МОДЕЛЬ ОПРЕДЕЛЕНИЯ РЕОЛОГИЧЕСКИХ ПАРАМЕТРОВ КЛЕТКИ

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Предлагается модель определения реологических параметров клетки по результатам ее наноиндентирования. Предположение, что формы индентора и клетки известны, позволяет набрать статистику для ядра ползучести клетки в норме и по отклонению от нее диагностировать системные заболевания. Метод основан на решении прямой задачи о внедрении жесткого индентора в криволинейный биологический объект конечных размеров посредством сведения к двум задачам, которые решены с использованием наследственной теории ползучести на основе обобщения модели Винклера.

Ключевые слова: основание Винклера; вязкоупругий материал; нелинейная ползучесть; наследственная ползучесть.

THE MODEL OF CELL RHEOLOGICAL PARAMETERS DETERMINATION

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Proposed the model of cell rheological parameters determination based on nanoindentation. It is assumed that shapes of cell and indenter are known, which allows to get stats for creep kernel of normal cell and to diagnose systematic disease based on stats aberration. The method is based on solution of the direct indentation problem (indentation of curvilinear biological finite-size object with a rigid stamp of an arbitrary shape). Complicated spatial creep problem is reduced to two contact problems, which are solved based on generalization of the Winkler model and using the hereditary creep theory.

Keywords: the Winkler foundation; viscoelastic material; nonlinear creep; hereditary creep.

INTRODUCTION

Biomechanics of a cell studies cell mechanical properties and their changes. It was established experimentally that course of certain diseases leads to significant changes in cell mechanical properties [1, 2]. Cell mechanical properties to be measured are the following: Young's modulus, viscosity, relaxation time, etc. [1].

Atomic-force microscopy is widely acknowledged as method of cell mechanical properties determination [2, 3]. However, a number of methodological issues were overlooked. Obviously, cell should be modelled as a composite body. This means that all cell mechanical characteristics are effective parameters (averaged over the cell volume).

Work [4] is devoted to methodical research of possible hereditary creep state equations, which can be used in solving contact problems using the simplest model of a deformable composite coating of a constant thickness. However, using the assumption of constant thickness of a coating makes it impossible to use this model in cell indentation modelling. This problem for finite-size body modelling was solved without considering creep in [5].

THEORETICAL SOLVING OF THE DIRECT PROBLEM OF BIOLOGICAL OBJECT INDENTATION

One can divide finite-size object into two objects by means of horizontal plane. Thus, the original problem of biological object indentation can be reduced to following contact problems (Fig. 1): indentation of half of a cell lying on rigid halfspace with curvilinear stamp and compression of half of a cell by two rigid halfspaces.

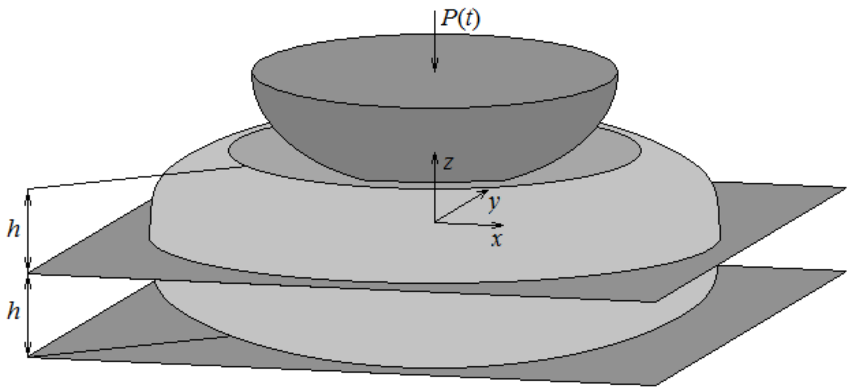

Fig. 1. The reduction of the original indentation problem to two contact problems

It should be emphasized that there is no directional liquid flow in biological materials and consequently internal pressure compensated by membrane tension. Internal static liquid pressure can be increased in connection with volume decrease caused by indentation. Assume that tensile modulus of cell membrane is negligibly small compared to tensile moduli of other cell organelles and cell membrane is incompressible in transverse direction. Then elastic modulus of cell membrane and internal pressure magnitude can be neglected.

