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Author for correspondence:
Feodor M. Borodich
e-mail: BorodichFM@cardiff.ac.uk

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Contact probing of prestressed adhesive membranes of living cells

Feodor M. Borodich[1], Boris A. Galanov[2], Leon M. Keer[3], and Maria M. Suarez-Alvarez[1]

[1]School of Engineering, Cardiff University, Cardiff, UK
[2]Institute for Problems in Materials Science, National Academy of Sciences of Ukraine, Kiev, Ukraine
[3]Department of Mechanical Engineering, Northwestern University, Evanston, IL, USA

Atomic force microscopy (AFM) studies of living biological cells is one of main experimental tools that enable quantitative measurements of deformation of the cells and extraction of information about their structural and mechanical properties. However, proper modelling of AFM probing and related adhesive contact problems are of crucial importance for interpretation of experimental data. The Johnson-Kendall-Roberts (JKR) theory of adhesive contact has been often used as a basis for modelling of various phenomena including cell-cell interactions. However, strictly speaking the original JKR theory is valid only for contact of isotropic linearly elastic spheres, while the cell membranes are often prestressed. For the first time, effects caused by molecular adhesion for living cells are analytically studied taking into account the mechanical properties of cell membranes whose stiffness depends on the level of the tensile prestress. Another important question is how one can extract the work of adhesion between the probe and the cell. An extended version of the Borodich-Galanov (BG) method for non-direct extraction of elastic and adhesive properties of contacted materials is proposed to apply to experiments of cell probing. Evidently, the proposed models of adhesive contact for cells with prestressed membranes do not cover all types of biological cells because the structure and properties of the cells may considerably vary. However, the obtained results can be applied to many types of smooth cells and can be used to describe initial stages of contact and various other processes when effects of adhesion are of crucial importance.

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1. Introduction

A quantitative understanding of the cell mechanical properties is of importance for various fields of medicine and biology. There are many tools for experimental studies of these properties [18,63,75]. These include such popular techniques as atomic force microscopy (AFM) and micropipette aspiration. If the former technique may be used for topographic imaging of surfaces, measurement of interactive forces, in the range down from microNewtons to nanoNewtons [49], estimation of material properties and manipulation of very small objects [51], the latter one is very specific for quantifying cell mechanics [64]. The contact mode AFM technique involves touching cells by mechanical probes. AFM elastic cantilevers with tips of various shapes, e.g. pyramidal, spherical, flat ended cylindrical (plateau), may be used (see, e.g. [63,70,74]). However, the tipless cantilevers are also used [5,76].

To interpret experimental data obtained by AFM indentation, one needs to employ both mechanical models of cells and contact theories. Various solutions to contact problems are employed to model interactions between the AFM tip and a cell membrane [74]. In particular, these include solutions for sphere (approximated as a paraboloid of revolution), derived by Hertz [39], and other non-adhesive contact problems. On the other hand, it is known that adhesion is important when the contacting bodies are sufficiently small or sufficiently compliant [67] and living cells satisfy often both conditions. Cell adhesion is of crucial importance for numerous physiological and pathological processes, including embryonic development, and cancer metastasis, as well as for numerous biotechnological applications [57]. Therefore, the models of adhesive contact such as the JKR (Johnson-Kendall-Roberts) [44] and DMT (Derjaguin-Muller-Toporov) [22] models, are also used to consider cell-indenter and cell-cell interactions. It is important to note that although the original JKR model was used for describing adhesion of two cells [20,52], strictly speaking the model in its original form is valid only for contact of isotropic linearly elastic spheres. Therefore, one has to modify the JKR theory to take into account some specific features of cell membranes and to model their contact properties.

Here we follow the approach used in mechanics of composite materials: a cell will be modelled as a sample made of a material with some effective properties. To consider the contact problems for cells, we assume that first the sample made of the effective non-linear material is prestressed and then it comes into contact with a probe or another cell; the stress field due to the contact is just a small perturbation of the large initial stresses; and the initial stress field can be considered as homogeneous. In our previous papers, it has been shown that the JKR theory for a spherical indenter can be extended to transversely isotropic [13] and prestressed materials [7]. Here we will apply our results to effective material of the cell. Following [21], the cell effective materials are described as materials of the neo-Hookean type, i.e. the Treloar potential is used.

Evidently, the present approach does not cover all types of biological cells because the structures and properties of biological cells may vary. Nevertheless the obtained results can be applied to many types of smooth cells, in particular to red blood cells (RBCs). The RBCs are often regarded as a 'model system' in the study of single living cells [21] and they have been extensively studied as a relatively simple example of biological cells. Thus, the problems under consideration cover the large variety of contact problems for biological cells such as (i) nanomanipulation of biological cells; (ii) probing of cell membranes by AFM; (iii) determination of the elastic modulus of biological materials and biological samples; and (iv) determination of the work of adhesion for two cells or a cell and an artificial material of a probe.

