Scientific Research Publishing

Yangtze Medicine, 2017, 1, 202-215
http://www.scirp.org/journal/ym
ISSN Online: 2475-7349
ISSN Print: 2475-7330

Molecular Motors—Self-Organization of Cytoskeletal Network

Kishore Dutta

Department of Physics, Handique Girls' College, Guwahati, India
Email: kdkishore77@gmail.com

How to cite this paper: Dutta, K. (2017) Molecular Motors—Self-Organization of Cytoskeletal Network. *Yangtze Medicine*, **1**, 202-215.
https://doi.org/10.4236/ym.2017.14021

Received: September 14, 2017
Accepted: December 10, 2017
Published: December 13, 2017

Abstract

Molecular motors play an important role in the organization of cytoskeletal filament networks. These nanometer-sized natural molecular machines opened up a new frontier of nano-technology. This article describes biomolecular nano-machines, their internal structures, and dynamical interactions between molecular motors and their molecular tracks which reorganize a network of long protein filaments, particularly during cell division to form cytoskeleton of daughter cells. Towards the end, the article also takes up some still-to-be resolved matters and prospects for future developments in this exciting multidisciplinary area of science.

Keywords

Cell Motility, Molecular Motors, Self-Organization

1. Introduction

Spontaneous, self-generated movement is a hallmark of almost all biological systems. Even cells that are incapable of active movement within their environment perform essential intracellular motility processes. *Cell motility* is a complex and integrated process governed by the dynamics of cytoskeleton filaments and collective activities of a series of biological nanomachines in the cell machinery [1] [2] [3] [4] [5]. Most forms of movement in the living world are powered by these tiny protein machines known as *molecular motors*. Molecular motors are essential molecules of life which actively involve in diverse functions of cells such as muscle contraction, vesicle transport, chromosome separation, replication, transcription, and translation. Although recent advent of highly sophisticated novel biophysical techniques, such as fluorescence microscopy, high speed atomic force microscopy, and optical tweezers [6] [7] [8] [9] [10], has signifi-

cantly increased our understanding regarding the function and role of molecular motors in the cell, how Nature designed these tiny powerful ingenious nano-scale devices to achieve coordination and collective action in all living organisms, is still remains a mystery.

Nature offers a wide variety of different motor families characterized by their chemical structures, environments, and direction of motions. From a broad theoretical perspective, a molecular motor can be imagined as a microscopic object that moves predominantly in one direction along the molecular track—a polarized one-dimensional periodic structure. Within the cell, there are several molecular tracks, namely, cytoskeletal filaments, DNA, RNA, and mitochondrial membranes. The movement of the molecular motors along these molecular tracks is characterized by unidirectionality (yielding non-equilibrium behavior), discrete steps, and intrinsic stochasticity. All these events that take place stochastically and characterized by the intrinsic rate are known as Poisson processes in statistical physics. Interestingly, the dynamic interactions of the motors and filaments exhibit cooperative collective behavior yielding a rich variety of stable self-organized structure [11] [12] [13]. In this review article, we shall first introduce and elucidate few common molecular motors and their dynamic characteristics. Focusing on fundamental physical principles underlying the collective phenomena resulting from the interaction of many molecular motors and linear protein filaments, we then describe the self-organization of long protein filament networks, particularly during cell division to form cytoskeleton of daughter cells. Our discussion suggests a new perspective to our understanding of collective motion, a topic of increasing interest among physicists, mathematicians, engineers and biologists.

2. Various Molecular Motors and Their Tracks

Based on the tracks on which they move, the motor proteins are classified as cytoskeletal based, nucleic acid based, and membrane based motor proteins. Among various molecular motors, *kinesin*, *dynein*, and *myosin* are cytoskeleton-based motors which move in a directed manner along cytoskeletal filaments [1]. The majority of active transport in the cell is driven by these three classes of molecular motors. The *helicases*, *polymerases*, and *ribosomes* are nucleic acid based motors which move in the track of single-stranded DNA or mRNA. On the other hand, pumps, protein translocation motors, ATP synthase (commonly called ATPase), and flagellar motors are associated with membranes. Recent revolutionary advances in single molecule detection techniques enable to observe directly the activity and performance of individual molecular motors [9]. In **Table 1**, we summarize some common characteristics of these molecular motors. In what follows, we shall briefly elucidate the dynamic behavior of these molecular motors.

