BULLETIN OF THE POLISH ACADEMY OF SCIENCES
TECHNICAL SCIENCES
Vol. 57, No. 1, 2009

Nanomechanics = biomechanics[§]

L. SKUBISZAK*

Institute of Biocybernetics and Biomedical Engineering, Polish Academy of Sciences, 4 Trojdena St., 02-109 Warsaw, Poland

Abstract. The knowledge of the mechanism of mechanical energy production by the so-called bioengines, living cells, could be very helpful for resolving different tasks concerning nanomechanics, e.g., construction of nanorobots. The present work considers a new idea, namely that the conformational changes within the so-called track, actin filament or microtubule are crucial for production of the mechanical energy by all bioengines. This concept contrasts with the presently prevailing view, according to which the force is generated as a result of conformational changes within the so-called motor proteins: myosin, kinesin or dynein.

Key words: nanomechanics, cell motility, mechanism of force generation.

1. Introduction

Nanomechanics is a branch concerning transformations of a physical body in time and space at the level of 10^{-9} m. Such transformations are observed first of all in macromolecules; these are the so-called conformational changes. Macromolecules are usually described as very large molecules consisting of more than 1000 atoms. Such substances are often called polymers (e.g. nylon, cotton, glass, cellulose, rubber, carbohydrates, proteins, lipids, etc.). In the present work the term "macromolecule" will be used in relation to particular protein and "polymer" in relation to an aggregate of proteins. It will be considered the proteins and polymers which play crucial role in the fundamental function of each living cell – motility.

Protein macromolecules are characterized by four specific structure levels: primary (polypeptide chains formed by specific sequences of amino acids); secondary (specific folding of an amino acid chain into the alpha helix and pleated sheets called β-structures); tertiary (different subdomains formed by irregular 3D contortions of the chain), and quaternary (the overall 3D structure that results from subdomain aggregation). The primary structure is maintained by strong covalent bonds between amino acids. The amino acid sequence depends on genotype, and single changes in it may have essential impact on the macromolecule function. The secondary structure is determined mostly by H-bonds occurring at regular intervals of polypeptide backbone, thereby it also depends on the genotype. The α- and β- structures determine the so-called allosteric features of the macromolecules: they transfer the information about the local changes within the molecule. The subdomains specific for the tertiary structure are responsible for the so-called stereo-specific interactions: the correct 3D folding of the polypeptide determines correct recognition and binding of other molecules (the lock-and-key principle). The quaternary structure determines the molecule conformation. The last two structures depend on the environment, e.g. on temperature, pH or salt concentration, as well as on the molecules bound to the specific sites. Experimental data gathered during the last two decades clearly indicate that the features specific for the macromolecules are crucial for each cell to be alive.

The work casts light on some problems concerning the structure and functioning of the living cell, which is considered as a bioengine (Fig. 1). In the literature bioengines are usually presented as a system consisting of two elements: the track (actin filament or microtubule) and motor protein (myosin, kinesin or dynein). But only one of the two constituents is taken into account as an active element at force generation. The lever-arm model focuses on conformational changes within motor proteins, and the track is believed to be rigid. The concept of polymerization/depolymerization of actin filament considers the track to be an active element. In the present work it is suggested that the mechanism of force generation is universal in all cells [1]; it is based on conformational changes of polymers (actin filaments or microtubules), and not of separate proteins.

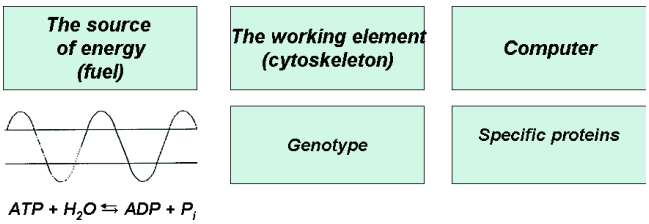

Fig. 1. Three elements determining main features of each engine. The bioengine, i.e. the living cell could be presented similarly to a technical machine. But it is worth noting that in contrast to the technical engine, in the living cell all three elements are inseparable parts of the whole. The source of energy for action – ATP (or GTP) hydrolysis (Fig. 2) – is identical in all cells. The part producing mechanical work is called the working element; it is equivalent to that called in biology the cytoskeleton. By computer is called the system responsible for regulation of the bioengine action

Understanding of the mechanism of force production for cell motility seems to be indispensable for construction of the

[§]Presented at 1st National Conference of Nano and Micro Mechanics (KKNM08), Krasiczyn, July 2008.

*e-mail: lskubiszak@ibib.waw.pl

XXI century machine, i.e. nanorobot. Some aspects of bioengine action, e.g. cycle of the ATP hydrolysis, have been already used for the nanorobot building [2, 3]. But construction of a nanorobot for medical needs, i.e. construction of a machine which would find a damaged protein within a cell, repair it and include into the proper cell organelle, is a much more complex challenge. To perform such task, the nanorobot must first of all reach the target, i.e. it must produce mechanical work.

