Gravitational settling of a cell on a high-aspect-ratio nanostructured substrate – An asymptotic modeling approach

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\section{Abstract}

The problem of contact deformation of an elastic body loaded by gravitational forces and laying on several small rigid supports is considered in the framework of the linear theory of elasticity. Using the method of matched asymptotic expansions, the limit asymptotic model for determining the support reactions and the kinematic parameters of the body settling is derived. The effect of the body surface reinforcement is discussed. The case of a uniform (symmetric) settling is considered in detail.

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\section{1. Introduction}

High-aspect-ratio nanostructured substrates made of nanopillars have become useful tools in bioengineering for sensing the intracellular environment of living cells \cite{1}. Recently, high-aspect-ratio nanostructured surfaces have been introduced \cite{2} as biological metamaterials, by highlighting aspects of cross-field importance that stem from the structure.

A gravitational seeding is one of techniques used to interface nanostructured substrates with cells. It is important to note that an additional loading can be provided by centrifugation \cite{3,4}, though a careful optimization of the interfaces parameters is needed \cite{5}. Notwithstanding the fact that the centrifugal loading can be regarded as a less broadly occurring scenario of cell loading, it is still very relevant, as centrifugation allows to control the gravitational force acting on the cell to the level comparable to that of adhesion forces. It is of interest to note that by reverting the direction of the nanopillars, the super-gravitational force can be set to act in the direction opposite to the adhesion forces, which are operating across the contact interface between the cell membrane and the nanostructured surface.

In recent years, a number of theoretical studies have attempted to develop a mechanistic understanding of the problem of cell settling on a high-aspect-ratio nanostructured substrate (see Fig. 1), mostly concentrating on the cell-nanostructure interface \cite{2}. The majority of the existing models \cite{6} primarily focus on the contact deformation of the cell membrane, usually treated as an elastic membrane. However, as it was highlighted \cite{2}, the cell membrane may not be the only barrier

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to penetration of nanostructures into the cell, and cytoskeletal proteins can contribute to the deformation response of the cell on a nanostructured substrate. The nanostructure geometry and the cell stiffness are shown to be critically important parameters governing the adhesion-mediated penetration of nanostructures into the cell’s interior [7].

In the present study, we formulate the problem of cell settling from a general point of view in the continuum mechanics framework and apply an asymptotic modeling approach [8]. In this way, the issue of the cell-nanostructure interaction has appeared as a contact problem of boundary-layer type for the inner asymptotic representations. A characteristic feature of the solutions to the corresponding boundary-layer problem, which is formulated in a half-space domain [9], is a polynomial decay at infinity (in contrast to the boundary-layer phenomena in thin elastic structures [10] and composite materials [11]).

It is to underline that here we develop a formal asymptotic analysis, and its justification (that is proving an a priori estimate of the discrepancy left by the asymptotic solution in the problem equations) falls outside the scope of this study. The issues of solvability of the Signorini problem of unilateral frictionless contact [12,13] and regularity of its solutions [14] are not highlighted below, since the asymptotic solution is presented in explicit form. It is to note that the established regularity properties for the displacement and stress-strain fields in the Signorini problem are in accord with physical intuition (in particular, under practically reasonable assumptions on regularity of the domain occupied by the elastic body, the stresses are continuous up to the boundary).

It should be emphasized that the results of the asymptotic analysis of the original model of multiple unilateral contact are formulated in the form of a new mathematical model, which is much simpler than the original one, since it is formulated in the Euclidean space $\mathbb{R}^N$, where $N$ is the number of supports (see Fig. 1). This resulting algebraic problem is called an asymptotic model. The solvability of such algebraic models of multiple unilateral contact has been proved in [15,16]. In view of the approximate nature of the developed mathematical modeling framework, which is based on the linear elasticity, we aim at constructing not only the leading order asymptotics, but also at deriving simple estimates in explicit closed form for the contact reaction forces, while still maintaining a reasonable compromise between mathematical rigorosity and mechanobiological applicability.

We recall [2] that the spacing, geometry (including the height, tip-width, and the base-width of individual nanostructures), and uniformity are main design parameters of high-aspect-ratio nanostructured substrates. To model the shape of individual nanostructures (henceforth called nanopillars or simply pillars), we develop a simple two-parameter description, which encompasses a wide range of axisymmetric geometries, including the cases of sharp conical and blunt cylindrical forms.

It is to emphasize that the problem of gravitational settling of a cell on a high-aspect-ratio nanostructured substrate is exceedingly difficult for a realistic mathematical modeling, as many biophysical phenomena should be considered. That is why, we employ a hierarchical modeling approach by introducing a basic model of an elastic body laying on several small rigid supports and being loaded by gravitational forces. The effects of the body surface reinforcement and adhesion are then discussed from the point of view of modifications needed to improve the basic model. Whereas it is well known [17] that for living cells interfacial phenomena are dominant upon external effects due to gravity or inertia, it should be taken into account that in experiments on gravitational settling of cells the gravitational loading can be controlled by means of centrifugation in a wide range, and therefore, it makes sense to investigate the basic model independently by abstracting from the interfacial phenomena.

2. Problem formulation

2.1. Geometry of nanostructured substrate

Let $h$ and $r_e$ denote the height and radius of nanopillars. By introducing a dimensionless small parameter $\varepsilon$, we put

$$r_e = \varepsilon r_1,$$

where $r_1$ does not depend on $\varepsilon$. Without loss of generality, we may assume that $r_1 = h/2$. Then the aspect ratio of nanopillars, which is defined as the ratio of the nanopillar height $h$ to the nanopillar diameter $2r_e$, will be equal to $1 : \varepsilon$. In other
words, we introduce the parameter \( \varepsilon \) as the ratio \( 2r_{\varepsilon}/h \). We note \cite{2} that the term “high-aspect-ratio” is typically applied to nanostructured surfaces with an aspect ratio about 10 : 1 or greater.

To describe a wide range of high-aspect-ratio nanostructures, we consider a monomial shape function \( \Phi(r) = B r^\beta \), where \( r \) is the polar radius (see Fig. 2a). It is worth noting here that the monomial function \( r \mapsto B r^\beta \) is characterized by two parameters, one of which \( B \) has a dimension of \( L^{1-\beta} \), where \( L \) is the dimension of length, and the other one (exponent \( \beta \)) is dimensionless.

