This article is devoted to mathematical modelling of motility of a single cilium. After some simplifications, a mechanical model of a cilium as well as a mathematical model of the mechanism of ciliary motility were proposed. These models are based on the hypothesis which was formulated earlier.

Key words: ciliary motility, cilium, mucociliary transport, mathematical modelling

1. Introduction

The ciliary motility plays an essential role in human health. The ciliary type of transport is used for numerous vitally important functions. First of all, it is the mucus transport in the lungs [1]. The cilia arise from the epithelial layer. One of the main protective mechanisms of the lung is the airway surface liquid (ASL), which is a fluid layer coating the interior epithelial surfaces of the bronchi and bronchioles. The ASL exhibits two-layered structure. The periciliary layer (PCL), a region of low viscosity, is situated in the proximity to the epithelium [2]. The region between the PCL and the airway is occupied by a more viscous mucus layer. The cilia beat within the PCL layer in a coordinated manner forming the metachronal wave. The tips of the cilia have been observed to penetrate the mucus during their beat cycle. Ciliary movements lead to the propelling of the ASL towards to the trachea and then out of the human body. This process is known as mucociliary transport. Foreign objects contained in the bronchi and bronchioles (e.g., inhaled particles, bacteria spores) are trapped in the viscous mucous layer. The proper functioning of this process is fundamental to maintaining a healthy state. A major disease associated with the breakdown of mucociliary transport is cystic fibrosis. Specific genetic defects associated with this disease lead to reduced mucociliary transport, leaving the lungs prone to chronic infections from, e.g., bacterial spores that are not eliminated from the bronchioles. Other mechanisms can eliminate the foreign objects (cough, airway constrictions), but a fundamental observation is that a healthy state is characterized by a good functioning of mucociliary transport, while other mechanisms such as cough are invoked as a response to a diseased state.

Another important example of the ciliary transport is women’s reproductive function. The oviductal cilia play a major role in ovum pickup by the oviduct, and the ovum transport within the oviduct.

At the same time, the cilia are well known as organelles providing the cellular motility. Some examples of the cilia were found in protozoa (e.g., Opalina, Paramecium, Pleurobrachia), where they perform the propulsive function. The typical length of a cilium is about 5–10 μm, the diameter is about 0.25 μm [3]. The cilium has a complex internal structure, which is called the axoneme. It is composed by 9 doublets of microtubules.
(located around its cross-section with dynein arms distributed along each pair, as is shown in figure 1A, B), the central pair of microtubules, nexin links and radial spokes. Dynein arms are complex molecules, which generate a bending momentum for microtubules.

A visual characteristic of the ciliary beating is the asymmetric pattern with the rapid effective and slow recovery strokes. During the effective stroke the cilium rotates around the base being slightly bended and pushes the surrounding liquid. This is followed by the recovery stroke during which the cilium returns to the initial position and bends in such a way as to avoid a reverse liquid stream (figure 1).

Most of the proposed models for the ciliary beating mechanism are based on the sliding filament theory. This theory supposes that a bending moment results from an active sliding process, which is caused and controlled by dynein arms – active elements of the axoneme. RIKMENSPOEL and RUDD [4] assumed two different types of active moments – standing and travelling moments, generated by active elements of ciliary microstructure. To take into account the ciliary beating asymmetry, MURASE [5] assumed that functional properties of active elements differ between the opposing microtubular doublets. Incorporating the aforementioned property into the mechanical model, the ciliary-like repetitive beats were simulated. DILLON and FAUCI [6] presented a finite-element model of the cilium, with elements of the axoneme incorporated, the control mechanism of ciliary beating based on the algorithm using the curvature of the organelle for the motility control.

Unfortunately, although the cilium inner structure is known, the function of each structure element is not clear and the beating mechanism is still not understood. Previous mathematical models were constructed by incorporating the mathematical formalization of some hypotheses on the ciliary motility mechanism into a mechanical model. After that, varying the model parameters, authors tried to reproduce an experimentally observed beating pattern. From a computational point of view, such a method is quite difficult and time-consuming.

2. Method

The mathematical model is based on the hypothesis, which was earlier proposed by TREGOUBOV et al. [7]. We proposed the method based on solving the first problem of the dynamics, that is a definition of inner cilium forces from laws of motion. This problem can be solved with an arbitrary degree of accuracy. In doing so, forces can be seen as time functions. After that the forces are subdivided into active positional forces and passive dissipative forces. Then an identification problem is solved to determine the model parameters, which allow the reconstruction of forces. For this procedure a mechanical model must be constructed.

The simple mechanical model of the cilium has been constructed, on the assumption that all movements occur in single plane. The model consists of the successively hinged rods. The number of rods \( n \) is arbitrary and defined by a specific pattern of ciliary beating. Positions of the rods are defined by a set of generalized coordinates \( \phi_i, i = 1, n \), which are the angles between rods and vertical lines. The rods are considered to be the same length \( l \) and mass \( m \). The governing equations of this mechanical system were derived in the form of Lagrange’s equations:

\[
\frac{d}{dt} \left( \frac{\partial T}{\partial \phi_i} \right) - \frac{\partial T}{\partial \phi_i} = Q_i, \quad i = 1, n,
\]
where $T$ is the kinetic energy of the mechanical system, $\phi_i$ are the generalized coordinates, $\dot{\phi}_i$ are the generalized velocities, $Q_i$ are the generalized forces.