2. Bioengine

Every engine can be schematically represented by three basic elements (Fig. 1): the energy source, or fuel; the working element (e.g. the structure transforming the energy stored in the fuel into mechanical work), and "computer" (e.g. the object controlling and regulating the work of the engine). The living cell may be considered a bioengine because it contains all elements listed above. The working element (the cytoskeleton) transforms the chemical energy released in cellular metabolic processes into mechanical work, i.e. into the cell motion. In contrast to the engines constructed by people, the transformation goes trough a set of different biochemical and biophysical events. The chronology of the events is controlled and regulated by specific proteins.

The bioengine differs from technical engines also by their mechanical parameters which are not constant; they continuously change with the change of the cell state. For this reason the term "motion" in relation to the cell has not only strictly physical sense (i.e. an opportunity of changing position in the environment), but is also related to cell development or maintenance of its vitality (e.g. reproduction, division, metabolism, etc.).

It is worth noting that the two terms are often used in literature as equivalent to cell motion: cell motility and cell migration. The term "cell motility" is usually used for description of every changes of the cell mechanical parameters, within the cell as well as outside, while "cell migration" means cell movement to a specific location. It is commonly believed that the mechanism of force generation for the both forms of cell motion is identical; however, in the present work it is suggested that the mechanism of migration can be identical in all types of cell, despite the different way of locomotion utilized by different cells; nevertheless, it may differ, for instance, from the mechanism of cell growth or regeneration.

2.1. The bioengine energy source. The energy source in living cells is adenosine-5'-triphosphate (ATP) which is synthesized within a cell, in mitochondria. The ATP molecule consists of adenine, ribose, and three phosphate groups, P_i (Fig. 2). The ATP hydrolysis, i.e. reaction ATP + $H_2O \rightarrow$ ADP + P_i, is exergonic, what means that the energy of the product (ADP + P_i) is lower than that of the reactant, ATP. Under typical cell conditions the overall negative change of the Gibbs free energy (ΔG) is approximately -57 kJ/mol (or -14 kcal/mol) [4]. The ability of ATP to store the chemical energy in its terminal phosphate group bonds is successfully exploited by the nature; the reaction of ATP hydrolysis is always coupled with thermodynamically unfavorable reactions.

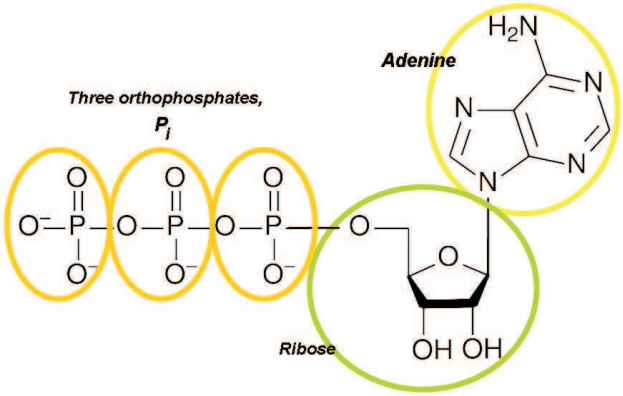

Fig. 2. Schematic representation of ATP molecule. Dissociation of the phosphate group gives rise to ADP and then to AMP

Three adjacent phosphate residues (Fig. 2) determine the high affinity of ATP to some enzymes (e.g. to myosin or kinesin). On that reason ATP in living cells appears rather not as a free molecule but as a specifically binding substrate. The process of ATP hydrolysis and synthesis takes place cyclically (Fig. 1, left panel). On the basis of the ATP specificity, the first nanorobot has been designed [2, 3]. In such nanorobot, the cyclical processes of ATP hydrolysis are transformed into rotational motion of actin filament.

2.2. The ways of bioengine work. Biological cells move within three major types of extracellular matrix: on solid substrate, in liquid, and across tightly packed membranes of other cell. Because of this, they use various locomotion strategies. Muscle cells, for instance, cyclically contract along their axis, ([5, 6], Fig. 3). Non-muscle cells, especially prokaryotic, can crawl, glide, swim, or rotate. Crawling is specific for migration on solid surfaces. It is characterized by deformation of cell membranes and can be described by exploration of the leading edge, attachment, maturation of adhesions, advancement of the cell body, and release of adhesions to pull the rear forward. In this relatively slow crawling mode, cells migrate at 0.5–1 μm/min. It is characteristic for *Amoeba*, *Dictyostelium*, neutrofils, or microphages; this type of motion is often called amoeboid. Gliding is a smooth and continuous movement. It is characteristic of apicomplexan parasites, e.g. *Listeria*. The gliding mode is unique because it enables parasites of migrating across biological barriers, i.e. across the host-cell membrane, and egress it. The cells living in liquid environment demonstrate the ability of swimming (*E.coli*, *Chromatium*, spermatozoa) and rotation (fish and amphibian keratinocytes).

