生物力学的最新进展

Recent Advances in Biomechanics

国家自然科学基金委员会 组编

Organizer National Natural Science Foundation of China

朱 承 龙 勉 主编

Editors Cheng ZHU Mian LONG

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朱 承　龙 勉 主编

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前　言

为了探讨生物力学在21世纪的发展，加强中外青年生物力学工作者之间的学术联系和合作，由国家自然科学基金委员会和中国力学学会主办、中国科学院力学研究所和中国力学学会生物力学专业委员会承办的“首届中外青年生物力学工作者学术研讨会”于2001年7月30日至8月3日在北京召开。

世纪之交，生物力学无论在其深度和广度上都经历着重大的变化，力学与其他传统的工程科学将进一步与生命科学融合。这不仅大大推动生物医学的进步，而且必将使力学和工程科学焕发青春。在改革开放进程中“走出去”的一批青年科学家在国际生物力学领域占据愈来愈重要的地位，在某些领域逐渐形成群体优势。而国内青年一代生物力学工作者大都具有生命科学和工程科学的良好的交叉训练，具有较大的发展潜力。为使之更好地成长，与国际学术界的密切交流与合作是十分必要的。本次会议正是在这样的背景下召开的。

会议通知发出后，得到了国内外生物力学界的热烈响应，包括许多资深学者都十分关注本次研讨会。会议特邀27位国内外有代表性的青年学者做学术报告，其中16位海外报告者分别在美国、英国、日本、香港等国家和地区的大学或研究所主持独立的研究室，11位国内报告者分别来自中国科学院所属研究所、教育部所属高校以及其他科研院所。本文集收录的文章主要涉及细胞与分子生物力学、组织力学与组织工程、生物流体与传热传质等方面的内容。会议同时将就这几个领域的主题进行自由讨论。

“首届中外青年生物力学工作者学术研讨会”得到了各方面的关心和支持，国家自然科学基金委员会是本次会议的发起者并提供了有力的赞助，美国国家科学基金委员会、中国科学院国际合作局、中国科学院力学研究所等也提供了经费支持。在此，会议组委会向关心和支持的单位和个人表示衷心地感谢。

朱　承　　龙　勉

2001年7月2日

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CELL AND MOLECULAR MECHANICS

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Molecular Biomechanics: An Emerging Field

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Abstract: With the advent of molecular biology and biophysics over the last decade, molecule biomechanics is emerging as a new field. Different techniques have been developed to study the mechanical properties of DNA and protein molecules; various models have been created to quantify the deformation of biomolecules under force. Here we review some of these advances, explore the connection between mechanics and biochemistry, and discuss the concepts, issues and challenges in developing molecular biomechanics.

Introduction

As the basic unit of life, living cells are complex biological systems. To perform their specialized funtions, cells must express genetic information; synthesize, sort, store and transport biomolecules; convert different forms of energy; transduce signals; maintain internal structures; and respond to external environments. Many of these processes involve mechanical aspects. For example, recent studies have confirmed that mechanical forces can affect cell growth, differentiation, locomotion, adhesion, signal transduction, and gene expression. Yet little is known about how cells sense the mechanical forces and deformations, and convert these mechanical signals into biological or biochemical responses. There is an increasing need to understand the molecular mechanisms by which cells generate, detect, and respond to mechanical forces.

Mechanical forces can induce deformation as well as biological responses in cells. There is ample evidence to suggest that many normal and diseased conditions of cells are dependent upon or regulated by their mechanical environment. The effects of applied forces (or deformations) may depend on the type of cells and how the forces are applied to cells and transmitted into and distributed within cells. A possible pathway for mechanochemical transduction in adherent cells is the force balance within the cell cytoskeleton (CSK), and through the cell-extracellular matrix (ECM) interactions (1). Such a balance may play a key role in regulating the shape, spreading, crawling, and polarity of cells. The question is again how mechanical force balance is transduced into biochemical signals that induce biological responses.

