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APPLICATIONS OF MOLECULAR MOTORS IN INTELLIGENT NANOSYSTEMS

H. R. Khataee[a], A. R. Khataee[b*]
[a]*Department of Computer Engineering, Payam Noor University of Hashtrood, Hashtrood, Iran*
[b]*Corresponding author: Department of Applied Chemistry, Faculty of Chemistry, University of Tabriz, Tabriz, Iran*

All cells of living organisms contain complex transport systems based on molecular motors which enable movement on their polymer filaments. Molecular motors are responsible for various dynamical processes for transporting single molecules over small distances to cell movement and growth. Molecular motors are far more complex than any motors that have yet been artificially constructed. Molecular motors are ideal nanomotors because of their small size, perfect structure, smart and high efficiency. Recent advances in understanding how molecular motors work has raised the possibility that they might find applications as nanorobots. Constructing of biomimetic nanorobots and nanomachines that perform specific tasks is a long-term goal of nanobiotechnology. Thus, in this paper we have summarized some of potential applications of molecular motors. Our reviewing of potential applications of molecular motors indicates that these extraordinary systems can be had potential applications in nanorobots, nanodevices and nanomedicine. This review indicate that molecular motors might be the key to yet unsolved applications in vast variety of sciences that are only imagined today.

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1. Introduction

It is obvious that movement, in one form or another, is an essential feature of all life at both the macroscopic and cellular level. Organisms, from human beings to bacteria, move to adapt to changes in their environments, navigating toward food and away from danger. By evolutionary modification over billion of generations, living organisms have perfected an armory of biological nanomachines, structures, and processes. Cells, themselves, are not static but are bustling assemblies of moving proteins, nucleic acids, and organelles. Therefore, life is made possible by the action of a series of biological nanomachines in the cell machinery. A general class of these biological nanomachines is called molecular motors (e.g. the kinesin, myosin and dynein nanomotors) that move in a linear fashion. Most of molecular motors are able to pull vesicles, organelles and other types of cargo over large distances, from micrometers up to meters, along the surface of a suitable substrate. These nanomotors are able to recognize the rail polarity and so the direction of transport [1]. Differences in function are observed between these classes of nanomotors, but in the cell they often function together [2]. Molecular motors convert the chemical energy into mechanical work directly rather than via an intermediate energy [3]. These motors are powered by the hydrolysis of adenosine-5′-triphosphate (ATP), Nature's universal energy currency, through which they convert chemical energy into mechanical work [4].

*Corresponding author: a_khataee@tabrizu.ac.ir (ar_khataee@yahoo.com)

Biology provides brilliantly developed set of examples: in living systems, molecular motors do exist, and they do perform extraordinarily sophisticated functions. Biological nanomotors are rather new and are attracting a diverse group of researchers keen to find more. Study of biological applications of nanotechnology will be important to the future of biological research, engineering and medical science [5]. Therefore, we have recently reviewed the beautiful highly sophisticated F_0F_1-ATP synthase biological protein nanomotor [6] and in this paper we review potential applications of protein molecular motors including kinesins, dyneins and myosins. The organization of this paper is as follow: In section 2, we have introduced these three molecular motors, briefly. This is followed, in section 3, by the providing of the examples of emerging applications of molecular motors.