2.3. The working elements of bioengines. Force for cell migration is generated by a working element known in biology as a cytoskeleton (Fig. 1). The cytoskeleton depends on the genotype, but from the point of view of its structure, there is rather similarity, not variety. In most cells, the so-called actin-myosin cytoskeleton exists. The prerequisite of motion in such

cells (to which belong all types of muscle and majority of eukaryotic and prokaryotic cells) is the interaction between the actin monomers and myosin heads. The muscle, for instance, contract due to sliding in the opposite directions of two kinds of filaments, myosin-based and actin-based (Fig. 3). In other cells, for example neurons, the cytoskeleton consists of microtubules (formed by tubulin) and kinesin or dynein. In this case, the interaction between tubulin and kinesin (or dynein) is needed.

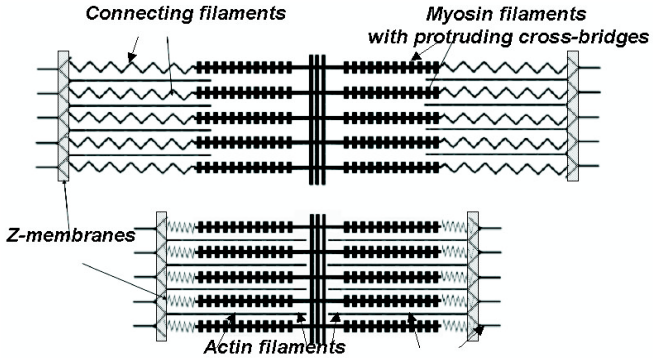

Fig. 3. Contraction of sarcomere, a muscle quasi-cell, in accordance with H. Huxley and A. Huxley Refs. 5, 6. Two groups of the filaments, thin actin-based (about 1 μm long) and thick, myosin-based (about 1.6 μm long) slide in the opposite directions. As a result, the length of the sarcomere can change from about 3 μm to about 2 μm

There is, however, a group of cells in which the cytoskeleton consists of actin filaments only. Such cells can crawl, glide or rotate. The crawling movement, demonstrated by membrane deformation, is coupled with formation of pseudopodia (filopodia and lamellipodia, Fig. 4; [7–9]). The experiments, mostly based on fluorescence [10], have revealed that lamellipodia and filopodia consist of actin filament bundles. In lamellipodia, two sets of actin filaments are oriented at about 70° relative to one another and about 50° relative to the membrane surface [7, 8]. They cross-link and form quite dense networks. In filopodia, actin filaments oriented at about 90° relative to the front edge of the cell, are arranged parallel to one another. A cell migrates along a surface by extending filopodia at the leading edge or by curving the cell membrane. Deformation of the cell membrane is probably caused by structural changes within the specific actin filament network.

The gliding movement takes place without any noticeable deformation of the cell body. But locomotion, for example, of *Listeria* is coupled with appearing of the so-called comet tail outside the cell body; the "comet tail" consists of the bundles of actin filaments [11].

For swimming, the cells use specific structures called flagella and cilia [12]. These hair-like projections extend outwards from the cell body (Fig. 5). There is a large difference between eukaryotic and prokaryotic flagella; the eukaryotic flagellum is similar to the cilium, while the bacterial flagellum is composed of the protein, flagellin. The cilia can cover the whole body of the cell or only a part of it. The cilia are uniform in shape, and their length is about 5–10 μm and diameter of about 0.04 μm. The flagella are typically larger than the cilia; they can be up to 70 μm long and 0.8 μm wide. Flagella may occur one per cell, as in spermatozoa, or a few, as in *E.coli*, at one or both poles of the cell. These organelles propel the fluid over the cell surface. As to cilia, there are two types of them: motile and non-motile. The motile cilia constantly beat in a single direction; they work cooperatively, in a synchronized fashion or with a constant phase difference. The non-motile cilia play the role of cellular antennae, they coordinate a large number of cellular signaling pathways, e.g. cell division or differentiation. As to the structure, the cells of this type belong to the group in which tubulin-kinesin or tubulin-dynein cytoskeleton participates in force generation. Tubulin is aggregated in the so-called "9+2" structure (Fig. 6). It is clear that in action of cilia and flagella the interaction between tubulin and dynein is involved. The interaction between tubulin and kinesin is characteristic mostly of various intercellular processes.