There are a number of candidates for the molecular mechanisms responsible for the regulatory role of mechanical forces in biological systems. For example, components of the cell cytoskeleton such as actin filaments and microtubules may deform under mechanical forces (2). Such deformation may induce conformational changes of other proteins attached to them. ECM molecules may also deform under force, leading to altered biological responses. It has been found that when the ECM is disrupted, fibronectin can contract to a fraction of its original length (3). This may serve as a mechanosensitive control of ligand recognition (4).

Another candidate involves integrins which are a family of heterodimeric membrane glycoproteins expressed on diverse cell types which function as the major receptor for ECM and as cell-cell adhesion molecules (5). There have been studies indicating that mechanical forces can influence the formation of integrin-cytoskeleton focal adhesion complexes (6). It is likely that interins change their conformations under force, altering their binding to the ligands and thus changing the down-stream biochemical processes. Stretch-activated ion channels may be yet another candidate for mechanochemical transduction. It has been shown that ion transport through the cell membranes can be altered by mechanical forces, especially tension in the cell membrane (7).

It has become clear over the last few years that conformational changes of DNA and protein molecules under mechanical forces may be the key to understanding mechanochemical transduction in cells. In a broad sense, it may also be a critical aspect in understanding the connection between mechanics and biochemistry, which is a new frontier in mechanics in general and biomechanics in particular. Deformation of biomolecules under force and mechanical forces generated by the conformational changes of motor proteins are just examples of this fundamental connection. In simple words, mechanics is the study of force, motion and deformation, while biochemistry involves the conformation, binding/reaction and transport of biomolecules. There is ample evidence

suggesting the connection between the two; however, basic understanding of this connection is lacking (8).

In this article we review some of the progresses, explore the connection between mechanics and biochemistry, and discuss the concepts, issues and challenges, aiming to stimulating a broader interest in molecular biomechanics. Emphasis is placed on the basic facts and ideas; technical details may be found in the references.

Deformation of Biomolecules

As deformable bodies, biomolecules such as proteins and DNA change their shapes and sizes (or 3D conformations) under mechanical forces. But why deformation of biomolecules under force is of interest? How do such deformations affect biochemical processes in living cells? To answer these questions, it is necessary to elucidate the mechanisms by which forces and deformations regulate the structure-function relation-ships of biomolecules.

The deformation of protein molecules can have various modes under different forces. These modes include domain motion (9), domain deformation, domain unfolding (10-14), and denaturing of secondary structures such as α-helices and β-sheets (15), as shown schematically in Figure 1. In general, in domain hinge motion (Figure 1a), the individual domains have very little deformation; the motion largely consists of rotations of domains around the flexible hinge (loops and turns that join the domains together). Such motions are typically driven by Brownian forces or moments, which involve forces of 1-10 pN (16). When the force becomes large, e.g. 10-100 pN, the domains may begin to deform. For protein molecules such as titin and tenascin, domain unfolding occurs when the applied force is ~ 100 pN (13-14). The denaturing (i.e. unfolding) of α-helices and β-sheets (Figure 1c) may require an even larger force. Although very rough, the above order-of-magnitude estimates for the force scales can provide some guidance to the analysis of protein deformation.

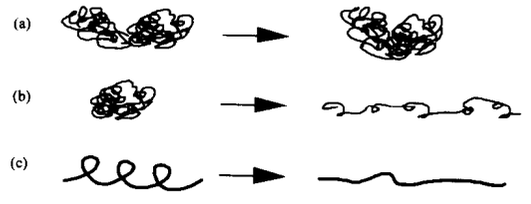

Figure 1 Modes of protein deformation: (a) domain motion, (b) domain deformation and unfolding, (c) unfolding of secondary structures.