2. A Brief introduction to molecular motors

Molecular motors are the active workhorses of the cells [7, 8]. The majority of active transport in the cell is driven by the three classes of molecular motors namely kinesin, dynein and myosin. They have evolved to enable movement on their polymer filaments, either on cellular or supra-cellular levels and are able to recognize the direction of movement. Molecular motors utilizing the cytoskeleton for movement fall into two categories based on their substrates: (1) actin-based motors such as myosin carry its cargo along short actin filaments [9], which are found throughout the cell but are most highly concentrated near the cell membrane; and (2) microtubule-based motors such as dynein [10] and kinesin [11] move along microtubules (MTs), which are long polarized filaments with their plus-ends located in the cell periphery and their minus-ends located at the microtubule organizing center (MTOC) near the nucleus. Most of these molecular motors are dimers with two 'heads' connected together at a 'stalk' region and a 'tail' domain opposite the heads. The head of the molecular motors contains the motor domain that provides the motion along the filaments (MTs or actins) whereas the tail of the molecular motors contains the subunits responsible for cargo binding and regulation [12]. Intracellular transport occurs along filaments when the appropriate molecular motor binds to a cargo through its tail and simultaneously binds to the rail through one of its heads. Most kinesins transport cargos unidirectionally towards the plus-end of a MT [13]. However, a different kinesin-like protein was identified from *Drosophila*, called Ncd (Non-claret disjunctional), move toward the minus-end of a MT [14, 15]. This movement of kinesins is in a hand-over-hand mechanism [16-29]. How the steps of kinesin mechanism are coordinated is yet to be more understood [30]. Dynein molecular motors are in two groups: (1) cytoplasmic dyneins that perform various intracellular cargo transport functions; and (2) axonemal dyneins that powers the motion of cilia and flagella in some eukaroytic cells and are anchored in large linear arrays along MTs inside cilia and flagella [31]. All dyneins walk toward the minus-end of MTs. Electron microscopy reconstructions of cytoplasmic dynein show a structure similar to axonemal dynein, so it is likely that inducement of mechanical torque of their functions occurs in a similar way [32]. Several studies showed that compared with kinesin and myosin, the precise molecular details of the dynein conformational changes that induce the motion are not well understood [33, 34]. Myosin molecular motors function in a wide variety of cellular tasks, from cellular transport to muscle contraction. Therefore, myosins are in two groups: (1) non-muscle myosins that are involved in organelle transport along actin filaments very similar to the mechanism of kinesins; and (2) muscle type myosins that drives muscle contractions and is an important component of the muscle. These cellular movements, cellular transport and muscle contraction, depend on the interactions between actin filaments and myosin [35, 36].

On the basis of these finding, it can be concluded that molecular motors specifically bind to a particular filament and are actively moving only in one direction of the polarized filaments. Therefore, there are two kind of cargo transport inside sells: (1) for short distance transport, myosin carries its cargo along short actin filaments; and (2) for long distance transport, most kinesins carry cargo inside cells away from the nucleus along MTs and cytoplasmic dyneins and a few kinesins transport cargo towards the cell nucleus along MTs. Some cargos moved by such molecular motors are vesicles, mRNA, mitochondria, endosomes, virus particles, etc (see Figure

1). Moreover, each class of molecular motor has different properties, but in the cell they are known to cooperate and even to compete with each others during their function [2, 37-39]. It is now clear that myosin, kinesin and dynein interact with each other either directly or indirectly, but it is still unknown how the nanomotors determine which cargo is to be transported and when to transport the cargo to its proper location within the cell [1].