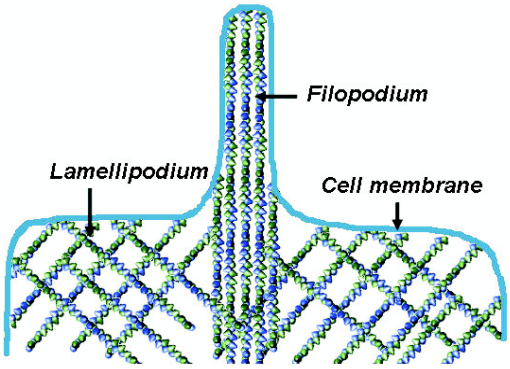

Fig. 4. Arrangement of actin filaments in pseudopodia (according to Refs. 9–11). The "barbed" ("plus") end of the actin filament is localized from the side of membrane. Filopodia are typically 0.1–0.5 μm thick and extend to 5–50 μm. The structure of the lamellipodia depends on the cell type

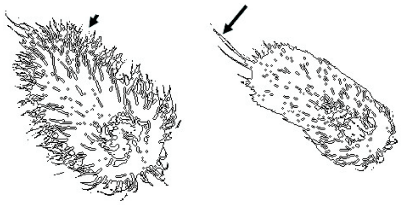

Fig. 5. Two phases of the *E.coli* movement. The bacteria migrates due to movement of the flagella (long arrow) and cilia (short arrow)

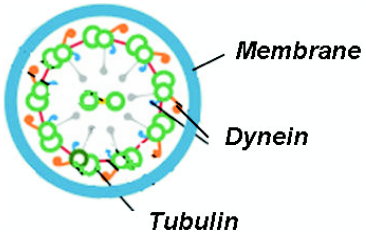

Fig. 6. Structure of cell cilium and flagelium. Most of cilia and flagella are build from tubulins and dyneins. Tubulin dimers aggregate into the so-called 9+2 microtubules. Sometimes the central pair is lacking; such structure is called 9+0

3. The present day concepts of the force generation mechanism

Despite a large number of different observations, there is still a great uncertainty of how cell migration really takes place. The above mentioned experimental data clearly show that different types of cells use a variety of strategies to perform motion. At the same time, it is well established that the conformational changes of one or two specific proteins are always coupled with cell migration. That suggests that the mechanism of force generation may be universal.

Now, two concepts of force generation mechanism are accepted: the so-called lever-arm model and the model of polymerization and depolymerization of actin. The first concept refers to the cells with actin-myosin cytoskeleton (all types of muscle cells, e.g. skeletal, cardiac, and smooth, and majority of non-muscle cells). By the second mechanism (polymerization/depolymerization) the cell migration involving lamellipodia, filopodia, and comet tails (e.g. *Amoeba* or *Listeria*) is described.

3.1. The lever-arm model. The lever-arm model [13–15] is a modern version of the so-called cross-bridge model proposed simultaneously, but independently, by two English scientists forty years earlier [5, 6]. The concept was devised for muscle cells. According to it, muscle contract due to sliding of two kinds of filaments into opposite directions, and the movement is generated by the cross-bridges protruding from myosin filaments towards actin filaments (Fig. 3). Originally, the bending of the myosin molecule within the two hinge domains (Fig. 7; for review, see [16]) has been considered as the way of the cross-bridge action. According to the lever-arm concept, the cross-bridge consists of the head of myosin molecule, and the force is generated as a result of the myosin head bending (Fig. 8, for review, see [17]). The bending is caused by the strong interaction of the myosin head with the actin monomer, and the force production manifests in shifting of the actin filament. The mechanism of motion production specific for muscle is often transferred on the cells in which the actin-myosin cytoskeleton takes participation. The same mechanism is also considered when tubulin-kinesin or tubulin-dynein cytoskeleton works. In this case, the conformational changes of kinesin or dynein are taken into account.

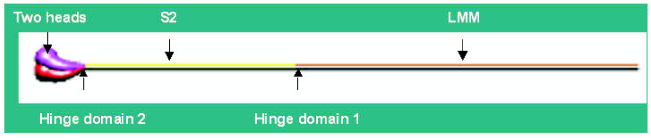

Fig. 7. Structure of myosin II, i.e. the myosin molecule occurring in all types of muscles (for review, Ref. 16). Myosin II consists of two globules, called heads (see Fig. 10), and the tail with the diameter of 2 nm and the length of 160 nm. The tail contains two specific segments called subfragment-2 (S2) and light meromyosin (LMM). In the part between these fragments, the tail demonstrates high flexibility

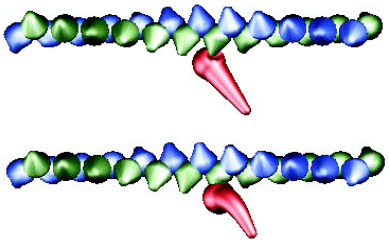

Fig. 8. The bioengine is usually described as a track (actin filament or microtubule) along which the motor protein (myosin, kinesin, or dynein) moves. The myosin head is depicted by a red globule, while actin monomers by green and blue globules. The parameters used for computation of the elements are discussed in Refs. 16, 17

3.2. Arguments for and against the lever-arm model. The lever-arm mechanism is usually described by the scheme proposed by Geeves and co-authors [18]. The main events which usually are taken into consideration are presented in Fig. 9. The biochemical events enclosed into the scheme and denoted by letters could be considered as well confirmed by experiments performed in solution on the following reasons:

(a) – The so-called rigor state (any nucleotides are absent). Under such conditions, the myosin head displays a high affinity to actin, and the interaction between the two proteins is strong.

