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CONTINUUM MECHANICS

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Molecular and Cellular Mechanics*

During the last decades biophysical and biomechanical properties of biomolecules and biomembranes became a subject of intensive investigations. Recently, classical and quantum mechanics successfully integrate with physics, chemistry and biology in such investigations. The reason is that dynamics of large biomolecules — proteins and nucleic acids — plays a fundamental role in life processes. A new trend in science has been started, known as molecular mechanics and, particularly, biomolecular mechanics. The term "molecular mechanics" appeared first in 1967 in the works of the American scientist L. S. Bartell and has been used later by Allinger [1]. Initially, the aim of these studies has been the calculation of conformations and conformational energies. At present, biomolecular mechanics aims at a wider application of basic laws of mechanics for the calculation of mechanical displacements, velocities, accelerations and their influence on the course of biological processes, as well as on the properties of biological tissues and fluids subjected to the action of external mechanical loading, thermal, electromagnetic, gravitational and other effects. As the famous American physicist Richard Feynman has said, everything that occurs in living beings may be undersood in terms of atomic motions and vibrations.

Molecular dynamics has been developed in two aspects: inter- and intramolecular dynamics. On principle, the motion of atoms and molecules has a quantum mechanical character, but, as a first approximation, methods of classical mechanics may be used. The study of the biomechanical behaviour of molecules begins with the definition of their biophysical model. A sound basis for that is given in the fundamental work "Biophysical Chemistry" by Ch. Cantor and P. Schimmel.

The protein structure represents a chain of up to twenty different aminoacids which is immersed in a biological fluid. The great variety of three-dimensional structures of proteins reflects the variety of their functions. This is especially true for enzymes.

The idealized computational model of a biomolecule represents a specific system of particles (atoms or groups of atoms) connected by imaginary massless springs. These springs represent the chemical bonds connecting pairs of neighbouring atoms. Long-range Coulomb forces may also be taken into account. The angle-depending interaction between two chemical bonds at bending and twisting may be represented by imaginary rotational elastic springs. The resistence effects of the biological fluid

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may be approximately taken into account by the addition of friction of the use of damping elements.

Some significant contributions in the study of molecular dynamics of proteins have been popularly described by Karplus and McCammon in *Scientific American* [5]. They use the method of molecular dynamics, which is based on the solution of Newton's equations of motion with the aid of powerful computers. Many other studies of the structure and dynamics of nucleic acids, proteins and membranes are described in the book by Clementi and Chin [3].

The calculation of mechanical vibrations of atomic chains with a large number of degrees freedom is a complicated problem. One may use the principle of replacing the original large molecule by a small one which approximately simulates its dynamical behaviour. For molecules with many degrees of freedom it is convenient to use the well-known Lagrange equations of motion in terms of generalized coordinates. Their most general form is:

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{\partial T}{\partial \dot{q}_i}\right)-\frac{\partial T}{\partial q_i}=-\frac{\partial V}{\partial q_i} \qquad (i=1,\ldots,n), \tag{1}$$

where

$$T=\frac{1}{2}\sum_{i,k=1}^{n} a_{ik}\dot{q}_i\dot{q}_k,$$

$$V=\frac{1}{2}\sum_{i,k=1}^{n}\Phi(q_i, q_k)$$

are the kinetic and potential energies, respectively. Vibrations are periodic atomic motions about the equilibrium positions. They are characterized by frequency and amplitude. Usually, small displacements are assumed which amounts to keeping only quadratic terms in the potential energy. In the case of one degree of freedom the equation of motion may be easily integrated for a general form of the potential well (large displacements). However, the large displacements problem in the case of many degrees of freedom is analytically untractable.

Rotations of the polypeptide chain around covalent bonds are one of the basic fluctuational motions. They give much flexibility to the chain. Under such rotations the side groups of the aminoacids are shifted too. It is considered that rotations play an important role in the transportation of small molecules, electrons and protons. A characteristic feature of protein chains is the appearance of dipole moments at the peptide bonds. It should be noted also that either the whole molecule or some fragments of it may rotate. Such motions take place under the influence of temperature, electric interactions, radiation etc. For example, the "retinal" molecule of vision undergoes rotational motion under the action of light photons (according to L. Streyer).