It is argued that the values of the effective contact modulus for two cells or between a cell and material of the probe and the work of adhesion for the same pairs may be quantified from a single test using a simple and robust BG method [8,12] or its extension [58]. The method is based on an inverse analysis of a stable region of the force-displacements curve obtained from the depth-sensing indentation of a sphere into an elastic sample. Of course, the results for the effective contact modulus depend on the employed model of non-linear elasticity. It is shown that if the cell membranes are described as materials of the neo-Hookean type, then the solutions may be given explicitly as a function of prestress of the membrane.

2. Specific features of cells and their mechanical models

There arise many questions related to modelling of cells, in particular the following ones. What are the sources of cell adhesion and how can it be quantified? Is a cell membrane incompressible two-dimensional (2D) or three-dimensional (3D) material? What contact models should be involved?

(a) Sources of adhesion of living cells

Adhesive interactions of cells are not a simple phenomenon. There are different opinions about the sources of cell adhesion. It is often argued that cell adhesion occurs from the action of complex proteins such as selectins, fibronectins, integrins, and cadherins. These proteins are called cell adhesion molecules or adhesins. It is often claimed that these molecules are sources of selective adhesion of cells, the so-called 'lock-and-key' model, and that the main determinants of adhesion energy at the cell contact are the adhesion molecules (see, e.g. [56]). Even if the cell–cell adhesion in soft biological materials may be caused by interactions among special proteins cadherins ("calcium-dependent adhesion"), the calculations showed that the van der Waals (vdW) interactions between cadherins could be the main physical mechanism for the measured adhesion [68]. Moreover, Kendall and his co-workers [49,50] provided arguments to state that in spite of enormous amount of work done by thousands of scientists to study the lock-and-key molecules, they are not the dominant mechanism of cell adhesion, while the key cause of adhesion are van der Waals forces. They demonstrated that effects from geometry, elasticity and surface molecules must all add on to the basic cell attractive force. The lock-and-key mechanism is important only if there are such molecules (adhesins) present on the cell membrane (their distribution is very specific and varies depending on the cell types) and their adhesive action depends not only on vdW, but also on chemical bonds.

We believe that an analogy between adhesion of living cells and polymer materials may be useful [53]. Studies of adhesion of polymer films showed the fundamental role of additional physical mechanism of adhesion of the films, namely the electrical forces. Derjaguin (Deryagin) and his co-workers [23] argued that in many cases electrical phenomena are the most important factor in determining the resistance of a film to detachment. The importance of this source of adhesion is also found in cell adhesion, in particular, it was found that electric double layer interactions play an important role in bacterial adhesion to surfaces, as adhesion has been shown to depend on ionic strength and pH of the suspending solution and on the surface potentials of bacteria and substrata [62] (see also [48] for details of the DLVO (Derjaguin, Landau, Verwey, Overbeek) theory and further aspects of adhesion phenomenon).

Actually, division of adhesion on phisiosorption and chemisorption is convenient but not very strict. Indeed, as it was noted by Derjaguin and his co-workers: "*from the viewpoint of quantum mechanics, the analysis of van der Waals forces and analysis of chemical bonding forces involve an examination of limiting cases of one and the same problem: the determination of the wave function and the calculation of energy for a complex multielectron system ... the question of where and when chemical forces begin to act, and when and in which compounds we must speak of a van der Waals bond between two molecules, does not have any significance in the strict sense*."

Thus, one can follow the opinion of researchers studied polymers (see, e.g. [53]): adhesion between macromolecular polymers has several different sources that include physisorption (van der Waals interactions), direct molecular bonding, i.e. creation of chemical bonds, and electrical forces including formation of an electric double layer. We can repeat here the prophetic words of Robert Hooke about sticky materials: [40] "*it is evident, that the Parts of the tenacious body, as I may so call it, do stick and adhere so closely together, that though drawn out into long and very slender Cylinders, yet they will not easily relinquish one another ... And this Congruity (that I may here a little* *further explain it) is both a Tenaceous and an Attractive power; for the Congruity, in the Vibrative motions, may be the cause of all kind of attraction, not only Electrical, but Magnetical also, and therefore it may be also of Tenacity and Glutinousness.*".

Surfaces of polymer solids may be considered as covered by hair-like brushes of macromolecules. Due to high flexibility of macromolecules, they are able to create easily very close contacts with many rough surfaces. The amount of energy of elastic deformation spent during bending of these macromolecules is very small. The adhesion of these 'brushes' may be caused by both van der Waals interactions and chemical bonding. Separation of the polymer solids involves the abrupt reduction of the adhesive force caused by van der Waals interactions between the bulk and further reduction of the force in a discrete manner due to separation of the macromolecules and the counterpart surface. Similarly to polymer brushes may be observed on living cells, e.g. cells with brush-layers consisting mainly of microvilli, microridges and cilia have been intensively studied by Sokolov and his co-workers (see, e.g. [42]), and discrete reduction of the adhesive force was observed on living cells [46].