2.1. Microtubule Based Motors

Microtubules are long rigid polymers made up of the dimer globular proteins

Table 1. Characteristics of some common molecular motors.

Motor	*Track*	*Type of motion*	*Direction of movement*	*Fuel*
Kinesin	Microtubule	Linear	Walks toward + end	ATP
Dynein	Microtubule	Linear	Walks toward - end	ATP
Myosin	Actin filament	Nominally linear	Walks toward barbed end	ATP
DNA helicase	DNA single strand	Linear	3′to 5′end of a DNA single strand or vice versa	ATP
RNA helicase	RNA strand	Linear	3′to 5′end of a DNA single strand or vice versa	ATP
DNA polymerase	DNA single strand	Linear	Choreographed movement	Hydrolysis of nucleotides
RNA polymerase	DNA single strand	Linear	Choreographed movement	Hydrolysis of nucleotides
Ribosome	mRNA strand	Linear	Forward movement	Hydrolysis of nucleotides
ATP Synthase	Mitochondrial membrane	Rotary	Unidirectional rotation	Proton flux

called *tubulin*. The α - and β -tubulins pairwise aggregate into tubulin heterodimers, which are longitudinally associated with one another to form protofilaments. Microtubules are hollow fibers consist of typically 13 such parallel protofilaments. As the heterodimers are polar in nature, the microtubules also possess a polarity, usually denoted as the (−) and the (+) end; plus-ends located in the cell periphery and minus-ends located at the microtubule organizing center near the nucleus. Due to this polarity, molecular motors such as kinesins and dyneins can walk unidirectionally on the microtubules and carry various cargo particles such as vesicles, mRNA, mitochondria, endosomes, virus particles, or other organelles many times the size of the motor, to their required destination [4] [5]. **Figure 1** depicts a schematic diagram for the unidirectional movement of a kinesin motor over a microtuble.

One of the astonishing dynamic properties of kinesins and dyneins is their stepwise movement over long distances without detachment from the filament [14] [15]. This movement is based on the alternated binding of the two motor heads to the following microtubule binding site. Structurally, kinesins and dyneins are dimers (molecule pairs) and resemble a structure with two feet. Walking occurs through sequential movement of the motor domains (feet) to the front. At each step the last foot moves to the front, passing the other foot. Usually, kinesins walk towards the positive end of the microtubule, *i.e.*, from the inner parts of the cell to the periphery, while the dyneins walk towards the negative end of the microtubule. These unidirectional motion along the microtubules are enabled by Brownian ratchet (or the thermal ratchet) mechanism [16] [17] [18] and powered by ATP—the chemical energy stored in the molecular bonds