Like all the polymeric materials, DNA and proteins are viscoelastic in nature. As such, their deformations are in general time-dependent (thus rate sensitive), especially in aqueous environment. The time scales for protein deformation in biological processes may span many orders of magnitude. For example, hinge motion of a protein may take only 100 ps, whereas local denaturing may take a few seconds (17). Given the complicated 3D structures of protein molecules, it may not be sensible to use continuous stress and strain distributions to define their internal forces and deformations as usually the case for engineering materials. Perhaps it is more convenient to use forces (or moments) and extensions (or rotations) to describe the overall mechanical behavior of DNA and proteins.

The deformability of DNA molecules is largely controlled by the entropic elasticity (18, 19). The simplest model of entropic elasticity is the freely joined chain (FJC) model (20), which treats the polymer as a chain of statistically independent segments whose orientations are uncorrelated in the absence of external forces. Consequently, the elastic response of the model molecule is purely entropic, leading to a linear relationship between force (f) and extension (x) (21). The FJC model works well for DNA molecules under small-stretch conditions, however, when the stretching is large, it is not very accurate owing to the omission of the thin-rod elasticity of DNA under bending. The worm-like chain (WLC) model includes, in addition to the entropic term, the elastic bending of the polymer chain in the free-energy calculation (22, 23). Although the exact force-extension relationship of the WLC model is complicated, it can be approximated fairly accurately by a simple equation (23)

$$\frac{fL}{k_B T} = \frac{x}{l} + \frac{1}{4(1-x/l)^2} - \frac{1}{4} \qquad (1)$$

where L and l are, respectively, the persistence length and contour length of the DNA molecule. As revealed by Smith et al (24, 25) through pioneering mechanical measurements, the force vs extension relationship for a single λ-phage DNA molecule can be represented by the WLC model under stretch conditions, with L = 53.4 nm and l = 32.8 μm. It follows from Equation 1 that when extension x is small, the DNA molecule behaves like a linear spring; however, the behavior is nonlinear as x becomes large. As illustrated in Figure 2a, a force of 2-3 pN is able to stretch the DNA to 90% of its contour length, with the force rising sharply when x approaches l. Because of the inextensible assumption in the WLC model, Equation 1 predicts that as x approaches l the force f required approaches infinity. Of course, when f is large, a double-stranded DNA may be overstretched, resulting in unwinding and unstacking of the DNA (25).

In living cells both DNA and protein molecules are in aqueous solutions; they can be deformed by thermal

fluctuation, by direct molecular contact, or by hydrodynamic forces. Owing to the interplay among entropic elasticity, Brownian motion and the hydrodynamic forces, individual DNA molecules in extensional and shear flows exhibit complex dynamics, as demonstrated by Perkins et al (26, 27), Larson et al (28), Smith and Chu (29), Smith et al (30) and by LeDuc et al (31) using fluorescence microscopy. DNA molecules can also undergo large twisting and bending deformations (32-35).

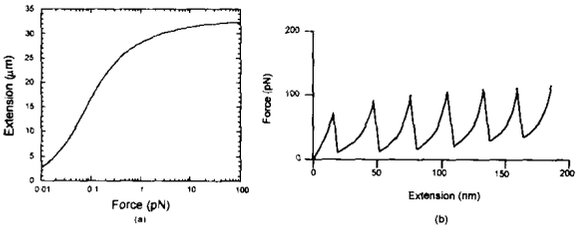

Figure 2 Schematics showing typical force versus extension relationships for (a) a λ-phage single strand DNA molecule, (b) the muscle molecule titin and ECM molecule tenascin.

Although proteins have far more complex structures compared with DNA, their deformations share certain common features with those of DNA. For example, measurements of the forces required for the deformation and unfolding of individual titin immunoglobulin domains (11-13) have revealed that the force-extension relationship of titin deformation exhibits a characteristic sawtooth pattern which can be described by the WLC model (Equation 1). A similar expression was found to fit the measured force-extension curve for tenascin (14). As can be seen from Figure 2b, a force of ~ 100 pN is required for domain unfolding of tenascin (14). It is very convincing that the WLC model works well for domain deformation of protein molecules containing multiple, individually folded domains with β-sandwich structures.