By reinforcing the aspect ratio condition, we will require that
\[
h = B r_{\varepsilon}^\beta,
\]
so that the nanopillar shape function becomes
\[
\Phi_{\varepsilon}(r) = h \left( \frac{r}{r_{\varepsilon}} \right)^\beta.
\]

Observe that by varying the value of the shape parameter \( \beta \) from 1 to infinity, the shape of the nanopillars will change from a conical shape (\( \beta = 1 \)) with the half-apex angle \( \theta_{\varepsilon} = \arctan r_{\varepsilon}/h \) (see Fig. 2b) to a cylindrical one (\( \beta = \infty \)) with the diameter \( 2r_{\varepsilon} \) (see Fig. 2d). When \( \beta = 2 \), the intermediate case of a paraboloidal shape (see Fig. 2c) with the tip radius of curvature \( R_{\varepsilon} = r_{\varepsilon}^2/(2h) \) is of special interest, as it is described by the Hertzian theory of local contact.

The in-plane location of nanopillars will be characterized by Cartesian coordinates \((x_1^j, x_2^j)\) of their centers, which will be denoted by \( P^j \) (\( j = 1, 2, \ldots, N \)). The apex of the \( j \)-th nanopillar will be denoted as \( P^j \), so that \( P^j \) is the projection of the point \( P^j \) onto the support plane \( x_3 = 0 \). The distance between two points \( P^j \) and \( P^k \) will be denoted by \( d_{jk} \). Namely, we have
\[
d_{jk} = \sqrt{(x_1^j - x_1^k)^2 + (x_2^j - x_2^k)^2}.
\]
The minimum distance \( d_{jk} \), when \( k \neq j \), defines the spacing between the nanopillars and will be denoted by \( d \), that is \( d = \min_{k \neq j} d_{jk} \). It is to note that this definition, strictly speaking, applies to the case of periodic location of nanopillars. By the construction, we have \( 2r_{\varepsilon} \leq d \), where the sign equality takes the place in the case of close packing of nanopillars.

Thus, by a suitable choice of the coordinate planes of the coordinate system \( O x_1 x_2 x_3 \), the surface of the nanostructured substrate can be described by the set of equations
\[
x_3 = -\Phi_{\varepsilon} \left( \sqrt{(x_1 - x_1^j)^2 + (x_2 - x_2^j)^2} \right), \quad j = 1, 2, \ldots, N,
\]
where each of equations above is applied locally.

To this end, the problem includes two dimensionless parameters \( \varepsilon \) and \( \beta \), and two main geometrical parameters \( h \) and \( d \) that have dimension of length.

2.2. Geometry and deformation of a cell

We assume that a cell in the undeformed state occupies a three-dimensional domain \( \Omega \) with the boundary \( \partial \Omega \) composed of two parts \( \Gamma_{\sigma} \) and \( \Gamma_{\varepsilon} \), such that \( \partial \Omega = \Gamma_{\sigma} \cup \Gamma_{\varepsilon} \) (see Fig. 3). To fix our ideas, we assume that \( \Gamma_{\varepsilon} \) is a plane surface (located in the plane \( x_3 = 0 \)), which may come into contact with the substrate. The surface \( \Gamma_{\sigma} \) is supposed to be free of stress.

The interior of the cell will be modeled in a simplified way by assuming that the cell contains a homogeneous isotropic nucleus \( \omega_0 \) (with Lamé parameters \( \lambda_0 \) and \( \mu_0 \)), whereas the cell medium \( \Omega_0 \) outside the nucleus \( \omega_0 \) is made of another homogeneous and isotropic material (with Lamé parameters \( \lambda \) and \( \mu \)).
The cell is supposed to be loaded by gravitational body forces with the vector densities
\[ \mathbf{f} = -\rho \mathbf{g} e_3, \quad \mathbf{f}^0 = -\rho_0 \mathbf{g} e_3, \]  
where \( \rho \) and \( \rho_0 \) are the mass densities of the bodies \( \Omega_0 \) and \( \omega_0 \), respectively, \( \mathbf{g} \) is the gravitational acceleration, and \( e_3 \) is the basis vector.

Let \( \mathbf{u}(\mathbf{x}) \) denote the vector of displacements of points belonging to both \( \Omega_0 \) and \( \omega_0 \). In the framework of the linear elasticity, they satisfy the Lamé equations
\[ -\mu \nabla_x \cdot \nabla_x \mathbf{u}(\mathbf{x}) - (\lambda + \mu) \nabla_x \nabla_x \cdot \mathbf{u}(\mathbf{x}) = \mathbf{f}, \quad \mathbf{x} \in \Omega_0, \]  
\[ -\mu_0 \nabla_x \cdot \nabla_x \mathbf{u}(\mathbf{x}) - (\lambda_0 + \mu_0) \nabla_x \nabla_x \cdot \mathbf{u}(\mathbf{x}) = \mathbf{f}^0, \quad \mathbf{x} \in \omega_0, \]  
where \( \nabla_x \) is the gradient operator, and the scalar product is denoted by a dot.

On the boundary \( \partial \omega_0 \) of the nucleus, we impose the boundary conditions of ideal contact. Namely, the vector-function \( \mathbf{u}(\mathbf{x}) \) is assumed to be continuous as well as the normal stress-vector across the contact interface, that is
\[ \mathbf{\sigma}^{(n)}(\mathbf{u}; \mathbf{x}) = \mathbf{\sigma}^{(0(n))}(\mathbf{u}; \mathbf{x}), \quad \mathbf{x} \in \partial \omega_0. \]  
Here, \( \mathbf{\sigma}^{(n)} \) and \( \mathbf{\sigma}^{(0(n))} \) are the stress vectors acting on the interface from inside of \( \Omega_0 \) and \( \omega_0 \), respectively.