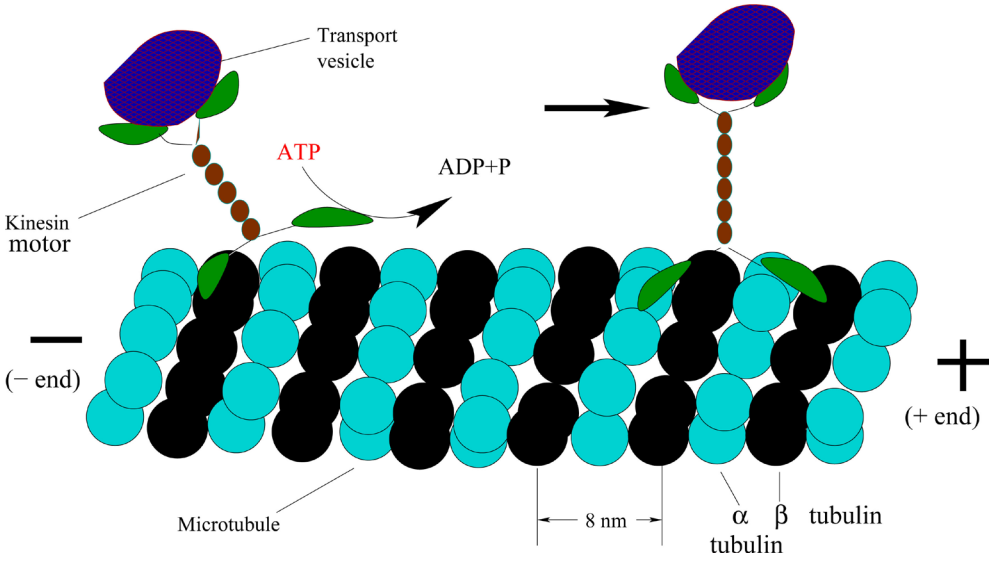

Figure 1. Schematic representation of the unidirectional movement of a kinesin motor over a microtubule filament.

of nucleotide triphosphates. The Brownian ratchet or thermal ratchet was designed and analyzed by Feynman [16] simply as an illustration of Carnot's principle. This mechanism is strongly rely on nonequilibrium statistical physics and it not only account for the general principles behind molecular motors, but has also been successfully applied as a prototype in various fluctuation-driven transport occurring in many mesoscopic and microscopic systems. Numerous single molecule experimental investigations [14] [19] have shown that, about one hundred times per second, kinesin hydrolyzes one ATP molecule, generates a force of up to 7 pico-Newton and takes an 8 nanometer step towards the positive end of a microtubule. These indigenous experiments suggested that the ATP hydrolysis is responsible for changing the local conformation of the microtubules that provides the information for the foot where to reattach.

2.2. Actin Based Motors

Actin filaments or F-actin are the most abundant proteins in a eukaryotic cell and mostly concentrated near the cell membrane. They are two-stranded helical polymers built from dimer pairs of globular-actin monomers (or, G-actin) which are polar in nature. The two halves of an actin monomer are separated by a cleft that can bind ATP or its hydrolyzed form ADP. This is responsible for the existence of two distinct ends to the whole filament, namely a fast growing end, known as plus end or barbed end, where mostly ATP-bound monomers are located, and a slow growing end known as minus end or pointed end, which is rich in ADP-bound monomers.

Motor protein myosins move along the linear tracks of actin filaments and usually walk towards the positive end of actin fiber [20]. **Figure 2** shows the schematic structure of a myosin protein. Elegant experiments revealed that many myosin molecules are spontaneously assembled by attaching their tails

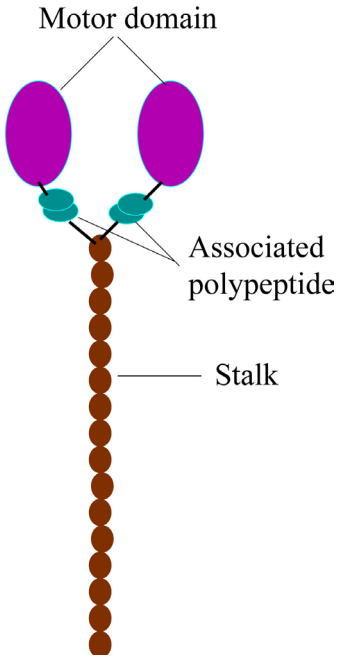

Figure 2. Schematic sketch of a myosin motor.

with each other and form myosin filaments. On the other hand, the heads of the myosin molecules are bound to polymerized actin filaments. Actin and myosin together exhibit a periodic arrangement organized in a polarity-alternated fashion. The motion at the heart of myosin motors is a rotary motion which is transmitted to actin fiber as a linear motion through a long lever-arm. This lever-arm amplifies the motion of the molecular motor from a few nanometers to 10 nanometers. During muscular contraction, the free energy of ATP hydrolysis by myosin drives the myosin filaments to slide along the actin filaments.