Thus, we employ the concept of the work of adhesion w per a unit surface that is defined as *equal to the tensile force integrated through the distance necessary to pull the two surfaces completely apart* [38]. This concept is quite close to the concept of surface energy used by Griffith [36] who noted that "*in the formation of a crack in a body composed of molecules which attract one another, work must be done against the cohesive forces of the molecules on either side of the crack.*" However, the use of w enables us to unite all sources of adhesive interactions including vdW and chemical (cohesive) forces. Hence, we will study the load-displacement curves within the range of positive compressive forces without any further discussion on the physical or chemical nature of adhesive interactions between living cells. Because w is the characteristic of a pair of interacting materials, the AFM tip can be functionalized (see, e.g. [65]) in order to get the work of adhesion values of the seeking pair of materials.

(b) Adhesive and non-adhesive contact models for cell membranes

To model cell-probe interactions, results of solutions to non-adhesive Hertz-type contact problems [64] are often employed, in particular results for spheres [39], cones [33], and for arbitrary blunt indenters of revolution [34] (note that the results by Love and Galin are often attributed to Sneddon).

The non-adhesive Hertz-type contact problem formulation assumes that initially there is only one point of contact between the indenter tip and the half-space. Let the origin (O) of Cartesian x_1, x_2, x_3 coordinates be at the point of initial contact between the indenter and the elastic half-space $x_3 \geq 0$. The cylindrical coordinate frame r, z, ϕ, $r = \sqrt{x^2 + y^2}$, $z = x_3$ and $x_1 = r\cos\phi, x_2 = r\sin\phi$. Hence, the equation of the indenter whose shape is given by a function f, can be written as $x_3 = -f(x_1, x_2), \quad f \geq 0$. If the problem is axisymmetric then it does not depend on the coordinate ϕ and we can write $z = -f(r)$.

It follows from the Hertz contact theory [35,43] that the problem of contact between a rigid indenter (a punch) and an isotropic linear elastic half-space characterised by the Young's modulus E and the Poisson ratio ν depends on a contact modulus (reduced modulus) of the half-space E^*

$$E^* = \frac{E}{1-\nu^2}. \tag{2.1}$$

In turn, the problem of contact between two elastic bodies having contact moduli E_1^* and E_2^* respectively is mathematically equivalent to the problem of contact between an isotropic elastic half-space with contact modulus E_I^*

$$\frac{1}{E_I^*} = \frac{1}{E_1^*} + \frac{1}{E_1^*} \tag{2.2}$$

and a curved body whose shape function f is equal to the initial distance between the surfaces, i.e. $f = f_1 + f_2$, where f_1 and f_2 are the shape functions of the solids. Usually the AFM probes are much harder than the soft biological materials or living cells. If one of the solids is much harder than another one, i.e. $E_2^* >> E_1^*$ then one can put $E_2 = \infty$ and $E_I^* = E_1^*$.

For contact between two elastics spheres of radii R_1 and R_2 respectively, one gets the equivalent indenter as a sphere of radius R,

$$\frac{1}{R} = \frac{1}{R_1} + \frac{1}{R_2}. \tag{2.3}$$

For example, an RBC can be locally approximated as a sphere of radius $R_1 = 8\mu m$. If the shape of a sharp AFM tip near its nose is approximated as a sphere of radius $R_2 = 10$ nm, then the curvature of the cell may be neglected because the effective radius $R \cong 10$ nm. However, to apply a geometrically linear contact theory for this radius of the tip, the depth of indentation should be below 1 nm. If a tipless AFM probe is used then $R_2 = \infty$ and $R = R_1$. If an AFM tip has spherical shape of radius $R_2 = 8\mu m$ (see, e.g. [54]) then $R = R_1/2 = 4\mu m$. If an elastic sphere (a cell) of radius R_1 is rested on a hard flat surface and it is compressed by a spherical AFM tip of radius R_2 then the total approach of the AFM tip and the sphere δ can be found as a sum $\delta = \delta_1 + \delta_2$ where δ_1 and δ_2 can be found by solving contact problems for spheres of effective radii R_1 and $R_1R_2/(R_1 + R_2)$ respectively. The described contact configuration of a spherical particle resting on a rigid substrate has been recently discussed in detail [2].

