be applied only to the modelling of small oscillations of the real cilia. Our mechanical model can be applied to modelling remarkably wider classes of physiological ciliary movements.

2. The equations of the motion of the mechanical model (2) form the system of ordinary differential equations which allows easier numerical simulation compared to that of the systems of partial differential equations, which describe the dynamics of the deformed elastic systems. Such systems of differential equations have another advantage over the systems of partial differential equations, namely the methods of control theory (e.g., optimal control theory) for ordinary differential equations are more widely developed. Therefore, the models proposed can be applied to the problems of the motion control of real cilia. These problems are very important in our time and have many applications in medicine – for example, in destabilizing parasite motion or initiating the movements of cilia of human epithelial cells.

3. The main computationally expensive mathematical problem, which is solved during the process of modelling, is parametric identification. In our algorithm, this problem is defined as a minimization problem: $\Im(\boldsymbol{\gamma}) \to \min\limits_{\boldsymbol{\gamma}}$. Generally, this problem is computationally very expensive, but according to formulae (6) for parameters its solution can be subdivided into the procedures of solving the minimization problems for functionals $\Im_{i,l}$ and depends only on *two variables*: $c_{i,l}$ and $\psi_{i,l}^{(0)}$. These problems are *quite simpler* than a general minimization problem. In our simulation, such problems are solved by the method

of gradient projection [17], using the C++ programing language. Another advantage of this piecewise presentation of the model parameters is the opportunity to parallelize the process of computation.

4. Analyzing data from the table, it can be seen that our model can reproduce the planar movements of the cilium with high accuracy. This may be done by increasing the number of the model parameters – according to (6) by increasing L.

Taking everything into consideration, it can be concluded that the model proposed is more efficient in a computational sense than some models proposed in previous works. This advantage of our model allows all the stages of modelling process to be programed for using in the systems of real time ciliary simulation and control.

The models proposed suffer from disadvantages connected with the mechanical model and the dependencies of generalized forces on ψ_i and $\dot{\psi}_i$ represented by formulas (4) and (5). The first one corresponds to the possibility of reproducing only planar movements by the model. This disadvantage restricts the class of the modelled movements, but it can be overcome by generalization of the model to 3D case, without any modifications in motion control algorithm. The second disadvantage of the model can be overcome by the *nonlinear* dependencies of generalized forces upon ψ_i and $\dot{\psi}_i$, which can significantly reduce the number of the model parameters. Such nonlinear dependencies can be found after analyzing of the solutions of inverse problem of the dynamics.

5. Conclusion

New approach to the mathematical modelling of the process of ciliary movement is proposed. The main task of the algorithm of this approach is to use the solution of inverse problem of dynamics for parametric identification.

Treating the real cilium as a planar discrete sequence of successively hinged rigid rods, the mechanical model is created. The mathematical model of the mechanism of ciliary movement consists of the equations of motion and the formulas for generalized forces as functions of time, generalized coordinates and velocities. The parameters of the model may be found by solving nonlinear programing problem.

The main advantages of the algorithm proposed are as follows: for the parametric identification of the problem it is not required to solve the problem for the

equations of motion and the moment of the modelling process completition is known – it is the moment of solving the minimization problem.

The mathematical model proposed is used for the modelling of *Paramecium multimicronucleatum* movement. As a result, it is shown that the accuracy of the model results can be increased via increasing the number of the mesh points.

Using the models proposed, it is possible to model the planar movements of another types of cilia of unicellular organisms, e.g., *Sabellaria, Stentor, Jorunna* and others [2], and of the cilia, which can be found in human organism.

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