Despite its success, single-molecule biomechanics is still at its infancy (36). In particular, the deformation of protein molecules under force has not been well studied either experimentally or theoretically. The complex 3D structure of proteins implies that their deformations can be very complex. The forces applied to proteins in a cellular environment owing to Brownian motion and protein-protein interactions are usually stochastic; the resulting deformations, therefore, are often stochastic as well. Further, the conformational changes of proteins can be quite sensitive to the solvent surroundings. Though a complicated system to analyze, protein deformation presents a rich class of mechanics problems and a new opportunity for mechanics to expand its horizons.

Protein Deformation and Receptor-Ligand Binding

Perhaps one of the most important aspects of protein deformation under force is its effect on receptor-ligand binding, an essential process in cells (37). The idea is that specific molecular interactions rely on conformational matches between the receptor and the ligand. In other words, although van der Waals forces and electrostatic and hydrophobic interactions are all important, the 3D geometry local to the binding pocket of the receptor and the ligand dictates the characteristics of the bond. Good conformational matches lead to strong and long-lasting bonds, whereas poor conformational matches do the converse. The underlying reason is that receptor-ligand binding is realized largely through noncovalent bonds such as hydrogen bonds, which are rather weak individually but, in sufficient number, can be strong collectively. However, hydrogen bonding operates only within narrow geometric ranges; thus, to have a large number of hydrogen bonds, a good conformational match between the receptor and the ligand at the binding pocket is necessary.

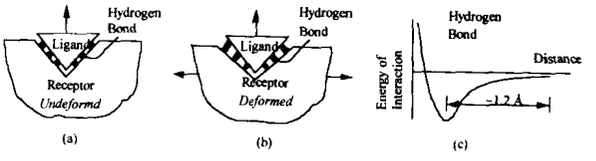

Figure 3 A good conformational match shown in (a) can be changed if the receptor deformes under force (b). The deformation need not be large (c).

When mechanical forces are applied to a receptor (and ligand), the receptor may deform, thereby altering the conformational match between the receptor and the ligand, as illustrated schematically in Figure 3. Most likely it does not take much deformation to significantly reduce the binding strength because, for hydrogen bonds, increasing the distance between the hydrogen-binding atoms by 1.2Å can reduce binding strength (in terms of the free energy) from 1 kcal/mole (~ 7 pN·nm) to almost zero (16). This suggests that small deformations of proteins could have large influences. The specific effect of force on receptor-ligand binding depends on the mode and the magnitude of deformations of a receptor or a ligand (or both), which, for a given loading history and solvent surroundings are in turn determined by the structure and mechanical properties of the molecules. In some cases, deformation can increase or decrease the kinetic rates (38, 39). In other cases, only deformation can expose the binding site, so the effect is to switch between the on- and off-conformers. It is also possible that deformation can change the specificity of

a receptor for ligands, i.e. binding to ligand B instead of ligand A upon deformation. The latter two effects are well known for molecules such as integrins that can be activated biochemically. It is possible that force-induced deformation may yield similar results.

While protein deformation can effect receptor-ligand binding, the reverse is also true, i.e. ligand binding can induce protein conformational change (40). Such conformational change can serve as a way to transduce biochemical signals, or to facilitate an enzymic reaction. As an example, consider protein hinge motion (see Figure 1) which, in the absence of protein-protein interactions, is largely driven by the Brownian force (41). When a ligand is bound to the receptor, the rotational motion of the domains about the hinge can be altered significantly. In fact, during the receptor-ligand binding processes, both the receptor and the ligand may change their conformations in order to have the 'best' fit, i.e. to realize the most energetically favorable state. Such conformational changes may be driven by entropic effects (42), hydrophobic interactions, and the formation of hydrogen bonds, e.g. 'caged' water molecules trapped in the binding pocket. Here again, in analyzing the effect of mechanical forces on receptor-ligand binding, the biochemical aspects of molecular interactions must be taken into account.