If AFM is used in indentation mode then the depth-sensing indentation (DSI) approach is widely used, when the contact effective elastic modulus E^* is often estimated using the slope S of the $P - \delta$ curve at the unloading branch and the following BASh (Bulychev-Alekhin-Shorshorov) relation derived for the Hertz-type contact problems

$$S = \frac{dP}{d\delta} = 2E^*a \quad \text{or} \quad S = \frac{dP}{d\delta} = \frac{2\sqrt{A}}{\sqrt{\pi}}E^* \tag{2.4}$$

where P is the force (the load applied to a probe) and δ is the displacement or the approach of the distant points of the probe and the material surface, a is the contact radius, and A is the contact area (see for details [7]).

The above Hertz-type contact problems and corresponding analytical tools do not take adhesion between the sample and the indenter into account. However, due to adhesive effects these models should not be involved. On the other hand, the proper mathematical interpretation of DSI tests requires to take into account not only mechanical but also adhesive properties of contacting materials [7]. For an axisymmetric indenter whose shape is described by an arbitrary function f, it is possible to derive using the JKR theory that the slope of the $P - \delta$ curve is

$$\frac{dP}{d\delta} = 2E^*a\left\{\frac{\left[\int_0^a r\Delta f(r)(a^2 - r^2)^{-1/2}dr - 1.5\,(2\pi w/E^*)^{1/2}\,a^{-1/2}\right]}{\int_0^a r\Delta f(r)(a^2 - r^2)^{-1/2}dr - 0.5\,(2\pi w/E^*)^{1/2}\,a^{-1/2}}\right\}. \tag{2.5}$$

Here Δ is the Laplacian. Using the original JKR approach to mechanics of adhesive contact, one can show that for spherical probe of radius R, the above expression is reduced to

$$\frac{dP}{d\delta} = 2aE^*\left[\frac{1 - 3\sqrt{(\pi R^2 w)/(8E^*a^3)}}{1 - \sqrt{(\pi R^2 w)/(8E^*a^3)}}\right]. \tag{2.6}$$

The above expression may be written explicitly not as function of the contact radius but rather the force or the displacement [10]. Evidently, if one neglects adhesion, i.e. $w = 0$ then the above expression reduces to the classic BASh formula. Thus, the use of the original BASh formula may lead to wrong estimations of the contact modulus. The above adhesive corrections are especially important for sticky soft materials.

(c) Effective material approach to cell membranes

Living cells consist of cytoplasm surrounded by a membrane wall that comprises a double layer of phospholipids, the underlying spectrin network and transmembrane proteins; the membranes are commonly modelled as an incompressible effective material [21]. It is often argued that the RBC membrane may be easily deformed keeping the constant area [30,69], hence, it was suggested to model the membranes as a 2D incompressible material. On the other hand,it was stated that the RBC modelled as a nonlinearelastic membrane filled with an incompressible fluid [69]. In fact, the internal space of the cell is not just fluid, but a kind of a fibrous composite material containing some fibres specialised to withstand tension and the others specialised in withstanding compression, i.e. it has hierarchical molecular structure that is stabilized based on tensegrity principles [41]. Very simple geometrical estimations show that the assumption of 2D incompressible material in application to all cell membranes is not correct. Indeed, let the initial cell shape be spherical of diameter D (radius $R = D/2$) and the cell is fully filled by the fluid. After complete aspiration of the cell by a micropipette of the internal diameter d (radius $r = d/2$) the cell shape can be described as a cylinder of some length L and radius r having two semi-spherical caps of radius r. If one denotes the ratios $m = R/r$ and $n = L/r$ then the ratios of the initial volume V_i of a cell and its surface area A_i to the final values V_f and S_f of the volume and surface are respectively

$$V_i/V_f = m^3/(0.75n + 1), \quad A_i/A_f = m^2/(0.5n + 1). \tag{2.7}$$

In experiments on chondrocyte cells (see Fig. 4 in [45] that shows almost ideally spherical cell fully filled by the fluid), one can observe that $m \cong 1.48$ and $n \cong 2.96$. Hence, one has $V_i/V_f = 1.007$ and $A_i/A_f \cong 0.88$, i.e. while the volume of the cell after complete aspiration is approximately the same, the surface would increase over 13%. An assumption that the cell surface area is constant leads to the conclusion that $n = 2(m^2 + 1)$. If for instance, one takes $m = 3$ then it follows from (2.7) that $V_i/V_f \cong 2.08$, i.e. the volume would reduce more than twice. This is in disagreement with the assumption that the membrane contains an incompressible fluid.

Thus, further we will study contact problems for cells. It will be assumed that the cell shape may be locally described as a sphere of radius R_1 and it is in contact with a rigid indentor of radius R_2. Although it is known that the cell membrane rupture and deformations are time-dependent phenomena (see, e.g. [66]), we will not consider here the viscoelastic effects. Following [21], the effective properties of the cell are described as a non-linear elastic material of neo-Hookean type whose principal stretches satisfy the condition of incompressibility. Because the membrane is incompressible, its thickness may vary.