2.3. Nucleic Acid Based Motors

Motors that utilize nucleic acid strands (DNA and RNA) as their linear tracks are classified into two groups—helicases and polymerases. Helicase motors unzip double-stranded nucleic acids (DNA or RNA) and translocate along one of the two strands either in $5' \to 3'$ or in $3' \to 5'$ direction. DNA helicase binds to DNA strands and, through conformational changes caused by nucleoside triphosphate (NTP) hydrolysis, breaks the hydrogen bonds between the bases of double-stranded DNA. As a result, it unwinds the parental double-stranded DNA to form the single-stranded DNA templates and uses one of the single strands as the track for its own translocation. Several studies suggest that helicases can translocate along single-stranded DNA in a unidirectional manner [21] [22]. Usually, the mechanism of DNA unwinding is classified as active and passive which are schematically shown in **Figure 3**. In passive mechanism, the helicase does not make direct contacts with the double-stranded DNA. Instead, it operates by trapping single-stranded DNA at a thermally fraying single stranded-double stranded DNA junction. In active mechanism, the helicase

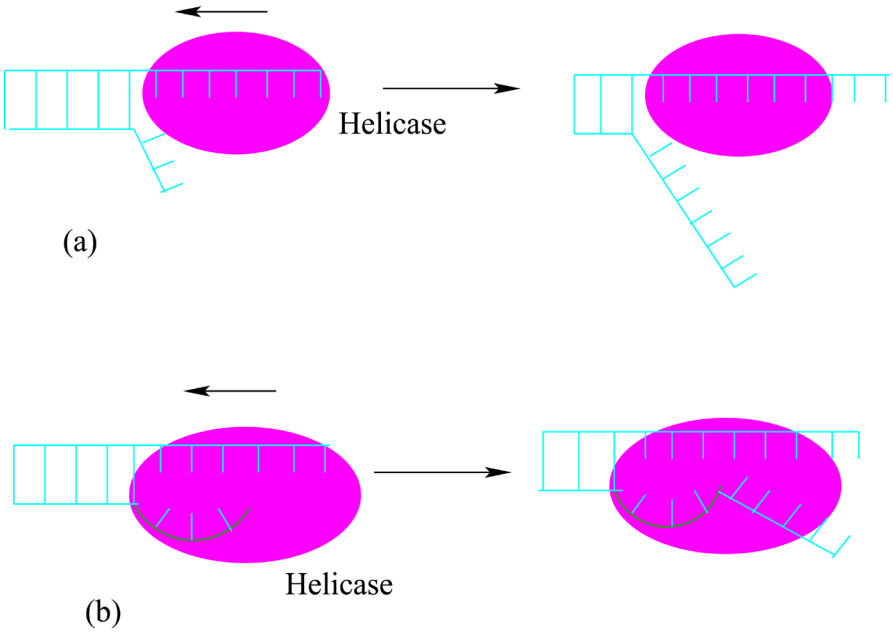

Figure 3. Unwinding the double-stranded DNA by a DNA helicase motor via (a) passive and (b) active mechanism.

interacts directly with the double-stranded DNA and plays a direct role in destabilizing the duplex DNA. However, the exact mechanism by which helicases accomplish unwinding the strands of double-stranded DNA and couple the NTPase activity to movement is still unclear and a subject of intense study [23]. Significant progress has been made and intense structural, biochemical, as well as genetic approaches are currently being pursued to gain insight into both the mechanism and role of helicases in various biological processes.

The helicases are involved in almost all DNA and/or RNA metabolic processes. They play a fundamental role in transcription, replication, DNA repair, and recombination [24]. The chromosome replication mechanism in all cells is solely dependent upon the action of DNA helicases. Malfunctioning of certain DNA helicases may lead to several severe human genetic diseases, such as Werner syndrome, Bloom syndrome or xeroderma pigmentosum [25].