Mechanochemical Transduction

Although it is well accepted that cells can sense mechanical forces and deformations and convert them into biochemical signals and biological responses, it is not clear how they do so. Therefore it is crucial to establish, at the molecular level, the link between mechanics and biochemistry as related to cell behavior and function. A possible mechanism of receptor-mediated signaling processes involves a change in the conformational state induced by the engagement of a ligand in the extracellular domain of the receptor, resulting in the exposure of a functional domain in the intracellular domain (5). Thus, it is not unreasonable to think that force-induced nonlocal deformation of proteins can serve as a mechanochemical transduction mechanism. Such a hypothesis is especially attractive when applied to integrins, whose functions include both adhesion and signal transduction. As discussed above, integrins are likely a major force transmitter, because they provide the mechanical linkage between ECM and cytoskeleton. As such, these receptors are in an excellent position to also serve as a force sensor. In addition to switching between resting and active states upon ligand occupancy, it is conceivable that more continuous conformational changes in response to various forces can also produce more gradual exposure of the functional domain or affect the binding rate for the downstream signaling molecules, thereby transducing mechanical forces into biochemical signals. This is analogous to ion transport through the membranes and intracellular vesicle trafficking, which may also be altered by mechanical forces.

Altered kinetics of biochemical reactions by mechanical forces is another possible mechanochemical transduction mechanism. It involves the deformation of DNA and protein molecules in DNA replication, condensation and transcription. It has been uncovered over the last few years that stretching and twisting of DNA molecules and forces applied to enzyme proteins can affect DNA replication and transcription in cells (43, 44). Specifically, it was found that the velocity of T7 DNA polymerase along their single stranded DNA templates is sensitive to tension in the templates, indicating that deformation of DNA under tensile forces may affect DNA-polymerase interactions. Further, torque in DNA molecules appears to influence the relaxation of DNA supercoils by topoisomerase molecules (35), indicating again that force in DNA can alter DNA-protein interactions (45). Although the exact role of forces in these interactions remains elusive, it is possible that deformation of DNA may change the energy barriers the motor molecules need to overcome (analogous to the tightened wires in a piano), or change the conformation (and therefore functionality) of the motor proteins. It is well established that DNA replication, condensation and transcription rely on the conformational matches between DNA molecules and the proteins binding to them. However, deformation of DNA such as bending, stretching and twisting can alter this conformational match. As such, the structural rigidity of DNA and associated proteins comes into play, and the single-molecule biomechanics studies of DNA- protein interactions can help answer important biological questions (19).

The Mechanics of Motor Molecules

Motor molecules, a special class of proteins, play an essential role in many cellular processes, including muscle contraction, cell movement, cell division, ion and vesicle transport, signal transduction, and DNA replication, condensation and transcription (40). Specific motor molecules include the kinesin and dynein superfamily (46), the myosin superfamily (47), and numerous proteins involved in the interactions with DNA. These motor molecules convert chemical energy into mechanical work via conformational changes induced by ATP hydrolysis. As more detailed 3D structures of motor molecules (e.g. 48) and images of their movements (e.g. 49) become available, the structure-function relationship of molecular motors has begun to be revealed. It is highly likely that

molecular motors utilize protein conformational changes to store energy, generate motion, and control/regulate motor function (50). However, for most of the motor proteins, their mechanics, i.e. how they move, how their conformational changes are related to ATP hydrolysis, how the force-generation is related to their structural rigidity, is still largely unknown.