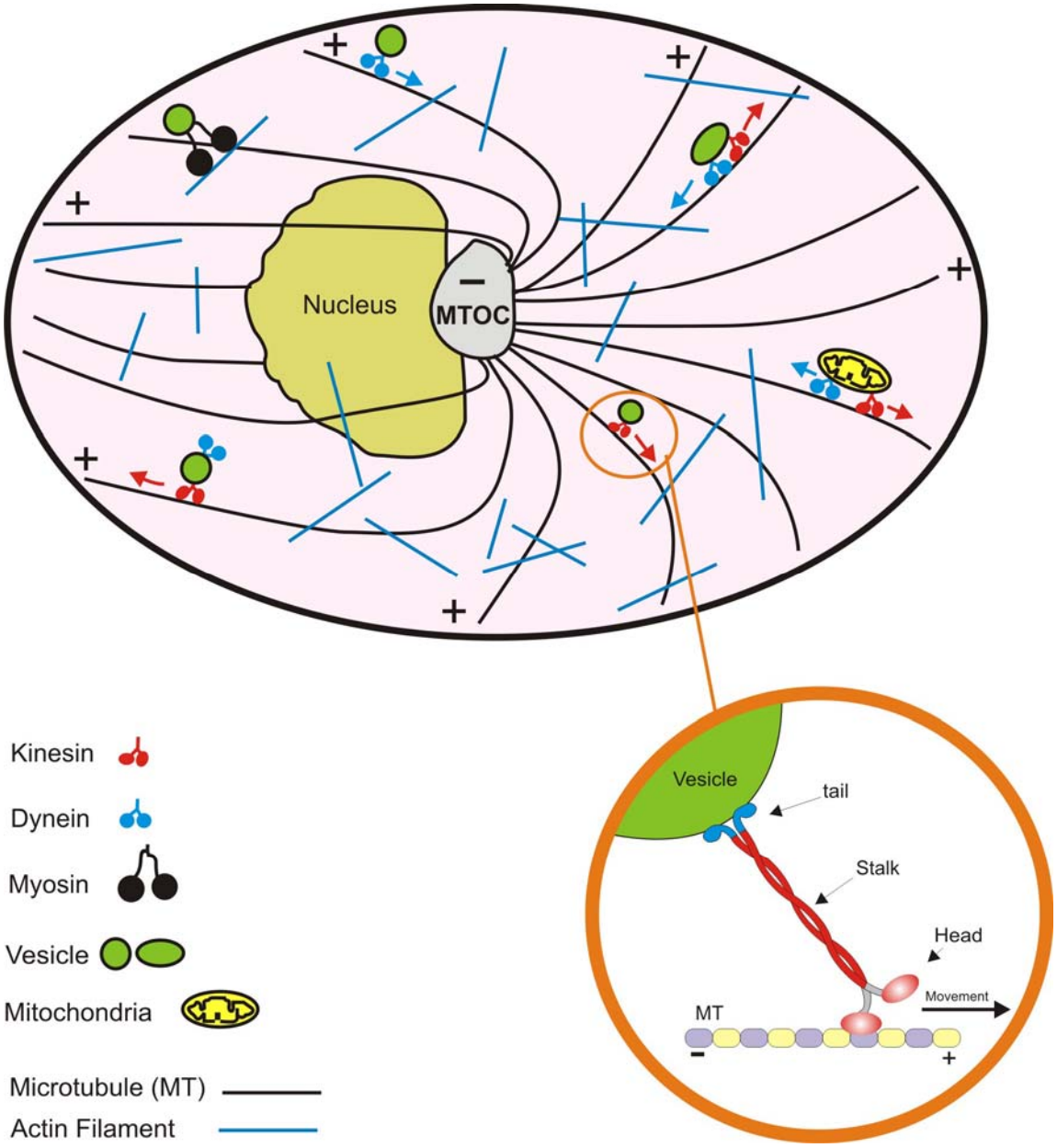

Fig. 1. Schematic of a typical interphase cell. MTs are shown in radial arrangement. Actin filaments are approximately randomly oriented. Actin filaments are generally found in cross-linked bundles and have been suggested to bridge the cap between MTs. A few different forms of cargo are being transported by MT-based nanomotor (kinesin and dynein) or an actin-based nanomotor (myosin). Multiple nanomotors, even of different kinds can attach to and transport a given cargo, usually in a bidirectional manner along the MT.

2. Potential applications of the molecular motors

The amount of research in engineering and biomedical science at the molecular level is growing exponentially because of the availability of new investigative nanotools based on protein molecules. These new analytical tools are capable of probing the nanometer world and will make it possible to characterize the chemical and mechanical properties of cells, discover novel phenomena and processes, and provide science with a wide range of tools, including materials, devices, and systems with unique characteristics. According to this, nanotechnology has been revolutionizing many important areas in molecular biology, especially in the detection and manipulation of proteins. This combination of molecular nanotechnology and biology opens the possibility of detecting and manipulating molecules, with the potential for a wide variety of applications. In this section we have presented some of these applications of protein molecular motors including kinesin, myosin and dynein.