The third form of mechanical motion of a molecule is connected to its three translational degrees of freedom. This form of motion becomes important in the study of drug transport. A number of scientists attempt at disclosing the mechanism of drugs action. To this end they use different techniques for experimental and theoretical investigations in the field of molecular and quantum pharmacology. The goal is to un-

derstand and control the interactions which take place in the system "drug-receptor". At oral drug intake one may consider a body of variable mass moving in the oesophagus. The corresponding equation of motion has the form

$$\sum_i \frac{d}{dt}\left(m_i \frac{dz}{dt}\right) = \sum_i F_i, \tag{2}$$

or, explicitly,

$$\frac{d}{dt}\left(m_0 \frac{dz}{dt}\right) + \frac{d}{dt}\left(M \frac{dz}{dt}\right) - \frac{d}{dt}\left[m_0(1 - e^{-\mu z}) \frac{dz}{dt}\right] = m_0 g + Mg - k \frac{dz}{dt},$$

where m_0 is the mass of drugs, M the mass of fluid, z — vertical coordinate, μ and k — coefficients, g is the gravitational acceleration.

The next basic problem is the molecular mechanics of nucleic acids. The structure of the nucleic acids DNA and RNA, discovered in 1953 by Watson and Crick, represents a double helix. DNA consists of four distinct base pairs which connect the two spirals and play the role of letters of the genetic alphabet. The information is grouped in sequences of base pairs called genes. The whole genetic message in a living being is the genome. It is interesting to mention that the genome of a human being contains information equivalent to a library of 1500 volumes, each of them having the information content of the Bible. With the use of special enzymes the molecule of DNA may be cleaved into fragments and after the modification of the fragments the molecule may be reassembled as a whole entity. This is the basic idea of genetic engineering.

We have considered a mechanical model of the helix in which each atom has two degrees of freedom: a vibration along the tangent and vibration along the radius of the helix. The corresponding shifts u_t and u_r have been assumed small and independent. The model of valent bond forces has been assumed. In terms of generalized angular coordinates β_i the equation of motion of the i-th atom has the form

$$m_i(r^2 + \lambda^2)^{1/2} \ddot{\beta}_i = \sum_{i=1}^{n} F_t = \sum_{i=1}^{n} k_{ij} \beta_j, \tag{3}$$

where $(r^2 + \ddot{\lambda}^2)^{1/2} \beta_i$ is the tangental acceleration, F_i — restoration forces, k_{ij} — elastic constants.

In the author's monography [2] the following examples have been considered: a sequence of three atoms, a fragment of a double helix with transverse interaction bonds, a fragment of a helix with mass distributed along the whole length.

Problems connected with the role of the electron potential in DNA molecules and in the living organism have been considered in detail by A. and B. Pullman, R Lavery, E. Clementi and others.

Biomembranes, considered as biomechanical objects, are of great interest because of the fact that their biological properties are closely related to their mechanical state. Deformations of a membrane are coupled to the transfer of electrical charges and to chemical reactions taking place on its surface. At the surface of the external cell membrane there are specific receptors (recognition sites) with the help of which the cells interacts with the surrounding medium and with other cells in particular. The structural basis of biomembranes consists of amphiphilic molecules which easily form bilayers

in water solutions. Besides the lipids, there is a considerable amount of proteins in the biomembrane. The membrane plays the role of a "pump", ensuring the active transport of molecules and ions from the side with lower concentration to the side with higher concentration. Of course, passive transport through the membrane takes place too. One of the most important characteristics is the electrical potential $\varphi(x, t)$ across the membrane. It affects the state of the membrane and plays the role of the main driving signal in biological systems.