HYPOTHESES USED IN THE MODEL OF A DEFORMABLE COATING OF A VARIABLE THICKNESS

Assume that the indentation surface of upper half of a cell is determined by the function $f_{ind}(x,y)$, where $f_{ind}(0,0)=0$. Upper half of a cell lies on the undeformable halfspace described by the equation $f_{coat}(x,y)=-h$ (h is a half of cell height). The dented body is undeformable, i. e. it is a rigid stamp described by the equation $f(x,y)$, where $f(0,0)=0$ (Fig. 2). Before loading the stamp touches the cell at the point $(0,0,0)$. In the case of compression of lower half of a cell by two rigid halfspaces surface equation is $f(x,y)\equiv 0$.

Let the open set $S(t)=\{(x,y)\,|\,\sigma_z(x,y,0,t)\neq 0\}\subset X0Y$ be the interior of the contact area ($\sigma_z(x,y,0,t)$ are contact stresses) then the closure $\bar{S}(t)$ is the contact area. The necessary condition is $f_{ind}(x,y)>f_{coat}(x,y)=-h$ for $(x,y)\in\bar{S}(t)$. Assume that both halves of a cell can be replaced by prismatic rods with the height $f_{ind}(x,y)+h$ and the constant cross-section $\Delta\times\Delta$ in the plane $X0Y$ (Fig. 2). Rods can be moved only in Z-direction and their stress-strain state is uniform [1, 3]. The size Δ is negligibly small compared to the smallest characteristic dimension of the contact area $\bar{S}(t)$ projection onto the plane $X0Y$.

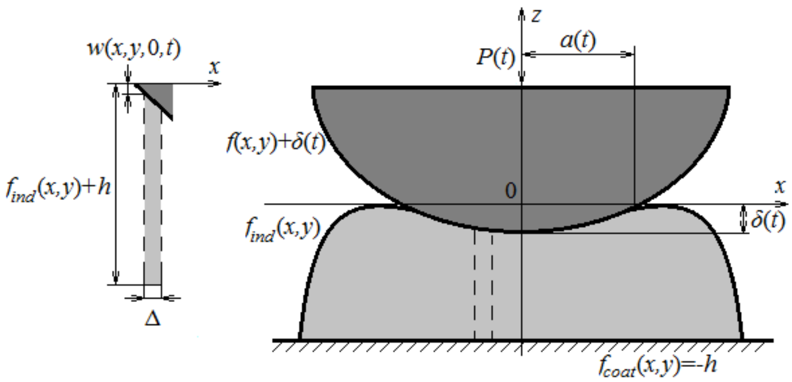

Fig. 2. Indentation of half of a cell with curvilinear stamp

The force $P(t)$ is nondecreasing function for $t\in[0,t_0]$ (t_0 is creep test duration), it is applied to rigid stamp and directed vertically downward along Z-axis. All linear dimensions of the contact area $\bar{S}(t)$ under the force $P(t)$ do not decrease, i. e. for all $t_1<t_2$ one has:

$$\bar{S}(t_1)\subseteq\bar{S}(t_2). \quad (1)$$

Creep deformation is slowly enough that problem can be considered as a quasistatic one [5], i. e. mass-inertial characteristics of prismatic rods do not affect the character of deformation. Consider steady-state creep of rods. The time required to achieve the indentation depth $\delta(0)$ is negligible small compared to the test time and one can assume that $\delta(0)$ is instantaneous value. Consider the following cell materials [5]: viscoelastic homogeneously aging material ($E(t)$ is instantaneous elastic modulus, $\Gamma(t,\tau)$ is creep kernel)

$$E(t)\,\varepsilon_z(t)=\sigma_z(t)+\int_0^t\sigma_z(\tau)\,\Gamma(t,\tau)d\tau\,, \quad (2)$$

aging material possessing properties of nonlinear creep ($\Im(\varepsilon)$ is nonlinear function)

$$\Im(\varepsilon_z(t))=\sigma_z(t)+\int_0^t\sigma_z(\tau)\,\Gamma(t,\tau)d\tau\,. \quad (3)$$