2.1. Molecular Motors in Nanorobots

Recent explosion of research in nanotechnology, combined with outstanding advances in molecular biology has created new interests in bio-nanorobots and bio-nanomachines [6, 40, 41]. A molecular machine has been defined as a discrete number of molecular components that have been designed to perform mechanical-like movements (output) in response to specific stimuli (input) [42]. The idea behind the biological nanomachine development is to use various biological elements as nanomachine and nanorobot components, such as molecular motors, that perform the same function in response to the same biological stimuli but in an artificial setting. To achieve this rather long-term goal, prototyping tools based on molecular dynamics (MD) simulators should be developed in order to understand the molecular mechanics of proteins and develop dynamic and kinematic models to study their performances and control aspects. A molecular mechanics study using a molecular dynamics software (NAMD) coupled to virtual reality (VR) techniques for intuitive bio-nanorobotic prototyping has been reported [43]. Their use as elementary bio-nanorobotic components were also simulated and the results have been discussed. Their objective had been to interface MD and kinematics computations with real-time truly VR simulations and measure the force, position and energy feedback for design evaluation of bio-nanorobots. Based on VR technology and MD simulators, their long-term goal is to prototype virtually bio-nanorobotic systems and control their movements in corresponding biological environment [44]. The ability to interact with a computer-generated object in the same manner that a person would interact with a physical object to investigate its structure by simply moving around it, to change its position by grabbing the object and moving the hand in space, without such artificial devices as computer mice would be the ultimate goal. It will allow the roboticians to use mechanical force to control the dynamics, time evolution and fate of chemical and biochemical reactions when connecting different bio-nanorobotic components together in series or parallel. The structural and functional analysis of biological macromolecules has reached a level of resolution that allowed mechanistic interpretations of molecular action, giving rise to the view of enzymes as molecular machines [45]. This machine analogy is not merely metaphorical, as bioanalogous nanomachines actually are being used as nanomotors in the fields of nanotechnology and robotics.

Another example of an engineering application of molecular motor is in molecular shuttles. Molecular shuttles have been built from molecular motors capable of moving cargo along engineered paths. The first prototypes of molecular shuttles are hybrid devices that employing molecular motors in a synthetic environment [46, 47]. Reports on the key problems for the construction of a molecular shuttle are as follow: guiding the direction of motion, controlling the speed, and loading and unloading of cargo. Various techniques, relying on surface topography and chemistry as well as flow fields and electric fields, have been developed to guide the movement of molecular shuttles on the surfaces [46]. Furthermore, the control of ATP concentration, acting as a fuel supply, can serve as a means to control the speed of movement. Finally, the loading process requires the coupling of cargo to the shuttle, ideally by a strong and specific link. Applications of molecular shuttles can be envisioned, e.g. in the field of nano-electro-mechanical systems

(NEMS), where scaling laws favor active transport over fluid flow, and in the bottom-up assembly of novel materials [46]. In another first steps in the development of a tool kit to utilize molecular motors for the construction of nanoscale assembly lines has been realized [48]. In that research, alternative methods of controlling the direction of motion of MTs on engineered kinesin tracks, how to load cargo covalently to MTs, and how to exploit UV-induced release of caged ATP combined with enzymatic ATP degradation by hexokinase to turn the shuttles on and off sequentially have been illustrated.