(a-b) – The myosin head also has a high affinity to ATP, so in solutions with high ATP concentration, the myosin heads quickly bind it by the so-called nucleotide binding site (Fig. 10). But myosin with bound ATP cannot interact with actin.

(b-c) – As myosin is an enzyme, ATP hydrolysis starts at ATP binding to myosin.

(c-e) – The ATP hydrolysis lasts long because the phosphate group, P_i (Fig. 2), detaches from the nucleotide in 3 phases. The product of the first phase of ATP hydrolysis, ATP-P_i leads to weak binding with actin monomer. The second phase, characteristic of weak binding of P_i to ADP, leads to strong interaction with actin. The third phase corresponds to complete detachment of P_i.

(e-a) – The strong interaction with actin causes the detachment of ADP from the myosin head, i.e. leads to the rigor state.

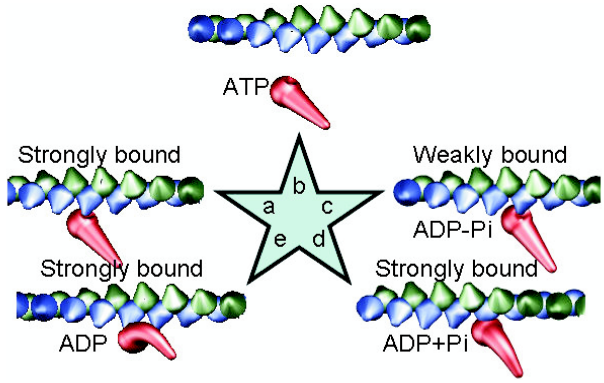

Fig. 9. Chronology of the events which are usually considered to be crucial in force generation (in accordance with Ref. 18). For description see the text. The parameters used for computation of the elements are discussed in Refs. 16, 17

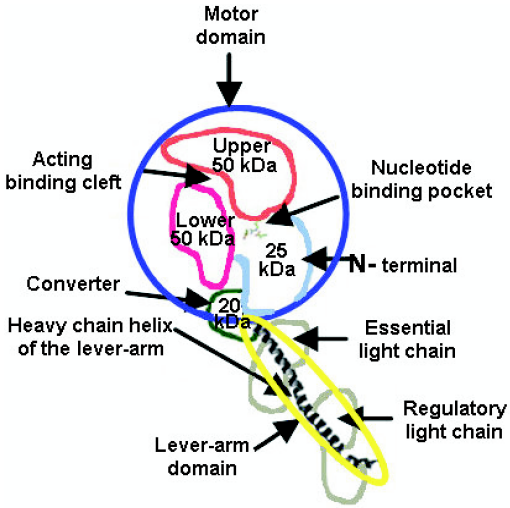

Fig. 10. Main elements of the myosin head determining its biochemical, biophysical and mechanical properties (in accordance with Refs. 13–15). The head length is 19 nm; the diameter of the motor domain is about 6 nm

The biophysical aspect of the lever-arm model, i.e. the mutual configuration of the two parts of myosin head (Fig. 10) shown in the scheme has not been verified experimentally. The experimental data have revealed only that the myosin head conformation without nucleotide is different from that with ADP [19–21]. The difference consists in orientation of the lever-arm domain in relation to the motor domain (see Fig. 10). But the degrees of rotation are conflicting; the values announced in literature are in the range of about 45° (Fig. 11) even for the same state. And what is mostly confusing, the conformational changes in myosin head caused by actin binding have not yet been established.

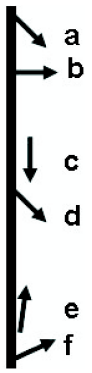

Fig. 11. Different orientations of the lever-arm domain of the myosin head (arrows) in relation to the actin filament axis (vertical line): a and b – chicken striated muscle in the absence of nucleotide (in accordance with Refs. 19, 20); c and d – scallop striated muscle in the presence of MgADP (in accordance with Refs. 20, 21); e and f – chicken smooth muscle in the presence of MgADP-AlF4- (in accordance with Refs. 19, 20).

The principle of the myosin lever-arm functioning (Fig. 8) is also controversial from the mechanical point of view. One of the indispensable elements of each lever is the fulcrum. If we presume that the fulcrum is in the place where myosin is connected to actin, then the force can be produced at the other end, i.e. at the free end. So, from the point of view of the lever-arm mechanism we can understand the transportation of different molecules bound to the free end of the myosin head. Shifting of the actin filament may be possible only if the fulcrum is at the opposite end, i.e. the lever-arm domain of the myosin head would need to be immobilized. However, such situation does not occur in the cells to which the model is usually applied (e.g. muscle).

Summarizing, it is worth noting that the lever-arm concept assumes that only myosin plays an active role in force generation. But, as mentioned above, some cells do not possess an actin-myosin cytoskeleton, but have a highly developed actin network at the leading edge (e.g. *Amoeba*) or at the rear edge, outside the cell body (e.g. *Listeria*). So classification of myosin as a motor protein seems to be unfounded.