Using the two unzip single strands as templates, the DNA polymerase motor synthesizes two copies of the DNA. RNA polymerase, on the other hand, polymerizes a RNA molecule by adding monomeric subunits one by one, while moving step by step on the DNA template itself. It's a highly processive molecular motor, capable of moving through thousands of base pairs without detaching from the DNA template. RNA polymerase plays a crucial role in gene expression, since it is responsible for making all mRNA in the cell. This highly regulated process of making RNA out of the template DNA molecule is commonly called transcription. Being a homologous multi-subunit enzyme, RNA polymerase executes a remarkable series of choreographed movement while transcribing DNA. The movement of RNA polymerase is powered by free energy liberated in nucleotide polymerization and RNA folding reactions. Although inten-

sive research work over the years has been devoted, analysis of RNA polymerase as molecular motor is still in its infancy.

2.4. Membrane Based Motors

Besides the aforementioned molecular motors that move along a linear substrate, there is an another class of motor namely, *rotary motors* which plays a key role in many biological membranes [18] [26]. As depicted in **Figure 4**, the molecular motor F_0F_1-adenosine triphosphatase (commonly called ATPase) comprises of two rotary motors F_0 and F_1, where the F_0 motor is driven by proton flow and the other one by ATP hydrolysis. It has been recognized that the collective swimming movement of bacteria is due to the presence of rotary motors that rotate their flagellum. The bacteriophage—a virus that infects bacteria, possesses a rotary motor which packs DNA into the bacteriophage head. All known biological rotary motors are driven by ion-gradient-based sources of energy, particularly, the hydrogen-ion (or proton) gradients that provides the necessary electrochemical forces. These rotary machines usually converts such electrochemical energy stored in proton concentration gradients, first into mechanical motion, and then back into chemical energy under the form of ATP. Surprisingly, rotary motors are reversible in the sense that they can harness the chemical energy of ATP to produce or maintain the transmembrane electrochemical gradient of proton concentration.

From the above discussions, we have seen that the hydrolysis of ATP with the release of ADP and inorganic phosphate is known to be the power source for many motor proteins which, in turn, powers cell motility by enabling the motors to bind to and move along their tracks in a stepwise linear or rotary motion. They are unique in their ability to transform the chemical energy stored in an energy-rich bond of ATP into mechanical work and thereby able to transport a wide variety of cargo, power cell locomotion, build or destroy other proteins, pump ions, drive cell division, and when combined in large ensembles, allow

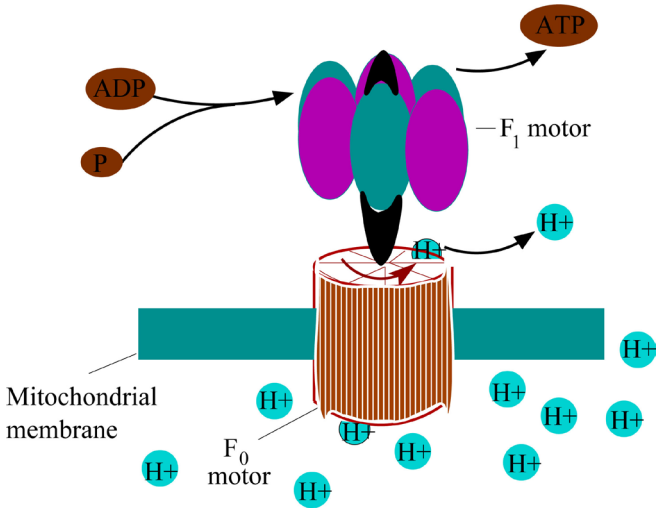

Figure 4. Schematic representation of an ATPase motor.

organisms to move.