3. Contact probing of prestressed cells

An important factor that can affect a variety of cellular functions such as motility, cell division and endocytosis is plasma membrane tension and corresponding lateral stresses [18]. A simple equation can be used to describe atomically thin membranes under homogeneous lateral tension (see, e.g. [9]), however, a cell membrane is relatively thick and simple equations are not applicable. The equations for prestressed plasma membrane should follow from the description of effective material of the cell.

The above mentioned Hertz-type contact problems and the JKR and DMT theories are based on the geometrically linear formulations of boundary-value problems, while the cell prestress and other factors may cause large deformation of initial shape of a cell (see, e.g. [73]). The changes of cell shapes that lead to geometrically non-linear formulations are excluded from the consideration. If a cell membrane has initial large stretches, however its shape may be locally modelled as spherical, then the contact problem will be formulated as a contact problem for solids with initial stress (prestress) [3,4,6,24,32]. This means that a membrane with the initial stretches is considered as a solid, whose effective elastic properties depend on the level of the prestress, while the additional stresses caused by action of the probe are just a small perturbation of the initial stress field. These perturbations of the stress field and corresponding displacements will be studied in a linearized formulation.

The formulations of boundary value problems for prestressed elastic half-space or plate may be found elsewhere (see, e.g. [3,6,47]). Let us consider a homogeneous, incompressible, elastic membrane M which possesses a natural unstressed state M_u. Let us assume that the non-linear material of M is deformed and, therefore it has some preliminary tension (prestress). It is assumed that probing of the membrane by a spherical AFM tip causes only small perturbations of the prestressed membrane. We denote by M_d and M_p the finitely deformed and the perturbed configurations of the membrane respectively. Following [47], we denote by X_A; $x_i(X_A)$ and $\widetilde{x}_i(X_A)$ the position vectors of a representative particle of M, relative to a common Cartesian coordinate system coincident with the principal axes of the primary deformation in M_u, M_d and M_p, respectively. Then one can write

$$\widetilde{x}_i(X_A) = x_i(X_A) + u_i(x_j) \tag{3.1}$$

where $u_i(x_j)$ is the component of small perturbed displacement caused by contact between the probe and the membrane, i.e. $\mathbf{u}(x_j)$ in (3.1) is the vector of small superimposed displacements.

Even if the state M_u of the effective material is initially isotropic then the equations of linearized elasticity for the perturbed state M_p are anisotropic. For example, many biological materials demonstrate high deformability at relatively small stresses and hyperelastic samples of these materials may show highly nonlinear stress-strain curves leading to material hardening with increasing deformation (see, e.g. [26]). Hence, a sample of such materials subjected to uniaxial stretch is much stiffer in the stretch direction than in the non-stretched directions. If all quantities are referred to the area in M_d state then the components of the stress tensor of M_p state may be connected to strains (derivatives of $\mathbf{u}(x_j)$) using the fourth-order elasticity tensor B_{ijkl} [47]. Thus, the equations of linearized elasticity for the perturbed state M_p are similar to equations of linear anisotropic elasticity. However, the linearized elasticity is formally more complicated then the linear case. In the later case one can reduce the fourth-order elasticity tensor C_{ijkl} to just 21 independent components, in the former case the tensor B_{ijkl} has less symmetry of the indexes than C_{ijkl} [37].

It was suggested to employ various models of effective nonlinear elastic materials of cells, e.g. models of hyperelastic materials whose elastic properties are described by Mooney-Rivlin potential [77] or by Treloar potential [21]. The later potential may be written as

$$W = \frac{1}{2}\mu(\lambda_1^2 - 1 + \lambda_2^2 - 1 + \lambda_3^2 - 1), \tag{3.2}$$

where λ_i is the extension ratio in the x_i direction, μ is the initial shear modulus of the material of the natural unstressed state M_u.

Further details related to values of shear modulus μ and membrane thickness for RBCs may be found in [21]. We would like to underline that we do not employ the constant membrane area constraint, i.e. the condition that $\lambda_1\lambda_2 = 1$. It is assumed here that M_u is isotropic and the shear modulus $\mu = E/2(1+\nu)$. For an incompressible material, one has $\nu = 0.5$ and

$$\lambda_1\lambda_2\lambda_3 = 1. \tag{3.3}$$

It is also assumed further that the initial prestress of the cell is homogeneous and this is equivalent to the following conditions for a stretch λ of the membrane

$$\lambda_1 = \lambda_2 = \lambda, \quad \lambda_3 = \lambda^{-2}. \tag{3.4}$$

The problem of contact between the cell and a spherical probe is still axisymmetric due to conditions of homogeneous prestress of the membrane (3.4). Although the problem satisfies the condition of rotational symmetry of elastic properties for small perturbations of the stress field, and therefore, it is similar to the contact problem for a transversely isotropic solid, the problem for prestressed membrane is formally more complicated as it has been mentioned above. For transversely isotropic solid, the non-adhesive contact problem can be solved just by replacing the contact modulus (2.2) by the corresponding contact modulus E^*_{TI} that depends on the constants of the transversely isotropic material (see, e.g. [6,7]). In the frameworks of the JKR and DMT formalisms, the adhesive contact problem for transversely isotropic solid was also solved [13,29].