The stress-free boundary conditions on the upper surface of the cell are expressed in the usual form as
\[ \mathbf{\sigma}^{(n)}(\mathbf{u}; \mathbf{x}) = 0, \quad \mathbf{x} \in \Gamma_\sigma. \]  

On the bottom surface \( \Gamma_c \) of the cell \( \Omega = \Omega_0 \cup \omega_0 \) we impose the boundary conditions of frictionless unilateral contact. Since the surface \( \Gamma_c \) is assumed to be plane, which is normal to the coordinate axis \( O x_3 \), the absence of friction implies that
\[ \sigma_{31}(\mathbf{u}; \mathbf{x}) = \sigma_{32}(\mathbf{u}; \mathbf{x}) = 0, \quad \mathbf{x} \in \Gamma_c. \]  

In the undeformed state (see Fig. 4), the gap, \( g_n(x_1, x_2) \), between the surface \( \Gamma_c \) and the substrate surface that is measured along the normal to \( \Gamma_c \), according to Eq. (4), is given by
\[ g_n(x_1, x_2) = \Phi_n(x_1 - x_1^{(j)})^2 + (x_2 - x_2^{(j)})^2), \quad j = 1, 2, \ldots, N, \]  
where each of equations above is applied locally.
Then, the Signorini boundary conditions can be written as follows:

\[
\sigma_{33}(\mathbf{u}; \mathbf{x}) \leq 0, \quad u_3(x_1, x_2) + g_n(x_1, x_2) \geq 0, \quad \sigma_{33}(\mathbf{u}; \mathbf{x})[u_3(x_1, x_2) + g_n(x_1, x_2)] = 0, \quad \mathbf{x} \in \Gamma_c. \tag{12}
\]

The third relation in (12) implies that either \( \sigma_{33}(\mathbf{u}; x_1, x_2, 0) = 0 \) or \( u_3(x_1, x_2, 0) = -g_n(x_1, x_2) \) at each point \((x_1, x_2, 0)\) of the surface \( \Gamma_c \). The latter equation determines the multiple contact zone, \( \Gamma_c \), which is composed of contact spots \( \Gamma_{c1}^i, \Gamma_{c2}^i, \ldots, \Gamma_{cN}^i \) established by individual pillars. We note that some of the contact spots \( \Gamma_{ci}^i \), regarded as subsets of the two-dimensional space, may be empty, since \textit{a priori} the contact can be established at a part of the pillars that potentially can come into contact with the cell surface \( \Gamma_c \).

Let \( P \) denote the convex hull of the set of points \( P^1, P^2, \ldots, P^N \), which is defined as the intersection of all closed half-planes containing these points. It can be shown [12] that the necessary condition for the existence of the solution to the problem (6)–(12) is that the central axis of the applied system of external forces (5) intersects the polygon \( P \) at an internal point. At the same time, the solution is uniquely determined up to a tangential rigid body displacement, since the boundary conditions of frictionless contact (10) do not prevent any sliding of the elastic cell in the tangential directions.

In the majority of mathematical studies (see, e.g., [18,19]), the problem formulation usually includes a homogeneous or nonhomogeneous Dirichlet boundary condition, which assumes that a part of the boundary is clamped or is displaced in a specified way, thereby providing a sufficient condition of uniqueness of the solution. In the case of a cell, such situation can occur when the cell is fixed or manipulated by means of micro-pipette aspiration technique [20,21]. We note that the corresponding frictionless contact problem for an elastic half-space has been solved [22] using a combination of regular and singular asymptotic expansions methods.

3. Asymptotic constructions

3.1. Outer asymptotic representation

Following [15], we apply the method of matched asymptotic expansions [23,24] and consider the limit problem as \( \varepsilon \) tends to zero, when the substrate pillars degenerate into infinitely thin needles and the boundary conditions (12) imply

\[
\sigma_{33}(\mathbf{v}; \mathbf{x}) = 0, \quad \mathbf{x} \in \Gamma_c \setminus \bigcup_{j=1}^{N} P^j. \tag{13}
\]

assuming that concentrated reaction forces may be applied at the points \( P^1, P^2, \ldots, P^N \). We recall that the method of matched asymptotic expansions in application to the singularly perturbed boundary-value problem under consideration assumes that we construct different asymptotic approximations for the sought-for solution, namely, the inner asymptotic representations near the contact spots \( \Gamma_{1i}^i, \Gamma_{2i}^i, \ldots, \Gamma_{Ni}^i \), and the outer asymptotic representation far from the points \( P^1, P^2, \ldots, P^N \), to which the contact spots shrink as \( \varepsilon \) tends to zero. (We emphasize that the boundary conditions (13) apply to the outer asymptotic representation only, which is not supposed to be used in small vicinities of the pillar apexes \( P^1, P^2, \ldots, P^N \).) It is assumed that these two approximations can be matched in the leading terms in some intermediate regions, where both of them are supposed to work. For an observer put on one of the pillar apexes \( P^1, P^2, \ldots, P^N \), the outer and inner asymptotic representations for the displacement vector field can be termed as far field and near field, respectively.

The limit displacement vector \( \mathbf{v}(\mathbf{x}) \), of course, should satisfy Eqs. (6)–(10), which do not depend on the parameter \( \varepsilon \). To describe the vector-function \( \mathbf{v}(\mathbf{x}) \), we introduce the generalized Green’s function with a singularity at the point \( P^i \), which is characterized by the solution of the Boussinesq problem of the action of a unit normal point force on the surface of an elastic half-space, that is

\[
\mathbf{G}^i(\mathbf{x}) = \mathbf{T}(\mathbf{x} - P^i) + O(1), \quad \mathbf{x} \to P^i. \tag{14}
\]

The Boussinesq solution \( \mathbf{T}(\mathbf{x}) \) is given by the following formulas (see, e.g., [25]):

\[
T_i(\mathbf{x}) = \frac{1}{4\pi \mu} \left( \frac{x_i x_3}{|\mathbf{x}|^3} - \frac{\lambda + 2 \mu}{2 \mu} \frac{x_i}{|\mathbf{x}|^2} \right), \quad i = 1, 2, \quad T_3(\mathbf{x}) = \frac{1}{4\pi \mu} \left( \frac{x_3^2}{|\mathbf{x}|^3} - \frac{\lambda + 2 \mu}{2 \mu} \frac{1}{|\mathbf{x}|^2} \right). \tag{15}
\]

By the definition, the vector-function \( \mathbf{G}^i(\mathbf{x}) \) satisfies the stress-free boundary conditions on the entire boundary \( \partial \Omega \), except for the point \( P^i \). This means that the unit surface concentrated force \( \delta(x_i - x_i^f) \delta(x_j - x_j^f) \mathbf{e}_j \) applied at the point \( P^i \) should be balanced by some body forces, \( -\mathbf{A}^i - \mathbf{B}^i \times \mathbf{x} \), which are distributed over the domain \( \Omega \). (Here, \( \delta(x) \) denotes Dirac’s delta function.) The components of the constant vectors \( \mathbf{A}^i \) and \( \mathbf{B}^i \) are uniquely determined from the system of six equations of equilibrium. Moreover, since the vector-function \( \mathbf{G}^i(\mathbf{x}) \) can be determined up to a rigid body displacement, we require that

\[
\iint_{\Omega} \mathbf{G}^i(\mathbf{x}) \, d\mathbf{x} = \mathbf{0}, \quad \iint_{\Omega} \mathbf{x} \times \mathbf{G}^i(\mathbf{x}) \, d\mathbf{x} = \mathbf{0}. \tag{16}
\]