THE BOUNDARY CONDITION AND THE SIMPLEST MODEL OF CELL RHEOLOGY

In the simplest model of a deformable coating stresses $\sigma_z(x,y,0,t)\neq 0$ can occur only at the point where displacements $w(x,y,0,t)\neq 0$. Thus, $S(t)=\{(x,y)\,|\,w(x,y,0,t)\neq 0\}$ and the boundary condition for displacements is the following [5]:

$$w(x,y,0,t)=\begin{cases} f(x,y)-f_{ind}(x,y)+\delta(t), & (x,y)\in S(t),\\ 0, & (x,y)\notin S(t).\end{cases} \tag{4}$$

where $\delta(t)$ is the indentation depth relative to the point $(0,0,0)$. Then for $(x,y)\in \overline{S}(t)\setminus S(t)$ the following equality holds:

$$\delta(t)=f_{ind}(x,y)-f(x,y). \tag{5}$$

Equilibrium equation of the stamp on the boundary has the following form [5]:

$$P(t)=-\iint\limits_{S(t)}\sigma_z(x,y,0,t)dxdy\ . \tag{6}$$

The simplest model which can be associated with a cell is homogeneous isotropic object which has geometric boundary of a cell and mechanical characteristics equal to effective one of a cell. Assume that $E(t)$, parameters of $\Im(\varepsilon)$ and $\Gamma(t,\tau)$ are determined. One can use the following equation to determine cell deformation in the contact area (Fig 1.):

$$\varepsilon_z(x,y,0,t)=\frac{w_{st}(x,y,0,t)+w_{coat}(x,y,0,t)}{2\left(f_{ind}(x,y)+h\right)}=\frac{1}{2}\left(\varepsilon_{z,up}(x,y,0,t)+\varepsilon_{z,low}(x,y,0,t)\right). \tag{7}$$

Since the indentation depth can be determined by the following equation $\delta(t)=2h\,\varepsilon_z(0,0,0,t)$, from the equation (7) one can obtain:

$$\delta(t)=h\left(\varepsilon_{z,up}(0,0,0,t)+\varepsilon_{z,low}(0,0,0,t)\right)=\delta_{up}(t)+\delta_{low}(t). \tag{8}$$

Values $\delta_{up}(t)$, $\delta_{low}(t)$ are determined by the equation (5) in accordance with the local coordinate systems based on contours of the contact areas $\overline{S_{up}}(t)\setminus S_{up}(t)$ and $\overline{S_{low}}(t)\setminus S_{low}(t)$. It is necessary to use one of the systems of equations to determine the contact areas [5]: viscoelastic homogeneously aging material of a cell

$$\begin{cases} \iint\limits_{S_{up}(t)}\frac{w_{st}(x,y,0,t)}{f_{ind}(x,y)+h}dxdy=-\frac{1}{E(t)}\left(P(t)+\int\limits_0^t P(\tau)\Gamma(t,\tau)d\tau\right),\\ \iint\limits_{S_{low}(t)}\frac{w_{coat}(x,y,0,t)}{f_{ind}(x,y)+h}dxdy=-\frac{1}{E(t)}\left(P(t)+\int\limits_0^t P(\tau)\Gamma(t,\tau)d\tau\right),\end{cases} \tag{9}$$

aging material of a cell possessing properties of nonlinear creep

$$\begin{cases} \iint\limits_{S_{up}(t)}\Im\left(\frac{w_{st}(x,y,0,t)}{f_{ind}(x,y)+h}\right)dxdy=-\left(P(t)+\int\limits_0^t P(\tau)\Gamma(t,\tau)d\tau\right),\\ \iint\limits_{S_{low}(t)}\Im\left(\frac{w_{coat}(x,y,0,t)}{f_{ind}(x,y)+h}\right)dxdy=-\left(P(t)+\int\limits_0^t P(\tau)\Gamma(t,\tau)d\tau\right),\end{cases} \tag{10}$$

where $w_{st}(x,y,0,t)$ and $w_{coat}(x,y,0,t)$ are displacements determined by the equation (4):

$$\begin{cases} w_{st}(x,y,0,t)=f(x,y)-f_{ind}(x,y)+\delta_{up}(t),\\ w_{coat}(x,y,0,t)=-f_{ind}(x,y)+\delta_{low}(t).\end{cases} \tag{11}$$