Fortunately, the linearized boundary value problems of contact for homogeneously prestressed materials can be also solved. A $2D$ contact problem for a prestressed plane whose elastic properties are described by Mooney potential was solved in [31]. The contact problems for incompressible materials of the neo-Hookean type were solved independently in [32] and [24]. It was shown that the solution of the Boussinesq problem for a concentrated load P acting on an elastic half-space whose properties and prestress are described by (3.2) and (3.4) respectively, may be written as

$$u_3(r,0) = \frac{P}{4\pi\mu r}N(\lambda) \tag{3.5}$$

where the coefficient N is

$$N(\lambda) = \frac{2\lambda^4(1+\lambda^3)}{\lambda^9+\lambda^6+3\lambda^3-1}. \tag{3.6}$$

It can be written in an equivalent form (see, [7] for details)

$$N = -2\frac{1-k^2}{\lambda_3^2[(1+k^2)^2-4k]}, \tag{3.7}$$

where $k=\lambda/\lambda_3=\lambda^3$. Because for incompressible solids $\nu=0.5$, (3.5) can be written as

$$u_3(r,0) = \frac{P}{E^*\pi r}N(\lambda) = \frac{P}{4\mu\pi r}N(\lambda). \tag{3.8}$$

Hence, the integral equation of an arbitrary contact problem for equally and uniformly prestressed solids differs from the integral equation of the corresponding classic contact problem only by a constant coefficient $N(\lambda)$. Later it was shown that all Hertz-type contact problems between a punch and a non-linear elastic homogeneously prestressed half-space coincide with the mixed problem for the harmonic potential of the contact problem for an isotropic linear elastic half-space up to a multiplier [3,4,6].

For a non-linear elastic homogeneously prestressed half-space, the contact modulus E^*_{PS} is

$$E^*_{PS} = E^*_I/N(\lambda) = 4\mu/N(\lambda) \tag{3.9}$$

where $N(\lambda)$ depends on the initial deformations λ within x_1x_2 plane and the non-linear strain potential of the material. The same statement is valid for contact between a transversely isotropic probe and a prestressed half-space [6], however the effective contact modulus E^*_{eff} should be taken as $(E^*_{eff})^{-1}=(E^*_{TI})^{-1}+(E^*_{PS})^{-1}$. For neo-Hookean materials, the expression of multiplier $N(\lambda)$ is given by (3.6).

Thus, an extension of the JKR theory in application to AFM probing of cells leads to the following relation between the external load P acting on the spherical probe and the adhesive contact radius a

$$P = (4E^*_{PS}/3R)a^3 - \sqrt{8\pi w E^*_{PS}a^3} \tag{3.10}$$

and

$$\delta_2 = a^2/R - \sqrt{2\pi w(E^*_{PS})^{-1}a} \tag{3.11}$$

where R is the effective radius of the spheres (2.3) and $E_{PS}=4\mu/N(\lambda)$. Note that the parametric expressions (3.10) and (3.11) for P and δ can be united as an explicit $P(\delta)$ relation.

4. Determination of elastic modulus and work of adhesion for prestressed cells

Evaluation of elastic and adhesive properties of cells is important not only for proper theoretical and numerical modelling of interactions between a cell and an AFM probe or among cells, but it has been argued that these properties are in connections with cell biological functionality (see, e.g. [42,70]). Hence, these questions were actively discussed. Both non-adhesive and adhesive contact models were involved in the studies (see, e.g., [19,25,72,78]. Usually elastic and adhesive characteristics of contacting materials are evaluated employing two independent and rather different indentation tests: (i) DSI of sharp pyramidal indenters for extraction of the effective contact modulus E^* from the unloading branch of the $P-\delta$ curve, see the BASh relation (2.4); and (ii) extraction of work of adhesion w from direct measurements of the pull-off force (the adherence force P_{adh} which is assumed to be negative) of a spherical indenter from the material sample

$$w = -\frac{2}{3}\frac{P_{adh}}{\pi R}. \tag{4.1}$$

and sometimes using in the calculation few other points of the indentation $P-\delta$ curve [27,72]. As it has been argued above, the BASh relation (2.4) may cause considerable errors due to neglecting adhesive effects (see (2.5) and (2.6)), while direct measurements of P_{adh} and calculations by (4.1) are prone to errors due to effects of roughness and surface contaminations. Therefore, P_{adh} is often calculated after many tests [72].