Observe that the generalized Green’s function is defined using the linear body force field \( -\mathbf{A}^i - \mathbf{B}^i \times \mathbf{x} \), whereas the outer asymptotic representation \( \mathbf{v}(\mathbf{x}) \) is supposed to satisfy Eqs. (6) and (7) with a piecewise-uniform distribution of the gravitational body forces. That is why, we consider an auxiliary solution \( \mathbf{v}^0(\mathbf{x}) \) that satisfies the stress-free boundary conditions on
the entire cell boundary \( \partial \Omega \) and the Lamé Eqs. (6) and (7) with the right-hand sides \( f - A^0 - B^0 \times x \) and \( f^0 - A^0 - B^0 \times x \), respectively. In other words, the vector-function \( \mathbf{v}^0(\mathbf{x}) \) is designed to eliminate the discrepancy produced by the linear combination of the singular solutions \( \sum_{j=1}^{N} Q_j \mathbf{g}^j(\mathbf{x}) \) upon its substitution into Eqs. (6) and (7), and therefore, the construction of \( \mathbf{v}^0(\mathbf{x}) \) depends on the definition of the singular solutions \( \mathbf{g}^1(\mathbf{x}), \mathbf{g}^2(\mathbf{x}), \ldots, \mathbf{g}^N(\mathbf{x}) \). The constants vectors \( A^0 \) and \( B^0 \) are uniquely determined from the equilibrium equations written for the entire cell \( \Omega = \Omega_0 \cup \omega_0 \). Also, the vector-function \( \mathbf{v}^0(\mathbf{x}) \) satisfies the normalization conditions similar to Eq. (16).

Thus, the outer asymptotic representation for the displacement field \( \mathbf{u}(\mathbf{x}) \) in the cell can be expressed in the form

\[
\mathbf{v}(\mathbf{x}) = e^{-\nu_1}(a^0 + b^0 \times x) + \mathbf{v}^0(\mathbf{x}) + \sum_{j=1}^{N} Q_j \mathbf{g}^j(\mathbf{x}),
\]

where \( \nu_1 \) is a scaling parameter, \( a^0 \) and \( b^0 \) are constants vectors describing a rigid body displacement. Due to the normalization conditions we have \( a_0^0 = a_0^0 = 0 \) and \( b_0^2 = 0 \).

Observe that the vector-function \( \mathbf{v}(\mathbf{x}) \) satisfies exactly Eqs. (6)-(10), provided the reaction forces \( Q_j, j = 1, 2, \ldots, N \), satisfy the equilibrium equations

\[
Q_1 + \ldots + Q_N = Q.
\]

(18)

\[
x_j^0 Q_1 + \ldots + x_j^0 Q_N = x_j^0 Q, \quad \alpha = 1, 2.
\]

(19)

The total weight of the cell \( Q \) is evaluated as follows:

\[
Q = g_0 |\Omega_0| + g_0 |\omega_0|.
\]

(20)

Here, \( |\Omega_0| \) and \( |\omega_0| \) are the volumes of the domains \( \Omega_0 \) and \( \omega_0 \), respectively.

Also, we have introduced the notation

\[
x_j^0 = \frac{1}{Q} \left( g_0 \int_{\Omega_0} x_j^0 \, d\mathbf{x} + g_0 \int_{\omega_0} x_j^0 \, d\mathbf{x} \right), \quad \alpha = 1, 2.
\]

(21)

We recall that it was assumed that the point of loading \((x_0^0, x_2^0)\) belongs to the interior of the convex hull \( P \) of the support points \( P^1, P^2, \ldots, P^N \).

Finally, the first term on the right-hand side of Eq. (17), which represents a rigid body displacement, remains undetermined to this point.

3.2. Inner asymptotic representations

We consider an arbitrary pillar with the number \( j \) and introduce the so-called stretched coordinates

\[
\xi^j = e^{-\nu_2}(x - P^j),
\]

(22)

where \( \nu_2 \) is a positive scaling parameter.

Then, according to Eqs. (1), (3), and (11), we evaluate the local gap function as follows:

\[
g_n = e^{\beta(\nu_2-1)} \Phi_1(\rho^j).
\]

(23)

Here, \( \rho^j = \sqrt{\xi_1^j + (\xi_2^j)^2} \) is the stretched polar radial coordinate, and we have introduced the notation

\[
\Phi_1(\rho) = h\left(\frac{\rho}{\rho_1}\right)^\beta.
\]

(24)

In complement to the outer asymptotic representation \( \mathbf{v}(\mathbf{x}) \), the inner asymptotic representation for the displacement field \( \mathbf{u}(\mathbf{x}) \) in a small vicinity of the contact spot \( \Gamma_{j}^3 \), in view of (23), will be sought for in the form

\[
\mathbf{w}^j(\xi^j) = e^{\beta(\nu_2-1)} \mathbf{w}^j(\xi^j) + e^{-\nu_3}(a^j + b^j \times \xi^j),
\]

(25)

where the vector-function \( \mathbf{w}^j(\xi^j) \) vanishes as \( |\xi^j| \rightarrow \infty \), and the scaling parameter \( \nu_3 \) is to be determined upon asymptotic matching considerations.

Moreover, due to Eqs. (6), (10) and the Signorini boundary conditions (12), the vector-function \( \mathbf{w}^j(\xi) \) satisfies the relations

\[
\mu \nabla_{\xi} \cdot \nabla_{\xi} \mathbf{w}^j(\xi) + (\lambda + \mu) \nabla_{\xi} \nabla_{\xi} \cdot \mathbf{w}^j(\xi) = 0, \quad \xi \in \mathbb{R}^3_+,
\]

(26)

\[
\sigma_{31}(\mathbf{w}^j; \xi) = \sigma_{32}(\mathbf{w}^j; \xi) = 0, \quad \xi_3 = 0.
\]

(27)

\[
\sigma_{33}(\mathbf{w}^j; \xi) \leq 0, \quad w_j^3(\xi) + e^{\beta(\nu_2-1)} \Phi_1(\rho) \geq 0, \quad \sigma_{33}(\mathbf{w}^j; \xi) \left[ w_j^3(\xi) + e^{\beta(\nu_2-1)} \Phi_1(\rho) \right] = 0, \quad \xi_3 = 0.
\]

(28)
where \( w_j^i(\xi) \) is the normal component of the vector-function \( \mathbf{w}^i(\xi) \), which is given by (25).