2.2. Molecular Motors in Nanodevices

A nanodevice is a tiny entity, a gadget or machine, capable of performing a task. Proteins can be brought properties for nanodevices. Such nanodevices might respond to the environment through proteins with built-in switches that operate in a simple on/off way or through more finely tuned and complex logic gates with graded or multiple inputs. In this way, nanodevices will sense their environment. Nanodevices might use molecular motors, as protein components, to move linearly, by rotation, or in a more complex three-dimensional manner. More advanced functions might include transport (uptake, movement and delivery of cargos utilizing protein transporters and pores) and chemical transformation, by enzymatic catalysis, for example. To perform these functions, the nanodevice must use energy and might even transduce and store it by using, for example, the biological energy currency of ATP. This description proposes that molecular motors can be function as components for nanodevices [49]. Some speculations about what might be possible and examine the progress that has been made in making components for nanodevices has been reported including that three classes of protein components for nanodevices are presented in order of complexity: planar crystalline arrays, engineered protein pores, and molecular motors [49]. Remarkably, molecular motors differ fundamentally from artificial devices in that the conversion from chemical energy to mechanical energy is done directly, rather than via an intermediary stage, as in, e.g., heat in thermal engines. Therefore, it has been reported that biological nanomotors are ideally suited to introduce chemically powered movement of selected components into devices engineered at the micro- and nanoscale level [50]. It was showed the design of such hybrid bio/nano-devices requires suitable synthetic environments, and the identification of unique applications. This fundamental difference, which translates into a very high energy efficiency of these natural devices compared to artificial mechanical devices, together with their very small scale, prompted an increasing number of studies focused on the integration of molecular motors in hybrid micro- and nanodevices [51, 52].

Molecular motors have been integrated in the last decade in primitive nanodevices based on the motility of nanobiological objects in micro- and nano-fabricated structures. Biological nanomotors, specialized proteins, also have unique advantages for integrated nanomaterials and systems. The integration of molecular motors into an artificial environment enables us to explore new space in the development of nanotechnology. Potential applications of devices and materials integrating nanomotors abound in biosensing, nanofluidics, molecular electronics, digital light processing, nanoscale and macroscale actuation, and adaptive materials. Some of these applications derive their inspiration from long-replaced macroscale technologies [53]. However, the motility of microorganisms powered by molecular motors has not been similarly exploited. Biocomputation with motile biological agents is in its infancy, but the development challenges appear to be more related to design and operation rather than fabrication. According to this subject, application of molecular motors in micro- and nano-biocomputation devices has been reported [51]. It was proposed that if it is conceived the use of ‘non-programmable’ motile biological agents, such as molecular motors, in nano-fabricated networks that code mathematical problems, then these will also solve the encoded problems, provided that the lack of ‘self-program-ability’ is replaced by means of control (and record) the movement of the nano-agents in the network. Cells perform computations when they explore (at times limited and confined) available space for nutrients and to allow for their growth. In that work the space searching of cells was in a sense a spatial biocomputation that was scaled down from multicellular ‘intelligent’ organisms, e.g., mice,

octopi and humans solving mazes. Conversely, if one can purposefully code mathematical problems in (micro) fabricated networks and let 'self-programmable' biological agents, such as microorganisms, explore this network, then this space search will solve the mathematical problem encoded. They solved mazes using fungi-microorganisms that were perfectly adapted to negotiate narrow natural networks, e.g., cracks in rocks, in order to find nutrients often in nutrient-scarce environments. They chose fungi because molecular motors were also critical to fungal growth.