In addition to transport vesicles and organelles, molecular motors actively participate in the process of self-organization of the cytoskeletal structures in the cell including physical separation of molecules or molecular aggregates [13] [27] [28] [29]. In what follows we shall make a comprehensive analysis on how these molecular motors actively take part in the self-organization of protein filaments.

3. Self-Organization of Protein Filaments

Self-organization is a fascinating physical process of many non-equilibrium systems and is a manifestation of nonlinearity. It is the spontaneous emergence of order, regularity, coherence, and coordination within the system from numerous short-range interactions among the constituents [27] [30] [31]. The simple microscopic local interaction rules are the key factors that give rise to a global self-organized collective state leading to various fascinating natural patterns. From a thermodynamic point of view, formation of such self-organized complex spatial patterns takes place due to constant work done against entropy increase. In order to maintain a high level of differentiation, all living organisms actively work against entropy increase by consuming energy from the environment. Living organisms are, therefore, far from thermal equilibrium. Approaching equilibrium would result in a decrease of the organisms internal structure and thereby a loss in its ability of performing basic tasks. This is akin to the possible heat death of the universe.

All eukaryotic cells rely on collective behavior of protein filaments, mainly microtubule and actin, to form a responsive intracellular cytoskeleton. It is the action of ATP-consuming molecular motors that drives the system out of equilibrium. The motors cross-link neighboring filaments and slide them with respect to each other and alter their dynamics. Maintained in a state far from equilibrium, the active filaments exhibit a strong tendency towards self-organization. The self-organization of motor-filament mixtures has been visualized in many recent experiments [10] [12]. A number of *in vitro* (in an artificial environment outside the living organism) experiments [11] [12] [32] [33] on mixtures of microtubules and associated motor clusters revealed complex patterns such as asters, vortices, and spirals depending on the type and concentration of molecular motors as well as ATP concentration. It has been found that kinesins cross-linked into clusters of several motors to interact with several microtubules simultaneously. Although at low molecular motor concentrations the filament distribution remains isotropic, at higher motor densities a lattice of microtubule vortices appears. With further increase of motor concentration, microtubule aggregates and vortices turn into asters in which all the filaments emanate radially outwards from one point. The structure of microtubule asters is similar to that of mitotic spindle poles. Finally, at very high motor concentrations, filaments bundle. Recent theoretical investigations also mimic these complex, non-equilibrium self-organized patterns.

Cross-linking with myosins, actin filaments organize into linear bundles, two-dimensional networks, and three-dimensional gels. Most notable examples of bundles are muscle sarcomere and stress-fiber of an adherent cell. Not only the *in vitro* experiments and integrated modeling efforts, but also analytic theories, demonstrated how the interaction of motors and active micro-filaments lead to a complex self-organized structure. Depending on the interactions with actin filaments, myosins perform a wide variety of cellular tasks, from cellular transport to muscle contraction. Myosin I perform transport of endocytic vesicles, myosin II family powers muscle contraction and cytokinesis, myosin V phagocytosis and transport of cellular elements, myosins VI and VII provide hearing and balance cells. When myosins bind tightly to actin in the absence of ATP, temporary stiffness of joints and muscular rigidity occurs—a physiological condition after death [29].

From the perspective of statistical physics, the active filaments are example of a many-degrees of freedom nonlinear dynamical system that are far from equilibrium and exhibit self-organizing property at certain critical values of external parameters [13] [31] [34]. As such, the fascinating self-organizing behavior of micro filaments continues to attract enormous attention and inspired many theoretical efforts directed towards modeling active filament solutions [35]. Since capturing the dynamics of individual nanomotors and microscopic filaments is a difficult task, coarse-grained modeling achieves increasingly important to elucidate generic features and emergent behavior. In the following sections, we shall discuss the role of motor proteins in chromosome segregation during mitosis and meiosis and their self organization process.