The BG method was introduced as an alternative approach for identifying elastic modulus and w from a single depth-sensing indentation test involving a spherical indenter [8]. The BG methodology intrinsically takes adhesion into account and the method is based on optimal fitting of the experimental data to possible adhesive $P-\delta$ curves. The BG method assumes that the experiments should be described by a mathematical model of the indentation process. The theoretical $P-\delta$ curve is used and it is written as the following dimensionless function F:

$$F\left(\frac{P}{P_c}, \frac{\delta}{\delta_c}\right) = 0. \tag{4.2}$$

Here $P_c > 0$ and $\delta_c > 0$ are so-called scaling parameters of the problem. The exact form of this relation depends on the assumed physical model of adhesive contact.

In contrast to other methods of extraction the mechanical and adhesive properties of soft material samples, the BG method uses the entire set of data points of unloading branch of the force-displacement curve on a selected interval of loads rather than some specific points on it. In particular, it can be applied just to an interval of compressive loads [11,12] when the $P-\delta$ curves are definitely stable.

The scope of the original BG method was limited to the classic JKR and DMT theories. For example, for the classic JKR theory applied to a spherical probe of radius R, (4.2) can be written as

$$\begin{cases} (3\chi-1)\left(\dfrac{1+\chi}{9}\right)^{\frac{1}{3}} - \dfrac{\delta}{\delta_c} = 0 & \text{for } \chi \ge 0,\ \dfrac{\delta}{\delta_c} \ge -3^{-2/3}, \\[2ex] (3\chi+1)\left(\dfrac{1-\chi}{9}\right)^{\frac{1}{3}} - \dfrac{\delta}{\delta_c} = 0 & \text{for } \dfrac{2}{3} \ge \chi \ge 0,\ -3^{-2/3} > \dfrac{\delta}{\delta_c} \ge -1 \end{cases} \tag{4.3}$$

where $\chi = \sqrt{1+\frac{P}{P_c}}$. The characteristic parameters P_c and δ_c are connected to the reduced Young's modulus of material E^* and work of adhesion w by means of the following formulae:

$$P_c = \frac{3}{2}\pi w R, \quad \delta_c = \frac{3}{4}\left(\frac{\pi^2 w^2 R}{E^{*2}}\right)^{1/3}. \tag{4.4}$$

In the case of the JKR theory the parameters P_c and δ_c have clear physical meanings, e.g. P_c is the maximum possible absolute value of the pull-off force during unloading phase of indentation.

The experimental force-displacement curve may be represented as an array (P_i, δ_i), $i = 1, \ldots, N$ of measured values of the compressing load $P \ge 0$ and corresponding values of the displacement $\delta \ge 0$. Here N is the number of points of the experimental measurements. According to the BG method, one needs to find the parameters P_c and δ_c along with the shift of the origin of the displacement coordinate (δ_s) in order to fit the experimental data by an appropriate theoretical curve, i.e. one can select the dimensionless JKR curve (4.3). Substituting the measured values (P_i, δ_i), $i = 1, \ldots, N$ into the selected expression of the theoretical curve (4.2), one obtains an array of equalities

$$F\left(\frac{P_i}{P_c}, \frac{\delta_i}{\delta_c}\right) = 0, \quad i = 1 \dots N. \tag{4.5}$$

that could be satisfied by a single pair of the scaling parameters P_c and δ_c only in the following ideal case: (i) the cell deformations can be described ideally well by the selected model of adhesive contact (4.2); and (ii) all measurements are error-free. Evidently, this cannot happen in a real experiment. Therefore, the problem of finding the scaling parameters boils down to an optimization problem of finding the optimal values of P_c, δ_c that provide the best fit of the theoretical force-displacement curve (4.5) to the experimental data according to some metric. Originally, the BG method used the least-squares metric (see, e.g. [11]). However, later it was suggested to employ in the extended BG (eBG) method another objective functional based on the concept of orthogonal distance curve fitting [58–60].