3.3. Actin polymerization/depolymerization model. To describe cell migration involving a complex actin skeleton located just under cell membrane, the mechanism based on polymerization and depolymerization of actin filaments [22] is usually considered. However, how the actin polymerization contributes to the events experimentally observed as coupling to the cell protrusion [23–26] is unclear.

The most controversial aspects are as follows.

(1) – It is not clear how the equilibrium occurs between polymerization and depolymerization. To obtain remarkable elongation of the actin filament during protrusion (i.e. to form the filopodia), a high concentration of actin monomers is required. The concept presumes that within a cell there is a pool of free actin monomers which attach to the so-called "barbed" ("plus") end of the actin filament and detach from the so-called "pointed" ("minus") end. But according to the experimental data [27–29], the actin filament manifests different dynamics of monomer aggregation, the plus end is fast-growing, and the minus end is slow-growing. So, the lack of free actin monomers should occur within the cell.

(2) – It is not clear what is the relation between the filament protrusion and cell adhesion to the substrate. It seems reliable that actin polymerization and depolymerization is controlled by the so-called Rho-family proteins [30–33]. But the mechanism by which the proteins coordinate the dynamics of actin filament network and cell migration is unknown.

(3) – In cells, the plus end of actin filaments is oriented towards the cell membrane and the minus end towards the cytoplasm. Some experiments clearly show [24, 34, 35] that the actin filaments are strongly attached to the leading front of cell membrane. So, it is not clear in what way the barbed end pushes the membrane forward if a gap is needful for actin monomer attachment.

(4) – One of the crucial questions is the relation between the speed of protrusion and the tempo of actin polymerization. So far we have no unquestionable experimental data, but only some estimations suggesting that polymerization goes much slower than cell protrusion. In the slow crawling mode, the cell migrates with the speed 8–20 nm/s [36]; in one of faster gliding modes (*T. Gondii*, [29]), the speed is 1 μm/s.

Simulation of the so-called treadmilling processes [37, 38], i.e. fluxing of actin subunits from the barbed to pointed ends of the actin filament, has revealed that slower polymerization takes place with the speed about 1.2 nm/s, and the faster mode goes at about 13.2 nm/s.

4. New model of cell migration

The short review presented above clearly shows that the actin filament (or its equivalent, microtubule) participates in production of mechanical work in all types of cells. Therefore, it seems reasonable to infer that the track (actin filament or microtubule) must be a generator of force.

In 1985, I proposed a new concept [39, 40]. According to it, in muscle cells, where actin and myosin are assembled in separate filaments arranged in a hexagonal lattice, the both proteins play active role in force generation. Each myosin cross-bridge generates force by unwrapping from myosin filament surface and moving towards the surrounding actin filaments [40, 41]. The actin filament generates force by elongation and rotation which are a result of strong interaction between actin and myosin ([1, 17, 42]). This model is in contrary to the commonly accepted view. In the field of muscle contraction, it is commonly thought that force for contraction is generated only by myosin cross-bridges, the actin filament is considered as a rigid rod. However, the performed by me simulation of muscle contraction [42] clearly reveals that the stereo-specific interaction between thousands of the actin monomers and myosin heads is possible only if each actin filament changes its conformation. The conformational change consists in axial shifting from 2.75 nm to 2.867 nm and rotation from 166.15° to 168° between adjacent actin monomers arranged into the so-called genetic helix, 42]. The elongation of actin filament by approximately 4% is limited by the so-called regulatory proteins, tropomyosin (Tm) and troponin (Tn). In non-muscle cells, the actin filament is not covered by the Tm-Tn complex; so, it can elongate to a larger extent (Fig. 12).

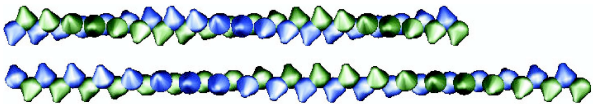

Fig. 12. Elongation of the actin filament caused by conformational change of the whole filament. The image shows the change consisting in axial shifting from 2.75 nm to 3.5 nm and rotation from 166.15° to 170° between adjacent actin monomers within the so-called genetic helix. The myosin binding site on each actin monomer is depicted by a cone. In this way, the changes in the helical structure are more prominent. The parameters used for computation of the elements are discussed in Ref. 17

Summarizing, we can say that the actin filament (or microtubule) can produce mechanical work both unaided (in cells where only actin cytoskeleton exists) or along with myosin (when the actin-myosin cytoskeleton participates in production of motion). The conformational change of the whole filament (or microtubule) could be caused by conformational changes within successive actin monomers (or tubulin dimers). The conformation changes of each actin monomer (or tubulin dimmer), in turn, could be induced by interaction with the so-called actin-binding proteins; in muscle, it is myosin [17], in *Amoeba* or *Listeria* that could be one (or a few) of the so-called actin-binding proteins (for review see [33]).