Different experimental patterns of ciliary beating were analyzed and laws of their motions were incorporated into equations of motion as given functions of time. As a result, generalized forces were obtained as time functions $Q_i(t)$, which are the rotational moments applied in hinges.

In order to subdivide generalized forces into active and passive ones, it is assumed that passive forces consist of only viscous dissipative forces representing the properties of a surrounding medium and depend only on generalized velocities $\dot{\phi}_i$. Active forces consist of only positional forces and depend only on generalized coordinates $\phi_i$ and time $t$. So it can be presented as:

$$Q_i(t, \Phi, \dot{\Phi}) = Q_i^{\text{active}}(t, \Phi) + Q_i^{\text{passive}}(\Phi), \quad i = 1, n, \tag{1}$$

where $\Phi = (\phi_1, ..., \phi_n)$, $\dot{\Phi} = (\dot{\phi}_1, ..., \dot{\phi}_n)$.

It is assumed that $Q_i$ is linearly dependent on $\phi_i$ and $\dot{\phi}_i$, so equation (1) takes the following form:

$$Q_i = -c(t)(\phi_i - \phi_i^{(0)}(t)) + c(t)(\phi_i - \phi_i - (\phi_i^{(0)}(t) - \phi_i^{(0)}(t))) - b\dot{\phi}_i + b(\dot{\phi}_i - \dot{\phi}_i),$$

$$Q_{i+1} = -c(t)(\phi_{i+1} - \phi_{i+1} - (\phi_{i+1}^{(0)}(t) - \phi_{i+1}^{(0)}(t))) + c(t)(\phi_{i+1} - \phi_{i+1} - (\phi_{i+1}^{(0)}(t) - \phi_{i+1}^{(0)}(t))) - b(\dot{\phi}_{i+1} - \dot{\phi}_{i+1}) + b(\dot{\phi}_{i+1} - \dot{\phi}_{i+1}), \quad i = 2, n-1, \tag{2}$$

$$Q_n = -c(t)(\phi_n - \phi_n - (\phi_n^{(0)}(t) - \phi_n^{(0)}(t))) - b(\dot{\phi}_n - \dot{\phi}_n).$$

According to the hypothesis formulated earlier [7], the cilium has two positions of the mechano-chemical equilibrium. The first one corresponds to the position from which a cilium comes into a recovery stroke. The second one corresponds to the opposite position from which cilium starts its effective stroke. These two positions are given by sets of angles $\{\phi_i^{(0)}(t)\}_{i=1}^n$ and $\{\phi_i^{(0),\Pi}(t)\}_{i=1}^n$, respectively. So in (2), function $\phi_i^{(0)}$ incorporates two values, $\phi_i^{(0),1}$ and $\phi_i^{(0),\Pi}$:

$$\phi_i^{(0)} = \begin{cases} \phi_i^{(0),1}, & t \in [\Delta_i^1, \Delta_i^\Pi], \\ \phi_i^{(0),\Pi}, & t \in [\Delta_i^\Pi, \Delta_i^1 + \theta]. \end{cases}$$

Transitions between equilibrium positions are made by incorporating $\phi_i^{(0)}$ and $c(t)$. According to the algorithm of motion control represented in [7], $c(t)$ incorporates its values in the following manner:

$$c = \begin{cases} c^1, & t \in [\Delta_i^1, \Delta_i^\Pi], \\ c^*, & t \in [\Delta_i^\Pi, \Delta_i^1 + \theta]. \end{cases}$$

Thus, the unknown parameters of generalized forces, such as: $c^1$, $c^*$, $\{\phi_i^{(0),1}\}$, $\{\phi_i^{(0),\Pi}\}$, $b$, $\theta$, $\{\Delta_i^1\}$, $\{\Delta_i^\Pi\}$ must be found. Parameters $b$, $\{\Delta_i^1\}$, $\{\Delta_i^\Pi\}$ can be found from the solution of FPTD directly. Other parameters can be derived using $Q_i(t)$ – the solutions of the FPTD by means of the solution of the identification problem by minimizing the functional of the least squares method:

$$I = \frac{1}{N} \sum_{i=1}^N \sum_{j=1}^N (Q_i(t) - Q_i(t, \Phi, \dot{\Phi}))^2.$$

This optimization problem was solved by the direct Powell’s method [8]. Cauchy problem for the system of governing equations was solved by the Cash–Karpe method.

### 3. Results

As the results of the series of computational experiments, different beating patterns, which are typical of a cilium in a normal state, were obtained (see figure 2A). The ciliary-like beating of Chlamydomonas flagellum was also reproduced. Although the model and the incorporation of parameters differ from the “classical” ciliary case, the general algorithm remains the same. Patterns which are typical of a cilium that underwent mutation were also reproduced by some changes in the algorithm (figure 2B). The possibility of modelling the pathological cases allows the model investigation in the cases of some diseases and their consequences.
4. Conclusion

The mechanical and mathematical models proposed allow us to reproduce ciliary and ciliary-like patterns in normal and pathological cases. These results make it possible to support the hypothesis of the ciliary beating mechanism. They also offer the possibility of testing some advanced hypotheses, formulating the new ones and incorporating this model into the general model of mucociliary transport.

References