3.1. Self-Organization during Mitosis

The most-spectacular event of intracellular transport occurs during the essential process of eukaryotic mitosis, in which duplicated chromosomes are segregated from the mother cell and delivered to each of the nascent daughter cells. Understanding the complex interplay between molecular motors and microtubules that carry out faithful segregation of genetic material in all eukaryotic cells, is a long standing goal among scientists to reveal the mechanism, structure, and organization in biological systems.

During mitosis, the accurate chromosome segregation is carried out by a complex and extraordinarily sophisticated macromolecular machine—the mitotic spindle [36] [37] [38]. The mitotic spindle itself is a highly dynamic structure comprises of two microtubule asters in which the minus ends are focused, and the plus ends extend outwards, overlapping into the characteristic bipolar shape as schematically depicted in **Figure 5**. Although the structure of the poles differs in different organisms, all spindles are bipolar in nature. Any defects in spindle bipolarity or chromosome bi-orientation lead to potentially lethal errors in chromosome segregation.

Two inherent properties of the microtubules are exploited to build a spindle.

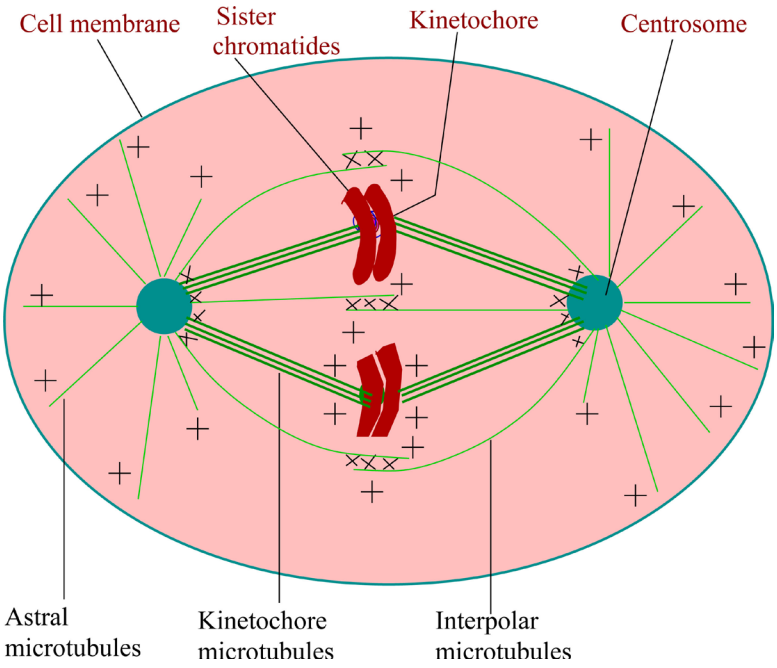

Figure 5. Schematic representation of mitotic spindle of somatic animal cells in metaphase. The minus ends of the microtubules (green) are embedded in a spindle pole (the centrosome) and the plus ends are pointing outward from the pole. Numerous motors and other proteins (represented by the symbol ×) cross-link the minus ends of microtubules at the spindle poles and the plus ends of inter-polar microtubules in the spindle midzone.

First, the microtubule ends undergo stochastic changes from a polymerizing to a depolymerizing state, a phenomenon known as *dynamic instability*. Hydrolysis of GTP by β-tubulin fuels this non-equilibrium property and generates the potential for polymerization dynamics to carry out useful mechanical work in the cell. Second, the polar microtubules serve as tracks for the dynein and kinesin motors. These motor proteins, as we already discussed, use the energy of ATP hydrolysis to move along microtubules in a unidirectional manner, transporting spindle cargo such as chromosomes or other microtubules toward either the plus or minus end of the microtubule polymer [39]. Indeed, numerous motor proteins are involved in microtubule self-organization, including motors that cross-link antiparallel plus ends, motors that focus minus ends at the poles, and chromatid associated motors that help orient the array. Particularly, it has been found that members of kinesin superfamily and dynein family are essential in all organisms for proper chromosome and spindle behavior [40]. These biomolecular motors arrange microtubules into the characteristic aster shape to form cytoskeleton of daughter cells [28]. The mitotic spindle, on the other hand, pulls the sister chromatids apart and moves a complete set of chromosomes to each pole of the cell, where they are packaged into daughter nuclei. The proper inheritance of sister chromosomes to cell daughters at the completion of mitosis depends on the correct organization and functioning of the spindle machinery. The morphogenesis and localization of centrosomes and mitotic spindle thus

seems to be an essential and remarkable physical self-organization process.