2.3. Molecular Motors in Nanomedicine

Medical nanorobots are envisioned that could destroy viruses and cancer cells, repair damaged structures, remove accumulated wastes from the brain and bring the body back to a state of youthful health. Over the past few years there has been a significant increase in the understanding regarding the function and role of molecular motors in the cell [54]. Perhaps the most exciting goal of these biological nanomotors is the molecular repair of the human body. Recently, researchers have begun to shift their efforts towards developing applications that utilize this technology in novel ways, such as part of nanomachines and for the delivery of genes or drugs to the nucleus of cells or to the central nervous system [45, 55]. On the other hand, complex biological environments can pose significant barriers to efficient therapeutic drug and gene delivery [56]. There has been little effort to overcome the barrier of transporting DNA towards the nucleus despite evidence that the mobility of DNA in the cytosol might be a barrier to gene transfer. Cohen *et al.* [57] attempted to use molecular motors as a DNA delivery vehicle by two approaches (see Figure 2). The first approach involves creating a fusion protein that contains Ncd and a DNA-binding domain from GAL4, a yeast transcription factor (Figure 2A). An alternative gene delivery method that have been proposed is the use of dynein nanomotor and a biomolecular adaptor for retrograde transport (BART), a synthetic adaptor that links DNA or other novel cargo to dynein (Figure 2B). In another work, Gunawardena *et al.* [58] reported that molecular motors might also be applied as a drug delivery vehicle to the cell bodies of motor neurons by axonal transport. They concentrated on MT-based molecular motors, their linkers, and cargos and discussed how factors in the axonal transport pathway contribute to disease states. They reported, as additional cargo complexes and transport pathways are identified, an understanding of the role these pathways play in the development of human disease will hopefully lead to new diagnostic and treatment strategies. It has been also proposed that traffic jams of molecular motors are involved in a variety of neurodegenerative diseases [59, 60]. Each cell of our body contains a huge number of small vesicles which exhibit complex patterns of intracellular traffic: some vesicles travel from the cell center to the periphery and vice versa, some shuttle between different organelles or cellular compartments. All of this traffic is based on two molecular components: cytoskeletal filaments and molecular motors. As one further increases the molecular motor concentrations, the filaments start to become overcrowded and the molecular motor flux becomes reduced by traffic jams [61-63]. Lipowsky *et al*. [39] proposed that, it is necessary to understand these traffic phenomena in a quantitative manner because active biomimetic systems based on these molecular motors and filaments have many potential applications in bioengineering, pharmacology and medicine. Such applications include sorting devices for biomolecules, motile drug delivery systems, molecular shuttles in 'labs-on-a-chip', and switchable scaffolds for tissue engineering. These results indicate that micro- and nanotechnologies are enabling the design of novel methods and materials in the application of micro- and nanosystems for drug administration.

Another nanomedicine potential application of molecular motors is reported by Bunk *et al*. [64]. They proposed that they reconstructed *in vitro* the behavior of two nanomotor proteins, myosin and actin, responsible for the mechanical action of the muscle cells. By transferring this *in vivo* system to an artificial environment, they were able to study the interaction between the proteins in more detail, as well as investigating the central mechanism of force production. Thus, the creation of *in vitro* nanostructured, ordered interactions between actin and myosin is of interest for potential applications in nanotechnology, such as the development of a 'factory on a chip'.