The parameters of the inner asymptotic approximation (25) are determined by matching the inner and outer asymptotics. According to the asymptotic relation (14), formulas (17) and (22) yield

\[
\mathbf{v}(\mathbf{x}) = e^{-\nu_1}(a_1^0 + \mathbf{b}^0 \times \mathbf{x}^l) + \mathbf{v}^f(\mathbf{P}^f) + \sum_{k \neq j} Q_k G^k(\mathbf{P}^f) + e^{-\nu_1} Q_j T(\xi^j) + \ldots.
\]

where the point of observation \( \mathbf{x} \) on the left-hand side is supposed to belong to a small vicinity of the point \( \mathbf{P}^f \), \( g^j(\mathbf{x}) = G^j(\mathbf{x}) - T(\mathbf{P}^f) \) is the regular part of the generalized Green’s vector-function, \( \mathbf{x}^l = (x_1^l, x_2^l, 0) \), and the three dots indicate terms which are neglected in the construction of the first-order asymptotic model. It is to note that though both \( G^j(\mathbf{x}) \) and \( T(\mathbf{x} - \mathbf{P}^f) \) are singular at the point \( \mathbf{P}^f \) (see formulas (15)), we have \( g^j(\mathbf{P}^f) = \lim_{\mathbf{x} \to \mathbf{P}^f} G^j(\mathbf{x}) - T(\mathbf{x} - \mathbf{P}^f) \).

Observe that all terms on the right-hand side of Eq. (29), except the last one, are constant, and thus, they do not depend on the stretched local coordinates \( \xi^j = (\xi_1^j, \xi_2^j, \xi_3^j) \).

3.3. Matching of the asymptotic representations

First, we determine the scaling parameters \( \nu_1, \nu_2, \) and \( \nu_3 \). In view of Eq. (18), we may assume that \( Q_j = O(1) \) as \( \nu \to 0 \). Hence, by comparing the right-hand sides of Eqs. (25) and (29), and paying attention to the terms that decay as \( |\xi^j| \) tends to infinity, we obtain \( -\nu_2 = \beta(\nu_2 - 1) \), from where it follows that

\[
\nu_2 = \frac{\beta}{\beta + 1}.
\]

Second, by comparing the rigid body displacements on the right-hand sides of Eqs. (25) and (29), we find that \( \nu_1 = \nu_3 \) and \( b^j_1 = 0, j = 1, 2, \ldots, N \). Moreover, since the tangential rigid body displacement is disregarded in view of frictionless contact (see, Eq. (10)), the only nontrivial component of the vector \( \mathbf{a}^j \) is that along the vertical axis, that is \( \mathbf{a}^j = a^j_3 \mathbf{e}_3 \). (We note that the local distribution of the tangential displacements around the \( j \)th contact spot is determined (up to a tangential rigid-body displacement) by the first term on the right-hand side of Eq. (25).)

Observe that the construction of the inner asymptotic approximation (25) employs two terms, namely, the polynomially decaying term \( e^{\beta(\nu_2 - 1)} W^j(\xi^j) \), which solves the boundary-layer type contact problem, and the rigid body displacement \( e^{-\nu_3}(a^j_3 + b^j_1 \times \xi^j) \), which facilitates matching with the outer asymptotic representation. This construction is quite flexible, and one degree of freedom can be removed by balancing the asymptotic orders of these terms, as otherwise there would be no possibility to satisfy the Signorini boundary conditions (28) in the limit as \( \nu \to 0 \). Now, by equating the order of the terms on the right-hand side of Eq. (25), we obtain \( \beta(\nu_2 - 1) = -\nu_3 \), and thus, in view of (30), we arrive at the relation

\[
\nu_1 = \nu_2 = \nu_3 = \frac{\beta}{\beta + 1}.
\]

Interestingly (see Eqs. (30) and (31)), all scaling parameters are found to be equal, and they will be denoted by \( \nu \).

When considering again the inner asymptotic representation (25), we observe that, by construction, the first term \( e^{\beta(\nu_2 - 1)} W^j(\xi^j) \) vanishes as \( |\xi^j| \to \infty \). Therefore, namely, the second term \( e^{-\nu_3}(a_3^j + b_1^j \times \xi^j) \) should be matched with the constant terms from the asymptotic expansion on the right-hand side of relation (29). In this way, we readily get \( b^j_1 = 0 \), so that near each nanopillar (in the local coordinate system) the cell experiences predominantly vertical translational displacement, and the local rotations (if there are any) can be neglected in the leading asymptotic terms. Moreover, it is to note that the matching procedure also yields the constants \( a^j_3 \) and \( a^j_2 \), which determine local tangential displacements (disregarded in the case of frictionless contact).

Thus, by equating the second term on the right-hand side of Eq. (25) with the sum of the first four terms on the right-hand side of Eq. (29), we obtain

\[
a_3^j = a_3^0 + b_1^j x_2^j - b_2^j x_1^j + e^{\nu} \left\{ u_3^f(\mathbf{P}^f) + Q_j g_3^f(\mathbf{P}^f) + \sum_{k \neq j} Q_k G^k_3(\mathbf{P}^f) \right\},
\]

where the terms of the order \( e^{\nu} \) may be neglected when considering only the leading asymptotic terms.