3.2. Self-Organization during Meiosis

Sexual reproduction, which involves the successful mixing and recombination of genetic material during meiosis, requires concerted movement of the nucleus [41]. This dynamic physical process is driven by molecular motors that move the nucleus back and forth inside the cell with the aid of microtubules. How motors and microtubules work together to produce these large-scale movements during meiosis, however, remains a mystery. Experiments on fission yeast revealed that asymmetric redistribution of motor proteins from microtubules behind the moving nucleus to those in front of the nucleus, creates nuclear oscillation. Recent highly sophisticated experiments demonstrated that this dynamic motor redistribution occurs purely as a result of changes in the mechanical strain sensed by the motor proteins. However, a complete understanding of complex meiotic processes requires a great deal of multi-disciplinary efforts.

4. Discussion and Conclusion

Over the last couple of years, the rapid development of single-molecule techniques and structural studies leads to a considerable progress in understanding how the biological motors operate. How do they move? How do they generate force? How much fuel do they consume, and with what efficiency? How do they determine which cargo is to be transported and when to transport the cargo to its proper location within the cell? Although the key proteins involved in the processes have been identified and localized, the underlying physical mechanism is still remains unknown. The intriguing complex behavior of these natural biomolecular machines represents a formidable challenge for theoretical descriptions and numerical approaches that aim at a fundamental analysis of the underlying interaction mechanisms.

This review article provides a glimpse that interactions between different species of filaments are crucial for cell motility, cell division, vesicular transport, muscle contraction, spindle assembly and chromosome motility in dividing cells, ion pumping, DNA replication and protein synthesis. We have discussed how under the action of biomolecular motors, the protein filaments align themselves exhibiting fascinated self-organizing behavior. The unidirectional motion of motor proteins along their tracks indicates that these systems operate far from thermal equilibrium. Detailed balance is broken, as molecular motors only move forward, not backward. How this complex molecular machinery can self-organize and lead to a coherent, purposeful movement at the cellular level is, however, still unclear. The detailed mechanisms are still a matter of debate and intensive research. Understanding and harnessing such collective biological organization at the molecular scale provides a strong incentive to design synthetic active nanostructures that can operate as molecular machines. Indeed, designing and constructing such synthetic molecular machines is a long term goal and signifi-

cant step towards future bio-nanomachines and bio-nanorobots.

Perhaps the most exciting goal of these ingenious biological nanomotors is the molecular repair of the human body. Molecular motors might be applied as a drug delivery vehicle to the cell bodies of motor neurons by axonal transport. Using currently available biochemical methods, scientists designed and created synthetic motors to disrupt specific cellular functions and to transport drugs or other substances to specific cells or regions of cells. Motor defects lead to motility defects of the animal cells which can, in turn, lead to severe diseases including male infertility, deafness, chronic inflammatory diseases, neurodegenerative diseases, or may even be lethal. Although Nature offers a maintaining and repairing mechanism for its damaged molecular systems, such complex repair mechanisms are beyond the capabilities of current nanotechnology. We hope that extensive experimental, theoretical and computational investigations in near future will lead to a deeper understanding of these collective physical phenomena, which will possibly help us to cure and control life-threatening diseases and will provide possible design principles that can be utilized to synthesize artificial nanomachines. At last, I hope this introductory article will encourage students and particularly young researchers to become the active participants in this challenging endeavor.

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