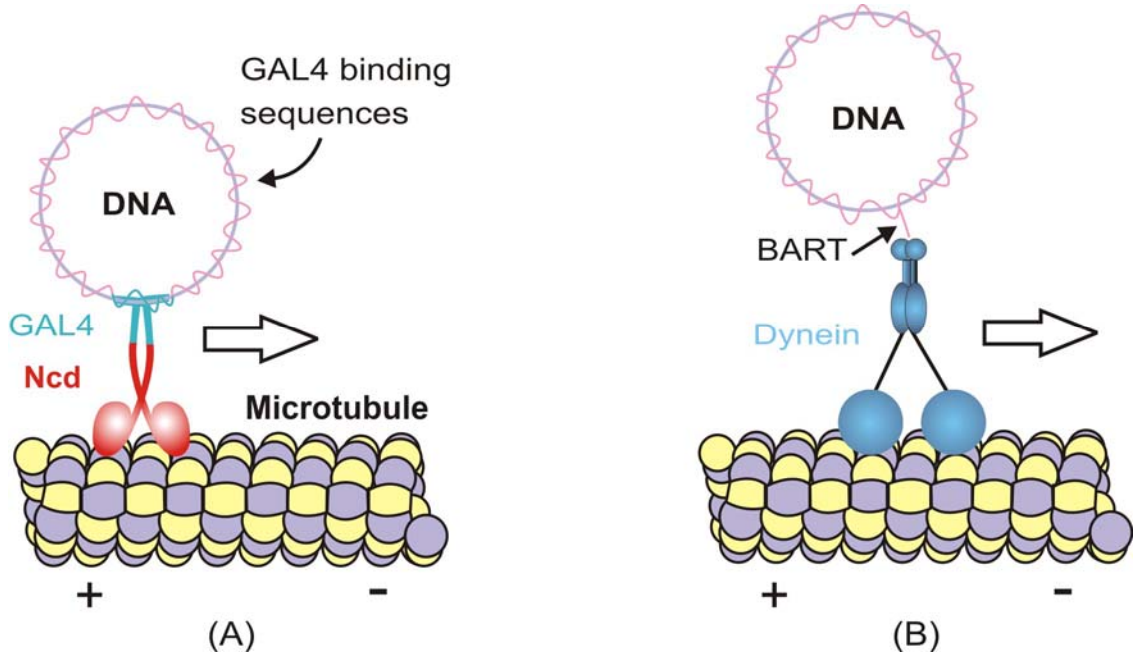

Fig. 2. Strategies to use molecular motors to actively transport DNA to the nucleus. (A) The chimeric protein was consisted of a Ncd and a DNA-binding domain, such as that from GAL4, a transcription factor from yeast. (B) A biomolecular adaptor for retrograde transport (BART) was linked DNA to endogenous dynein which then carried DNA along MTs. BART was covalently linked to plasmid DNA.

On the basis of these findings, it can be concluded that there are many challenges in applying protein nanomotors to nanotechnology. All these developments will be solely up to the imagination and skills of researchers, both in engineering and in natural sciences to envision the future and limitations of use for such highly intriguing devices that Nature has designed and perfected over billions of years and is giving to us for our own use. Thus, automatic movement of the nanoparticles (or nanomotor) is still under development and the field is under maturation in this decade [65**].** Moreover, it can be noted that molecular motors have some advantages and disadvantages that will be contributing in their future applications [6]. Thus, in termination, we point to these advantages and disadvantages gradually. The potential advantages in developing of bionanomotors are: (1) high efficiency that is but one feature making molecular motors attractive for nanotechnological applications; (2) ease of cheaply manufacture in vast quantities; (3) extent availability [66]; (4) small size so they can operate in a highly parallel manner; (5) easy to produce so they can be modified through genetic engineering; a wide array of biochemical tools have been developed to manipulate these proteins outside the cell [6]. Moreover, according to the biological processes of the molecular motors, these processes have received increasing interest owing to their cost, effectiveness and environmental benignity [67, 68]. Two main disadvantages of molecular motors are their limited *in vitro* lifetime, and the narrow range of environmental conditions that they are able to tolerate [53]. It is interesting to speculate about the limits of extending the lifetime of biological nanomachines [69], the causes of failure that cannot be avoided by changes in the environment, and the tradeoffs involved in balancing lifetime, force output, speed, and efficiency when designing high-performance synthetic nanomotors [70].

5. Conclusions

The possibility to exploit the structures and processes of biomolecules for novel functional materials, biosensors, bioelectronics and medical applications has created the rapidly growing field of nanobiotechnology. The recent explosion of research in nanotechnology, combined with important advances in molecular biology has created a new interest in biomolecular machines. The

first goal in the biomolecular machine development is to use various biological elements as machine components that perform the same function in response to the same biological stimuli but in an artificial setting. Molecular motors are well-established nanoscale molecular machines present in living systems. They are responsible for various dynamical processes for transporting single molecules over small distances to cell movement and growth. Molecular motors are self-guiding and ideal systems because of their small size, perfect structure, smart and high efficiency. In general, active biomimetic systems based on molecular motors and filaments have many potential applications in bioengineering, pharmacology and medicine. Molecular motors could form the basis of bottom-up approaches for constructing active structuring and maintenance at the nanometer scale. Although the first steps have been made towards the operation of molecular motors in engineered environments, many advances are necessary before these motors can be used in nanotechnological applications. The horizons are broad and the ability to engineer these systems might soon create fact from fantasy.

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