Finally, in view of (31), from Eqs. (25) and (29), it follows that

\[
\mathbf{W}^j(\xi) = Q_j T(\xi^j) + o(|\xi^j|^{-1}), \quad |\xi^j| \to \infty.
\]

whereas, in view of (30) and (31), the Signorini boundary conditions (28) imply that

\[
\sigma_{33}(\mathbf{W}^j; \xi^j) \leq 0, \quad W_3^j(\xi^j) + a_3^j + \Phi_1(\rho) \geq 0, \quad \sigma_{33}(\mathbf{W}^j; \xi^j) \left[ W_3^j(\xi^j) + a_3^j + \Phi_1(\rho) \right] = 0, \quad \xi^j = 0.
\]

We underline that the resulting problem for the vector-function \( \mathbf{W}^j(\xi) \) (which is obtained by collecting relations (26), (27), (33), and (34)), does not depend on the parameter \( \epsilon \).
4. Asymptotic model

4.1. Solution of the resulting problem

The resulting problem (26), (27), (33), and (34) for the inner asymptotic representation can be reformulated as the contact problem for an elastic half-space (see Fig. 5a) by noting that in the case of monomial shape function (24), which can be rewritten as

\[ \Phi_1(\rho) = B_1 \rho^\beta, \quad B_1 = \frac{h}{r_1^\beta}, \]  

(35)

the Signorini boundary conditions (34) reduce to the mixed boundary conditions

\[ W^j(\xi_1, \xi_2, 0) = -a^j_3 - \Phi_1(\rho), \quad \rho \leq \alpha^j_1, \]  

(36)

\[ \sigma_{33}(W^j; \xi_1, \xi_2, 0) = 0, \quad \rho \geq \alpha^j_1, \]  

(37)

with a priori unknown radius \( \alpha^j_1 \) of the circular contact area.

According to the known solution [26], we readily get

\[ Q_j = E^* B_1^{2\beta \beta - 1} \frac{[\Gamma(\beta/2)]^2}{\Gamma(\beta)} (\alpha^j_1)^{\beta + 1}, \]

(38)

\[ -a^j_3 = B_1 \beta 2^{\beta - 2} \frac{[\Gamma(\beta/2)]^2}{\Gamma(\beta)} (\alpha^j_1)^{\beta}. \]

(39)

where \( E^* \) is the reduced elastic modulus.

By excluding \( \alpha^j_1 \) from Eqs. (38) and (39), we obtain

\[ -a^j_3 = B_1^{(1/\beta + 1)} \left( \frac{Q_j}{E^*} \right)^{\beta/(\beta + 1)} \left( \frac{1}{\Gamma(1+\beta)} \right) (1 + \beta)^{\beta/(\beta + 1)} \left( \frac{\Gamma(\beta/2)}{2\sqrt{\Gamma(\beta)}} \right)^{2/(\beta + 1)}, \]

(40)

where \( B_1 \) is given by the second formula (35).

Let \( J_1(Q_j) \) denote the right-hand side of Eq. (40). Then, the substitution of \( a^j_3 = -J_1(Q_j) \) into Eq. (32) yields

\[ J_1(Q_j) = -a^0_3 - b^0_2 x_1^j + b^0_2 x_1^j - E^{\beta/(\beta + 1)} \left\{ \psi_2^j(P^j) + Q_j g_2^j(P^j) + \sum_{k \neq j} Q_k G_2^j(P^j) \right\}. \]

(41)

In the limit as \( \varepsilon \to 0 \), Eq. (41) simplifies as

\[ J_1(Q_j) = -a^0_3 - b^0_2 x_1^j + b^0_2 x_1^j, \quad j = 1, 2, \ldots, N. \]

(42)

To this end, all parameters of the outer (17) and inner (25) asymptotic representations are expressed in terms of the reaction forces \( Q_1, Q_2, \ldots, Q_N \) and the kinematic parameters \( a^j_2, b^0_2, b^0_2 \) of the rigid body displacement. To determine these \( N + 3 \) parameters, we have three linear equilibrium Eqs. (18), (19) and \( N \) non-linear algebraic Eq. (42). However, by the construction, \( Q_j \geq 0 \) and, thus, \( J_1(Q_j) \geq 0 \) for any \( Q_j \geq 0 \). Therefore, the solution to Eqs. (41) or (42) exists only when their right-hand sides are non-negative.

Fig. 5. Schematics of the boundary-layer type: (a) Homogeneous material in vicinities of the supports; (b) Piecewise homogeneous material in vicinities of the supports.
Let \( F^{-1}_1(a_1) \) denote the inverse function to \( F_1(Q) \), such that the equations \( F_1(Q) = a_1 \) and \( Q = F^{-1}_1(a_1) \) hold true. Moreover, let \( |x|_+ = (x + |x|)/2 \) denote the positive part function. Then, by solving Eq. (42) for \( Q_j \) and substituting the result into Eqs. (18) and (19) we arrive at the system

\[
\begin{align*}
\sum_{j=1}^{N} F^{-1}_1([-a_0^j - b_{1j}^0 x_{1j}^0 + b_{2j}^0 x_{1j}^0]) &= Q, \\
\sum_{j=1}^{N} x_{1j}^0 F^{-1}_1([-a_0^j - b_{1j}^0 x_{1j}^0 + b_{2j}^0 x_{1j}^0]) &= x_{0j}^0 Q, \quad \alpha = 1, 2.
\end{align*}
\]

(43)

(44)

After solving Eqs. (43) and (44) for \( a_0^j, b_{1j}^0, \) and \( b_{2j}^0, \) the reaction forces can be evaluated from the equation

\[
Q_j = F^{-1}_1([-a_0^j - b_{1j}^0 x_{1j}^0 + b_{2j}^0 x_{1j}^0]).
\]

(45)

We note that, in view of Eq. (40), we have

\[
F^{-1}_1(a_1) = E^*B_1^{-1/\beta} c(\beta) a_1^{(\beta+1)/\beta},
\]

where \( c(\beta) \) is given by

\[
c(\beta) = \beta^{(\beta-1)/\beta} \frac{2\sqrt{\Gamma(\beta)}}{\Gamma(\beta/2)} 2^{2/\beta}.
\]

(47)

Finally, it is to note that \( c(\beta) \) is an increasing function, and \( c(1) = 2/\pi. \)

4.2. Refined asymptotic model

First of all, we rewrite the derived Eqs. (43) and (44) in terms of the physical parameters

\[
a_0^j = e^{-\beta/(\beta+1)} a_0^j, \quad b_{1j}^c = e^{-\beta/(\beta+1)} b_{1j}^0, \quad b_{2j}^c = e^{-\beta/(\beta+1)} b_{2j}^0, \quad \alpha = 1, 2.
\]

(48)

by taking into account the scaling factor \( e^{-\nu_1} \) introduced in formula (17).