If an AFM probe is spherical then the classic JKR theory that represents the solid as an elastic half-space, enables us to write explicitly the $P(\delta)$ relation. However, for more general cases, the adhesive contact theory provides the $P - \delta$ curves as parametric relations $P(a), \delta(a)$ where the contact radius a is used as the parameter [7]. For problems of adhesive contact between a probe and a thin layer or a thin bilayer bonded to a rigid half-space, the adhesive force-displacement relationship cannot be reduced to explicit form unless indenter has a canonical shape, e.g. it is spherical [14,28]. Solutions to adhesive contact for coated elastic media may have very complex representation which cannot be reduced to explicit form for any indenter shape [1]; the same is valid for semi-analytical models containing some correction functions (see, e.g. [71]). Therefore, the original version of the BG method was not applicable directly for many problems of practical importance. However, its extended version can be used for determination of elastic and adhesive properties of elastic structures if they allow for the application of the JKR theory. Hence, the eBG method can be applied to adhesive indentation of coated, multilayered, and functionally-graded media [58–60]. It is possible to show that the JKR formalism is applicable to problems of adhesive contact for any linear or linearized materials and structures that allow the use of the principle of superposition of solutions [61].

As soon as the optimal values of the scaling parameters P_c and δ_c are extracted from experimental data, the contact modulus E^*_{PS} and the work of adhesion w can be evaluated from (4.4). Normally, for soft materials and spherical AFM tips, the JKR theory is applicable, however after the contact modulus and w have been extracted, one needs to check if the value of the corresponding Tabor parameter is within the interval of applicability of the JKR theory.

Thus, the approach developed here enables us to apply the JKR formalism to prestessed membranes of living cells and extract the elastic properties and work of adhesion using the eBG method.

5. Conclusion

It has been argued that the contact probing of living biological cells and depth-sensing indentation of the cells are effective experimental tools that enable the researchers to obtain quantitative data on deformation of the cells and extraction of information about their mechanical properties. However, proper extraction of useful information should be based on theoretical models that take into account specific features of the process under consideration. These features include mechanical properties of cell membranes, their adhesive properties and initial tensile stresses (prestress) of the membranes.

Explicit expressions (2.5) and (2.6) have been derived that showed that the slopes of DSI force-displacement curves may be significantly affected by adhesion. These expressions are generalizations of the BASh expression that is the corner stone of modern depth-sensing nanoindentation tests. The expressions are based on the use of an extension of the JKR theory to an axisymmetric indenter of arbitrary shape. It has been shown that the direct application of non-adhesive Hertz-type contact models may lead to significant errors in estimations of contact moduli of materials. Although both the original BASh expression and the above mentioned extension were derived assuming frictionless boundary conditions, this restriction is not very important because our previous studies [16,17] showed that the maximum error is below 10%.

A similar statement is applicable to the JKR theory. Indeed, the main formulae of the theory were derived assuming that the material points within the contact region can move along the probe surface without any friction. However, it is more natural to assume that a material point that came to contact with the probe sticks to its surface. This means that the non-slipping boundary conditions could better describe the contact phenomenon. However, again our previous studies [15] showed that the difference between solutions to frictionless adhesive contact problem and the problem with non-slipping boundary conditions is very small. Hence, the frictionless boundary conditions have been used in the above studies.

Following [21], we have modelled the cell membrane as made of effective neo-Hookean material. It has been argued that the contact mechanics of prestressed solids [3,4,6,24,32] along with an extension of the JKR theory [7] should be employed to study contact probing of adhesive cell membranes. It has been showed that the JKR theory is still valid, however the contact modulus of the material in its natural unstressed state (2.1) should be replaced by the contact modulus of the prestressed material E_{PS} whose value depends on the multiplier $N(\lambda)$ that in turn, depends on the initial stretch of the membrane. In the case of modelling the cell membrane by a neo-Hookean material, $N(\lambda)$ is given by (3.6).

Finally, we argued that the effective modulus of the membrane and the work of adhesion may be extracted from a single DSI test by employing the eBG method. Although it was proved that the BG method is simple and robust, our previous studies of polymer samples [11,12] showed that the extracted values of both characteristics (elastic contact modulus and the work of adhesion) may vary in the same sample. Indeed, the polymer macromolecules are rather long and the contact area may have interacting molecules in various orientations. We expect that such variations may be observed in living cell membranes. We expect that the membrane proteins may cause the variability of the extracted values. Therefore, even if the eBG method allows us formally to extract the seeking parameters from a single experiment, the statistical approaches may be helpful for proper understanding of the results. It has been argued that the present approach to both the JKR type contact problems and eBG method will be valid for more complicated elastic models of cell membranes. The presented studies demonstrated the ways of studying contact problems for prestressed living cells under action of AFM probes with spherical tips and extract the elastic contact modulus and work of adhesion depending on the current values of the cell membrane prestress.

Authors' Contributions. FB and LK: initial idea of the study, literature review (Section 1), FB and BG: developed the BG method and suggested to apply it to living cells (Section 4), derived the adhesive form of the BASh relation (Section 2b); FB and MMSA: Section 2a and 2c; FB:drafting of the manuscript and Section 3. All auhtors read and approved the manuscript.

Competing Interests. The authors declare that they have no competing interests.

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