The mechanical properties of actin filament and their consequences for the cell motility will be considered elsewhere.

5. Conclusions

The present review suggests that classification of the track as a passive element and myosin, kinesin, and dynein as the motor proteins is groundless. In view of available experimental data (for review see [17, 41, 42]), it is very probable that conformational changes into the track (actin filament or microtubule) generate force for migration of all cells. The conformation of the track is determined first of all by conformation of particular macromolecules as well as by the medium conditions (temperature, pH, or ionic strength). At the same time, the macromolecule conformation is strongly coupled with the phase of the ATP hydrolysis and with the phase of interaction with the specific substrate. What is important, both events take place within the macromolecule and are strongly coordinated (the law of cooperativity). The interaction of the macromolecule with the nucleotide as well as with the substrate is stereospecific (the law of key and lock). Thus, the conformational changes within particular protein macromolecule is essential but not sufficient for cell motion.

Summarizing, it seems reasonable to conclude that the macromolecule is a quasi-engine, because its features determine only the potential abilities of the bioengine. The mechanical work needful for the cell action depends on interaction between the macromolecules within the polymer. So, the polymer consisting of a number of the macromolecules is the integral bioengine. The network built of polymers (hexagonal lattice in muscles, lamellipodia, filopodia, comet tail, cilia, flagella) is only an amplifier.

The lengths of particular proteins and their polymers are ranging from about 6 to 20 nm and from about 35 nm to 100 μm, respectively, and the diameters – from 2 nm to 24 nm. Such particles float in water at 20°C with velocity from 0.5 μm/s to 25 μm/s; the force needed for such movement is approximately 2 pN. Therefore, we may say that nanomechanics is equivalent to biomechanics.

REFERENCES

[1] L. Skubiszak, "Force is generated by elongation of the actin filament", *FEBS J.* 274, E4–5 (2007).

[2] K. Kinosita, R. Yasuda, H. Noji, S. Ishiwata, and M. Yoshida, "F1-ATPase: a rotary motor made of a single molecule", *J. Cell* 93 (1), 21–24 (1998).

[3] M. Yoshida, E. Muneyuki, and T. Hisabori, "ATP synthase–a marvellous rotary engine of the cell", *Nat. Rev. Mol. Cell Biol.* 2 (9), 669–677 (2001).

[4] L. Stryer, *Biochemistry,* W.H. Freeman, New York, 2002.

[5] A.F. Huxley and R. Niedergerke, "Structural changes in muscle during contraction", *Nature* 173, 971–972 (1954).

[6] H.E. Huxley and J. Hanson, "Changes in the cross-striations of muscle during contraction and stretch and their structural interpretation", *Nature* 173, 973–976 (1954).

[7] J.V. Small, "Myosin filaments on the move", *Nature* 331, 568–569 (1988).

[8] J.V. Small and G.P. Resch, "The comings and goings of actin: coupling protrusion and retraction in cell motility", *Curr. Opin Cell Biol.* 17 (5), 517–523 (2005).

[9] A.K. Lewis and P.C. Bridgman, "Nerve growth cone lamellipodia contain two populations of actin filaments that differ in organization and polarity", *J. Cell Biol.* 119 (5), 1219–1243 (1992).

[10] J.P. Heath and B.F. Holifield, "On the mechanisms of cortical actin flow and its role in cytoskeletal organisation of fibroblasts", *Symp. Soc. Exp. Biol.* 47, 35–56 (1993).

[11] J.W. Shaevitz and D.A. Fletcher, "Curvature and torsion in growing actin networks", *Phys. Biol*. 5 (2), 26006 (2008).

[12] L.B. Pedersen, I.R. Veland, J.M. Schrøder, and S.T. Christensen, "Assembly of primary cilia", *Dev. Dyn.* 237 (8), 1993–2006 (2008).

[13] I. Rayment, H.M Holden, M. Whittaker, C.B. Yohn, M. Lorenz, K.C. Holmes, and R.A. Milligan, "Structure of the actin-myosin complex and its implications for muscle contraction", *Science* 261 (5117), 58–65 (1993).

[14] I. Rayment, W.R Rypniewski, K. Schmidt-Base, R. Smith, D.R. Tomchick, M.M. Benning, D.A. Winkelmann, G. Wesenberg, and H.M. Holden, "Three-dimensional structure of myosin subfragment-1: a molecular motor", *Science* 261 (5117), 50–58 (1993).

[15] T.Q. Uyeda, P.D. Abramson, and J.A. Spudich, "The neck region of the myosin motor domain acts as a lever arm to generate movement", *Proc. Natl Acad. Sci. USA* 93 (9), 4459–4464 (1996).

[16] L. Skubiszak and L. Kowalczyk, "Myosin molecule packing within the vertebrate skeletal muscle thick filaments. A complete bipolar model", *Acta Biochim. Pol.* 49 (4), 829–840 (2002).