Also, by collecting formulas (1), (2), and (35)_2, and noting that \( B_1 = e^\beta B \), we introduce the following function instead of (46):

\[
F^{-1}_1(a) = E^*B_1^{-1/\beta} c(\beta) a^{(\beta+1)/\beta}.
\]

(49)

Correspondingly, Eqs. (43) and (44) take the form

\[
\begin{align*}
\sum_{j=1}^{N} F^{-1}_1([-a_0^j - b_{1j}^c x_{1j}^0 + b_{2j}^c x_{1j}^0]) &= Q, \\
\sum_{j=1}^{N} x_{1j}^0 F^{-1}_1([-a_0^j - b_{1j}^c x_{1j}^0 + b_{2j}^c x_{1j}^0]) &= x_{0j}^0 Q, \quad \alpha = 1, 2.
\end{align*}
\]

(50)

(51)

We note that the parameter \( \epsilon \) is still kept in the notation in view of the relation

\[
B = \frac{h}{r_0^{\beta}}.
\]

(52)

By solving Eqs. (50) and (51) for the three kinematic parameters \( a_{0j}^c, b_{1j}^c, \) and \( b_{2j}^c, \) the substrate reaction forces can be determined by the formula

\[
Q_j = F^{-1}_1([-a_0^j - b_{1j}^c x_{1j}^0 + b_{2j}^c x_{1j}^0]).
\]

(53)

Equations (50), (51), and (53) constitute the so-called limit asymptotic model. The refined asymptotic model can be obtained from these equations by subtracting from \(-a_0^j - b_{1j}^c x_{1j}^0 + b_{2j}^c x_{1j}^0\) the sum \( \nu_2^j(P) + Q_j g_2^j(P) + \sum_{k\neq j} Q_k C_1^j(P) \) that accounts for the interaction between the contact spots and the global deformation of the cell.

4.3. Analysis of the symmetric settling

From a practical point of view, it is of interest to consider the case of settling without tilting, when \( b_{1j}^c = b_{2j}^c = 0 \) and Eqs. (50), (51) reduce to the single equation

\[
F^{-1}_1(-a_0^j) = \frac{Q}{N}.
\]

(54)

from where, in view of Eq. (53), it follows that \( Q_1 = Q_2 = \ldots = Q_N = Q/N. \)
By solving Eq. (54), we readily get

$$-\alpha_3^f = F \left( \frac{Q}{N} \right)$$

$$= B^{1/(\beta+1)} c(\beta)^{-\beta/(\beta+1)} \left( \frac{Q}{N E^*} \right)^{\beta/(\beta+1)}, \tag{55}$$

where $B$ and $c(\beta)$ are given by (52) and (47), respectively.

The substitution of (52) into Eq. (55) yields

$$-\frac{\alpha_3^f}{h} = \left( \frac{Q}{c(\beta) E^* N f r_c h} \right)^{\beta/(\beta+1)}, \tag{56}$$

where $Q/N$ is the average share of the total gravitational load carried by a single pillar.

Observe [7] that a net cell gravitational force is typically on the order of 10–100 pN. Thus, for a typical nanopillar radius of 50 nm, Fig. 6b shows a typical range of interest for the dimensionless quantity $Q/(E^* N f r_c h)$.

It is known [27] that the spatial dimensions of living cells are confined between 1–5μm (for bacteria) and 10–100μm (for plant and animal cells). Let $l$ denote the characteristic dimension (diameter) of a cell. Then, the net gravitational force, $Q$, can be estimated from above as $Q \lesssim (4π/3)(l/2)^3 \bar{\rho} g$, where $g = 9.8\text{m/s}^2$ is the Earth’s gravitational acceleration, and $\bar{\rho}$ is the averaged cell density, which, for the sake of a rough estimate, can be taken to be equal to that of water, that is $\bar{\rho} = 1.0 \times 10^3\text{kg/m}^3$. Hence, a rough upper bound for the maximal net gravitational force (achieved for a cell of spherical shape) is estimated to be 50N–0.5pN (for bacteria) and 5pN–5N (for plant and animal cells). It is to note that the actual weight of a cell, which in our model is evaluated according to formula (20), strongly depends on its shape. For instance, the human red blood cell, known to occupy the shape of a biconcave disk, has the mean volume of about 100fL, whereas the derived upper bound yields the value of 220fL for the average cell diameter taken to be 7.5μm, which is more than twice overestimated. Thus, the value of a few piconewtons is a quite realistic estimate of the net gravitational force of a cell for general considerations. It is also to note that for a cell immersed in fluid, according to Archimedes’ principle, the net gravitational force is defined by the cell’s buoyant mass (the mass of the cell minus the mass of the fluid it displaces).

Formula (56) shows both the effect of the aspect ratio of the substrate pillars $1: \varepsilon$ and also the effect of the pillar shape exponent $\beta$. It can be easily verified numerically (see Fig. 6b) that the factor $[c(\beta)]^{-\beta/(\beta+1)}$ is decreasing function of $\beta$. This means that for a fixed aspect ratio of the substrate pillars, the cell settling increases as $\beta$ decreases, that is as the pillars become sharper. On the other hand, for a given value of the shape parameter $\beta$, the relative cell settling is proportional to the $\beta/(\beta+1)$th exponent of the aspect ratio $1/\varepsilon$.

5. Discussion and conclusions

In this section, we consider some ways for generalizing the developed asymptotic model. Two main aspects that need to be highlighted are the effect of the cell membrane and the effect of adhesion.

5.1. Accounting for the cell membrane deformation

Observe that the cell Young’s modulus, as it is measured by nanoindentation, is about a few kPa [28]. At the same time, Young’s moduli of cell membrane are normally in the range of 10–200 MPa [7]. That is why, it is interesting to study the effect of the cell membrane deformation on the cell settling. While remaining in the framework of the linear theory of
elasticity, the cell membrane can be modeled as a relatively thin elastic coating of thickness $t_ε = εt_1$ (see Fig. 7). Provided the elastic modulus of the coating material does not depend on the parameter $ε$, the limit problem for the outer asymptotic representation will again be formulated in the domain $Ω = Ω_0 \cup ω_0$. In this way, however, the problem of boundary-layer type for the inner asymptotic representation is derived for a coated elastic half-space (see Fig. 5b). In the special case of cylindrical support pillars, when $β = \infty$, we have $ν = 1$, and the latter problem does not depend on the small parameter $ε$.

In the general case, when $β \in [1, +∞)$, the boundary-layer type problem contains the small parameter $ε^{1−ν}$ that characterizes the coating thickness in the stretched coordinates (see Fig. 5b), but this dependence can be kept in the asymptotic constructions by solving the unilateral contact problem for a two-layer elastic substrate [29]. This situation can be termed as the case of soft coating, since the tensile and bending coating stiffnesses diminish as $ε$ tends to zero. It is pertinent to note here that indentation problems for a two-layer elastic medium have been studied using analytical methods in a number of papers [30,31].