To illustrate, consider a special motor enzyme, ATP synthase, which can either pump protons against the electrochemical gradient using ATP hydrolysis, or manufacture ATP from ADP and phosphate using the energy derived from a transmembrane protonmotive gradient. The general structure of ATP synthase is shown schematically in Figure 4. It consists of a transmembrane component, F_0, comprising the proton channel, and a soluble component, F_1, containing the catalytic sites. As perhaps the world's smallest rotary engine, ATP synthase carries out both its synthetic and hydrolytic cycles through conformational changes of its β domains in the F_1 component (Figure 4a). For example, in pumping protons the rotation of the γ-subunit in the F_1 component, which contains catalytic sites located at the interfaces, is due to the hinge motion of the β domain driven by ATP hydrolysis (Figure 4b). In analyzing energy transduction in ATP synthase, it is critical to understand how the protein enzyme converts the free energy of nucleotide binding into elastic strain energy. Here, protein deformation serves as the key mechanism for mechanochemical coupling, generating mechanical torque from the free energy of ATP binding, or producing ATP using torques generated by the protonmotive force (51, 52).

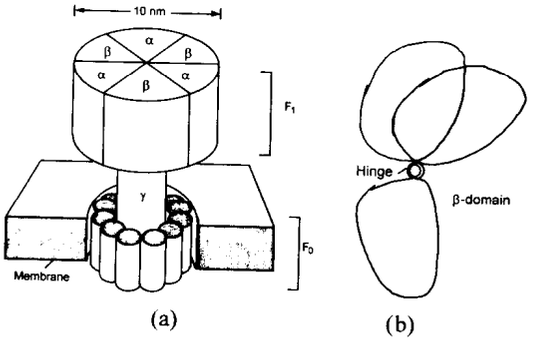

Figure 4 Schematic of the structure of ATP synthase (a). It has a transmembrane portion, F_0, and a soluble component, F_1, which contains catalytic sites located at the αβ interfaces. Hydrolysis of ATP causes hinge motion of the β domain (b), which in turn drives the rotation of F_1.

Major Biomechanical Challenges

Similar to problems in the classical mechanics of materials and structures, to understand how forces regulate cell function it is necessary to know how the forces are transmitted through the cell-ECM and cell-cell contacts and then distributed within the cell. Traction forces generated by cells during locomotion (53, 54) and mitosis (55) have been measured recently with a deformable substrate method or microelectro-mechanical systems (MEMS) technology (56). However, there is still no experimental method to quantify how these forces are distributed among various structures inside a cell. A major challenge is that cells are active and the CSK structures are dynamic. It is likely that a significant portion of forces is supported as well as generated by CSK, which changes with time. There is extensive literature on the kinetic and mechanical properties of isolated CSK components, e.g. the polymerization and crosslinking of actin. However, the direct applicability to cellular deformation has yet to be demonstrated.

Theoretically, once the applied forces and moments are known, the deformation of DNA and protein molecules can be measured through well-designed experiments, or obtained through numerical simulations. A major difficulty, however, has been the ultra-small scales of the phenomena under consideration. Summarized in Table 1 are typical sizes, forces and bond energies involved in DNA and protein deformations (40, 57). The recent advent of experimental techniques such as AFM, optical tweezers, surface force apparatus (SFA), and micropipette/microneedle have allowed direct mechanical measurements of single molecules, including how they move, deform, generate forces, and response to forces. However, it remains technically very challenging to conduct mechanical testing of the deformation of proteins due to their small sizes. For small protein molecules, their sizes may be just a few nanometers, and the deformation (in terms of length change) may be just a few angstroms. Even with the most advanced techniques such as FRET (fluorescent resonance energy transfer), quantifying such small deformation is very challenging. Advanced computer simulations, therefore, can be a powerful tool in studying protein deformations and protein-protein interactions.

Numerical simulations of protein deformation can be carried out using molecular dynamics (MD) or molecular mechanics (MM) approaches (58). While MD simulations are very generic and versatile, they are limited to phenomena with very short time duration (< 100 ns), and are computationally intensive if the entire protein molecule and the surrounding solvent are considered. Alternatively, analysis and

simulations can be simplified by considering specific deformation modes. For example, to analyze hinge motion of proteins, one can assume that the domains are rigid and treat the hinge (a turn or a loop) as a linear spring (16).