EXAMPLE OF INDENTATION OF AN AXISYMMETRIC CELL WITH AXISYMMETRIC STAMP

Let a cell with a height $2h$ has the same equations describing the both parts of a cell, namely, $f_{ind}(x,y)=-(x^2+y^2)/2R_{cell}$. Let an indenter has a shape of paraboloid described by the equation $f(x,y)=(x^2+y^2)/2R_{st}$. In this case (11) have the following form:

$$\begin{cases} w_{st}(x,y,0,t)=(x^2+y^2)(1/2R_{st}+1/2R_{cell})+\delta_{up}(t), \\ w_{coat}(x,y,0,t)=(x^2+y^2)/2R_{cell}+\delta_{low}(t). \end{cases} \quad (12)$$

From (5) and (12) one can obtain by means of substitution $r^2=x^2+y^2$:

$$\begin{cases} \delta_{up}(t)=-a_{up}(t)^2(1/2R_{st}+1/2R_{cell}), \\ \delta_{low}(t)=-a_{low}(t)^2/2R_{cell}, \end{cases} \quad (13)$$

where $a_{up}(t)$ and $a_{low}(t)$ are the contact area radii.

From (9), (12), (13) one can obtain for viscoelastic homogeneously aging material:

$$\begin{cases} 2\pi\int\limits_0^{a_{up}(t)}\frac{r^2-a_{up}(t)^2}{2R_{cell}h-r^2}rdr=-\frac{R_{st}}{E(t)(R_{st}+R_{cell})}\left(P(t)+\int\limits_0^t P(\tau)\Gamma(t,\tau)d\tau\right), \\ 2\pi\int\limits_0^{a_{low}(t)}\frac{r^2-a_{low}(t)^2}{2R_{cell}h-r^2}rdr=-\frac{1}{E(t)}\left(P(t)+\int\limits_0^t P(\tau)\Gamma(t,\tau)d\tau\right). \end{cases} \quad (14)$$

Computing integrals on left sides of both equations (14), one can obtain:

$$\begin{cases} a_{up}(t)^2+(2R_{cell}h-a_{up}(t)^2)\ln\left|1-\frac{a_{up}(t)^2}{2R_{cell}h}\right|=\frac{R_{st}}{E(t)\pi(R_{st}+R_{cell})}\left(P(t)+\int\limits_0^t P(\tau)\Gamma(t,\tau)d\tau\right), \\ a_{low}(t)^2+(2R_{cell}h-a_{low}(t)^2)\ln\left|1-\frac{a_{low}(t)^2}{2R_{cell}h}\right|=\frac{1}{E(t)\pi}\left(P(t)+\int\limits_0^t P(\tau)\Gamma(t,\tau)d\tau\right). \end{cases} \quad (15)$$

Scheme of numerical depth determination is the following: assign the indentation time t; solve numerically nonlinear equations (15) and determine $a_{up}(t)$, $a_{low}(t)$; calculate the magnitudes of $\delta_{up}(t)$, $\delta_{low}(t)$ by equations (13) and the sum $\delta_{up}(t)+\delta_{low}(t)$.

CONCLUSIONS

The model of cell rheological parameters determination is proposed. It is assumed that shapes of cell and indenter are known, which allows to get stats for creep kernel of normal cell and to diagnose systematic disease based on stats aberration. The Winkler model generalization is extended to the case of hereditary creep of a coating of an arbitrary shape. The model of viscoelastic homogeneously aging material and the model of aging material possessing properties of nonlinear creep are considered

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