A special approach is needed in modeling the effect of stiff coating, which is the case for the cell membrane, when some singular dependence of the coating modulus on the parameter $ε$ is introduced in order to reinforce the effect of the coating deformation (see, e.g., [32–34]). It is also to note here that the effect of reinforcing elastic coating has been analyzed in several publications [33,35], including the use of asymptotic techniques [36–38].

5.2. Accounting for the cell membrane tension

It should be emphasized that the employed deformation model of a cell does not take into account the cell membrane tension. However, it is known [39,40] that the membrane tension and corresponding lateral stresses should be accounted for in atomic force microscopy (AFM) studies of living biological cells. The effect of surface tension can be incorporated into the model using the Gurtin–Murdoch surface elasticity theory [41] that treats the cell's membrane as a prestressed elastic layer of infinitesimal thickness, which is ideally adhered to the cell's bulk. Though this generalization lies outside the scope of the present study, we still can state that a similar asymptotic modeling approach will inevitably lead to the consideration of corresponding boundary-layer problems of unilateral contact for an elastic half-space with the surface tension. To date, the latter problem was considered only for special cases of cylindrical [42], paraboloidal [43–45] or conical [46] indenter.

The surface tension effect is governed by the so-called intrinsic material length, $s$, which is proportional to the ratio of the residual surface tension to the bulk reduced elastic modulus. Observe [45] that the range of large values of the ratio $a/s$ of the contact radius $a$ to the characteristic length $s$ corresponds to the Hertzian limit, where the results obtained above can be applied with a certain reliability for prediction of the contact reactions. On the contrary, in the so-called membrane limit when the ratio $a/s$ is small, the local contact reactions will be dominated by the surface tension effect.

5.3. Accounting for the adhesion effect

It should be emphasized that the effect of adhesion plays an important role in the cell-substrate interaction [7]. From a mechanical modeling point of view, sources of adhesion of living cells were discussed previously [40], and it has been argued that the concept of the work of adhesion [47] allows to unite all sources of adhesive interactions including van der Waals interactions and chemical (cohesive) forces. In applications to biological materials and tissues, the axisymmetric Johnson–Kendall–Roberts (JKR) model of adhesion contact [48] has shown its effectiveness in capturing the mechanisms of cell adhesion [49]. As it was shown [50], the JKR model can be reformulated in the linear fracture mechanics framework in terms of the stress-intensity factor (SIF) of the contact stress at the contour of the contact area. We recall that the SIF is proportional to the limit of the product of the stress and the square root distance to the contact contour. This means that the boundary condition of adhesive contact undergoes a rescaling transformation, when introducing the stretched coordinates (22), and thus, an additional analysis of the corresponding boundary-layer type problem will be required. In principle, the case of symmetric (uniform) settling can be approximately reduced to a model problem of adhesive contact with a single
support, when abstracting from the influence of the other supports. We note that the axisymmetric unilateral contact problems of the JKR type have been studied in a number of publications for an elastic half-space \cite{1,2,3} and a layered elastic medium \cite{4,5}.

Based on the analysis of the FEM solution \cite{6} for a bacterial cell (E. coli), it can be stated that the effect of the net cell weight on the deformation of the cell is negligible compared to the effect of adhesion of the cell membrane to the nanopillars. However, strictly speaking, the volume forces acting on a cell can be controlled in a wide range by means of centrifugation.

It is well known that even a supergravity environment can be induced by centrifugation. For example, in experiments with microfabricated nanoneedle arrays \cite{7} the relative centrifugal force was varied from 65 to 10,000 g-force, while the optimized force applied onto the cell membranes through nanoneedles was found in the range from 12.8g to 142g \cite{8}. Observe \cite{9,10} that in the depth-sensing indentation testing the contribution from the adhesion effect decreases with increasing the contact force. Hence, generally speaking, in the case of centrifugal loading, the effect of adhesion forces becomes less dominant, whereas the range of applicability of the asymptotic model, which is based on the linear elasticity theory, reduces as well. On the other hand, the incorporation of the adhesion effect into the basic model requires a separate detailed study that can be built on the present work.

5.4. Accounting for the friction effect

The assumption of frictionless contact can be relaxed as well. By imposing the boundary conditions of Coulomb's law, we introduce an additional dimensionless parameter into the analysis (coefficient of friction). In the absence of tangential (shifting) external forces (that is the case in gravitational settling when the substrate is positioned perpendicularly to the gravitational field), the system of tangential contact reactions will be self-equilibrated, and the global tangential rigid body tangential displacements of the elastic cell will be negligible in the leading asymptotic order. Correspondingly, the leading-order boundary layer problem for an elastic half-space will be axisymmetric, and its solution is known \cite{11}. The limit case of infinite coefficient of friction, which is known as the sticking (no-slip) contact \cite{12}, provides an upper estimate for the effect of friction. In the case of an incompressible elastic half-space, the friction effect on the axisymmetric contact vanishes.

Finally, it is pertinent to note here that the developed mathematical modeling framework does not account for forces actively generated by cells \cite{13}. In the case of high-aspect-ratio nanostructured substrates, such cell-generated forces exerted on the free ends of nanopillars cause nanopillar bending towards the cell's center. The corresponding boundary layer problem of tangential contact should include the effect of prestress on the cell membrane. The effect of friction in an adhesive tangential contact for a paraboloidal indenter was investigated \cite{14} in the Coulomb–Dugdale approximation, which accounts for long range adhesive interactions. Following the known argumentation \cite{15}, it appears that the presented mathematical modeling approach can be applied in the first place to smooth biological cells and, in particular, to red blood cells.

5.5. Conclusions

By treating the cell as an elastic body, we have developed an asymptotic modeling approach for the analysis of its gravitational settling on a high-aspect-ratio nanostructured substrate. As the main result, we arrived at the limit asymptotic model, which gives rise to a family of asymptotic models that allow to systematically account for several geometrical and physical effects, including the cell structure (nucleus, cytoplasm, and membrane) and the effect of adhesion at the cell-nanostructure interface. The derived simple mathematical model can be applied for the analysis of the balance between contributions from gravitational loading and the local cell deformation.

It should be remembered that the guiding idea behind mathematical modeling is that any mathematical model should not be applied outside the range of its applicability. To decide whether the developed simple model is applicable (at least for making rough estimates) or not, the researcher should decide in each case based on the whole body of information available at hand.

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