Comparatively the most well studied biomembrane is that of the red blood cell. The form and functions of red blood cells are described in detail by Fung [4]. It is interesting to note that the change in the form, size and strength of the red blood cell membrane may be indicative of disease. Various problems of biomembrane mechanics have been considered in greater detail by Fung, Skalak, Zarda, Brankov and others. Here we point out that the equilibrium equations for the strains and stresses are the same for all kinds of materials. The difference appears in the formulation of the stress-strain relationships which describe the properties of the material. These are also called constitutive equations. There are two approaches to the mathematical modelling of the relationship between the strain and stress tensors. The first one has been formulated by Cauchy. It consists in the establishment of a one-to-one relationship between the components of the two tensors. For example, in the case of an ideally elastic body for which the Hook's law holds, the stress tensor is linearly proportional to the strain tensor:

$$\sigma_{ij} = c_{ijkl}\varepsilon_{kl}. \tag{4}$$

Here c_{ijkl} is the tensor of the elastic constants (moduli).

The second approach has been started by Green. It consists in the representation of the potential energy of elastic deformation as a function of the components of the strain tensor. In this approach the energy is completely restored after the loading is removed. The elastic potential Φ depends on the basic algebraic invariants of the strain tensor in the form

$$\Phi = \Phi(A_1, A_2, A_3), \tag{5}$$

where

$$A_1 = \varepsilon_1 + \varepsilon_2 + \varepsilon_3, \quad A_2 = \varepsilon_1^2 + \varepsilon_2^2 + \varepsilon_3^2,$$

$$A_3 = \varepsilon_1^3 + \varepsilon_2^3 + \varepsilon_3^3.$$

In the study of red blood cells a number of authors accept the membrane theory of shells and some authors accept the bending theory. These theories may have some foundations if we consider biconcave shells in static states and the material has the properties of a deformable solid. However, the biophysical model of this shell has the following features:

— The lipid bilayer may undergo a phase transition, for example from a solid to a liquid state, which changes the membrane structure.

— Between the two lipid layers there is an intermediate fluid layer. With respect to the internal forces the membrane may act either as a whole unit, or as one or two disconnected layers due to the sliding of one of the lipid layers over the other.

— The total thickness of the membrane may change due to changes in the conformational states of the lipid molecules, their ordering or due to the dynamics of the intermediate fluid layer.

— Usual concepts of the shell theory for the stress distribution across the thickness, for isotropy, homogeneity and so on, should be applied with caution.

— From the descriptions given by Fung and others, it is seen that the membrane of the red blood cell is extremely deformable and may change very much its form, especially when the cell moves through capillary blood vessels with smaller diameter. In such cases the membrane curvature may become comparable with the membrane thickness and consequently the membrane theory will be inapplicable. Then a different calculational model should be sought, probably based on the discrete membrane structure.

Recently a new important problem appeared, namely, the interaction of the red blood cell membrane with the electromagnetic field generated by the pulsating blood flow in arteries. The blood plasma contains positive and negative ions which, when moving, generate both electric E and magnetic B fields. During the diastole the velocity of the pulse wave decreases and we may assume the existence of a quasistatic electric field. During the systole the velocity of the pulse wave increases to high values and we suggest that the generated magnetic field may become important, i. e. we have to treat the coupled electromagnetic problem. In the first case we have an electrostatic problem with $\dot{B}=0$. Then the first two Maxwell field equations are used

$$\nabla \cdot E=\frac{\rho_e}{\varepsilon}, \quad \nabla \times E=0, \tag{6}$$

where ρ_e is the electrical charge density and ε — the electrical permitivity. The equation of motion for the red blood cell is

$$\sigma_{ij,j}+X_i=\rho\ddot{u}_i, \tag{7}$$

or one may use the membrane equation due to A. L. Goldenweiser:

$$\left(\frac{h^2}{3}N_{ij}+L_{ij}\right)u_j+\frac{\rho}{E}\frac{\partial^2 u_i}{\partial t^2}=\frac{X_i}{2Eh}. \tag{8}$$

Here N_{ij}, L_{ij} are the bending and membrane operators, u is the displacement vector for the middle surface, ρ — mass density, h — halfwidth of the membrane, X_i — components of the electrical pressure, $\sigma_{ij}=N_{ij}/2h$.

The interaction of a membrane with an external electromagnetic field has been treated in my monograph [2]. In this direction new prospects are opening for theoretical and experimental investigations which aim at disclosing the fundamental role of electromagnetic fields in life processes. All living beings on the earth are subjected to the influence of natural electromagnetic fields, but man-made fields may have much greater intensity.

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