[17] L. Skubiszak, "Thin filament flexibility and its role in muscle contraction", *Biophysics* 51 (5), 692–700 (2006).

[18] M.A. Geeves, R. Fedorov, and D.J. Manstein, "Molecular mechanism of actomyosin-based motility", *Cell Mol. Life Sci.* 62 (13), 1462–1477 (2005).

[19] R. Dominguez, Y. Freyzon, K.M. Trybus, and C. Cohen, "Crystal structure of a vertebrate smooth muscle myosin motor domain and its complex with the essential light chain: visualization of the pre-power stroke state", *Cell* 94 (5), 559–571 (1998).

[20] A. Houdusse, V.N. Kalabokis, D. Himmel, A.G. Szent-Györgyi, and C. Cohen, "Atomic structure of scallop myosin subfragment S1 complexed with MgADP: a novel conformation of the myosin head", *Cell* 97 (4), 459–470 (1999).

[21] D. Risal, S. Gourinath, D.M. Himmel, A.G. Szent-Györgyi, and C. Cohen, "Myosin subfragment 1 structures reveal a partially bound nucleotide and a complex salt bridge that helps couple nucleotide and actin binding", *Proc. Natl Acad. Sci. USA* 101 (24), 8930–8935 (2004).

[22] C.S. Peskin, G.M. Odell, and G.F. Oster, "Cellular motions and thermal fluctuations: the Brownian ratchet", *Biophys J.* 65 (1), 316–324 (1993).

[23] T.D. Pollard, "The cytoskeleton, cellular motility and the reductionist agenda", *Nature* 422 (6933), 741–745 (2003).

[24] T.D. Pollard and G.G. Borisy, "Cellular motility driven by assembly and disassembly of actin filaments", *Cell* 112 (4), 453–465 (2003).

[25] J. Plastino and C. Sykes, "The actin slingshot", *Curr. Opin. Cell Biol.* 17 (1), 62–66, (2005).

[26] A. Mogilner, "On the edge: modeling protrusion", *Curr. Opin. Cell Biol.* 18 (1), 32–39 (2006).

[27] T.P. Stossel, "Contribution of actin to the structure of the cytoplasmic matrix", *J. Cell Biol*. 99 (1 Pt 2), 15–21 (1984).

[28] D.A. Begg, R. Rodewald, and L.I. Rebhun, "The visualization of actin filament polarity in thin sections. Evidence for the uniform polarity of membrane-associated filaments", *J. Cell Biol.* 79 (3), 846–852 (1978).

[29] D. Soldati and M. Meissner, "Toxoplasma as a novel system for motility", *Curr. Opin. Cell Biol.* 16 (1), 32–40 (2004).

[30] A.J. Ridley and A. Hall, "The small GTP-binding protein rho regulates the assembly of focal adhesions and actin stress fibers in response to growth factors", *Cell* 70 (3), 389–399 (1992).

[31] A.J. Ridley, "Rho family proteins: coordinating cell responses", *Trends Cell Biol.* 11 (12), 471–477 (2001).

[32] A.J. Ridley, "Rho GTPases and cell migration", *J. Cell Sci.* 114 (Pt 15), 2713–2722 (2001).

[33] E.A. Papakonstanti and C. Stournaras, "Cell responses regulated by early reorganization of actin cytoskeleton", *FEBS Lett.* 582 (14), 2120–2127 (2008).

[34] L.A. Cameron, T.M. Svitkina, D.Vignjevic, J.A. Theriot, and G.G. Borisy, "Dendritic organization of actin comet tails", *Curr. Biol.* 11 (2), 130–135 (2001).

[35] S.C. Kuo and J.L. McGrath, "Steps and fluctuations of Listeria monocytogenes during actin-based motility", *Nature* 407 (6807), 1026–1029 (2000).

[36] S. Even-Ram and K.M. Yamada, "Cell migration in 3D matrix", *Curr. Opin. Cell Biol.* 17 (5) 524–532 (2005).

[37] M. Bindschadler and J.L. McGrath, "Formin' new ideas about actin filament generation", *Proc. Natl Acad. Sci. U S A* 101 (41), 14685–14686 (2004).

[38] M. Bindschadler, E.A. Osborn, C.F. Dewey, and J.L. McGrath, "A mechanistic model of the actin cycle", *Biophys. J.* 86 (5), 2720–2739 (2004).

[39] L. Skubiszak, " Participation of the individual overmolecular muscular cell in movement", *VII State Scientific Conf. Biocybernetics and Biomedical Engineering* 1, 122–124 (1985), (in Polish).

[40] L. Skubiszak, "Force generation in muscle. Organization in working structures of muscle", *Lect. Not. ICB Sem.* 5, 237–297 (1989).

[41] L. Skubiszak, "On muscle contraction mechanism", *Lecture Notes Modelling in Biomechanics* 19, 537–566 (2005).

[42] http://sarcomere.ibib.waw.pl