TABLE 1 Typical size, force and bond energy involved in DNA and protein deformation

Size (nm)	Force (pN)	Bond Energy (pN·nm)
α-helix: ~ 1.7	Twist DNA: ~ 0.1	van der Waals attraction: ~ 0.7
β-sheet: ~ 2.0	Stretch DNA: ~ 5.0	Hydrogen bond: ~ 7.0
Domains: ~ 2-10	Motor molecules: ~ 5-25	Ionic bond: ~ 21
Whole protein: ~ 5-200	Domain unfolding: ~ 100	Covalent bond: ~ 630

Another basic aspect of molecular biomechanics is the statistical nature of the force, motion, and conformational changes. For example, Brownian motion plays an essential role in protein-protein interactions. It also sets a limit for the accuracy of force measurements using AFM. On the other hand, it is possible that 'biased' Brownian motion can power molecular motors (59) and biological ratchets (60). The interplay between Brownian forces, the viscous drag, and molecular machines in a cellular environment may provide the basis for a rich class of phenomena in living cells and is an exciting research topic in molecular biomechanics.

Concluding Remarks

With recent advances in cell and molecular biology, biomechanics research is entering a new era in which cellular functions and molecular mechanisms have become a new focus. The integrative behavior of cells as complex biological systems is a result of integrated and regulated interactions among many components such as cell cytoskeleton, extracellular matrix (ECM), signal transduction pathways, intracellular secretion/ transport, and gene expression. Mechanical forces and deformations may play an important role in all these aspects, and in regulating cell behavior and function. Further, mechanical analyses can provide useful tools for modeling and quantitative prediction. Continuum mechanics has been successful in modeling whole-cell and tissue deformation in response to applied forces. However, to understand mechanics issues at the cellular level, it may no longer be adequate to simply lump all specific force-bearing, force-generating, and force-sensing elements into a structureless continuum - more subcellular and molecular structures and mechanisms need to be studied.

Consistent with the recent developments in life sciences, biomechanics inevitably includes the studies of molecular issues. For example, a major issue in biomechanics is how cells sense mechanical signals and convert them into biochemical or biological processes. To develop a mechanistic understanding of this issue requires the identification of the players in the signaling cascade and the elucidation of the inner workings of the molecular converters of the mechanical and chemical signals. As possible mechanisms of such mechanochemical coupling, mechanical forces may regulate cell behaviors and functions by deforming DNA and proteins, influencing the transport of ions and other molecules, and altering receptor-ligand binding kinetic rates and specificity. In all of these mechanisms, the deformation of individual biomolecules under force may play a central role. However, we still do not know the dependence of protein deformation on their specific structures, solvent environment, and applied forces. We still do not know how such deformations alter biochemical processes such as receptor-ligand binding, cell-cell and cell-ECM adhesion, cytoskeletal dynamics, and gene regulation and expression. We are facing great challenges, both theoretically and experimentally, in the study of biomolecular deformation. Nevertheless, molecular biomechanics studies will provide new approaches to obtaining molecular understanding of cellular functions, thus impacting on the development of mechanics, biology, and medicine.

As a basic discipline in engineering and science, mechanics has made tremendous progress over the last century. There is little doubt that the new century is a biotech century and mechanics can play an important role in advancing biology and medicine. Cellular and molecular biomechanics, addressing issues in cell locomotion, cell adhesion, cell spreading, cell-ECM interactions, and the dynamics of cell cytoskeleton, is important to wound healing, immunology, cell and tissue engineering, and cancer studies. Mechanics issues in proteomics and biotechnology have also begun to attract attention, including those in protein and DNA conformational dynamics, diffusion, reaction and secretion of biomolecules, and the structure-function relationship of molecular motors. The rapid accumulation of sequence and structural information about proteins and nucleic acids, and fast development of advanced technologies over the last few