Engineering Applications of Biomolecular Motors

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Abstract

Biomolecular motors, in particular motor proteins from the kinesin and myosin families, can be used to explore engineering applications of molecular motors in general. Their outstanding performance enables the experimental study of hybrid systems, where bio-inspired functions such as sensing, actuation, and transport rely on the nanoscale generation of mechanical force. Scaling laws and theoretical studies demonstrate the optimality of biomolecular motor designs and inform the development of synthetic molecular motors.

Contents

1. INTRODUCTION

That nanotechnology and biology are related has been recognized from the very beginning (1). On one hand, biology with its ability to process material, energy, and information at the molecular scale can be seen as a proof of feasibility for nanotechnology. On the other hand, nanotechnology may be able to augment or supplant the capabilities of biomolecular systems, in particular in humans. Finally, progress in our ability to engineer complex molecular structures is necessary to advance our understanding of biology, or, as Richard Feynman expressed it, "What I cannot create, I do not understand" (2).

The large number of well-studied biological building blocks is a treasure chest for nanotechnology (3, 4). DNA (5), RNA (6), lipids (7), and proteins can serve as components with high functionality and the ability to self-assemble. As a result, the design of hybrid nanodevices that integrate biological and synthetic building blocks, both optimized for their specific functions, has become an active research field.

The ability of motor proteins to convert chemical energy stored in individual molecules into mechanical work is a particularly striking example of molecular functionality that is ubiquitous and highly optimized in nature (8) but that is only beginning to be realized in synthetic systems (9). Motor proteins, also referred to as biomolecular motors, perform essential biological functions acting individually or in small groups (such as in fast anterograde transport) and in large arrays, particularly in muscle.

Biomolecular motors are therefore exactly the kind of biological nanomachine whose integration into a hybrid system can advance the state of the art in nanotechnology. A key ingredient in this endeavor is the extensive expertise developed by biophysicists and biochemists in purifying, handling, and observing motor proteins in vitro. In particular, the vast interest in muscle physiology and the role of motor proteins in various pathologies (10) supported detailed investigations into the inner workings of these complex molecules, without answering all questions conclusively (11, 12).

Biomolecular motors achieve the cold conversion of chemical energy into mechanical work, in contrast to heat engines such as the internal combustion engine. The transition from heat engines to cold engines seems just as desirable as the transition from hot incandescent lamps to cold light-emitting diode (LED) lamps. However, nearly a century of research and development—from the invention of the LED in 1927 through its commercialization in 1962 as an indicator light—was required to enable the LED's application as a replacement for incandescent bulbs. Similarly, the development of cold engines is unlikely to be a short-term project.

The evolution of technology in the past decades has led to a proliferation of smaller and smaller motors. For example, a modern car still contains only one large heat engine, but dozens of electric motors perform tasks such as spinning a CD or adjusting a mirror. Even without knowing the exact size distribution of motors, one could suspect a power law (13). Because no obvious minimal power requirement applies to all applications, one can also postulate that microscopic motors will find a wide range of engineering applications if they become available at a reasonable unit price. As for macroscopic motors, these applications include force generation to overcome friction and drag, force generation for assembly and disassembly, and force generation to overcome other forces experienced by the system, such as gravity. In addition, microscopic systems can exploit mechanical work to reduce their entropy and increase their information content.

This review aims to complement recent reviews (14–18). It is structured to provide first an overview of fundamental problems relevant to the design and application of biomolecular motors, second, a perspective on potential applications of molecular motor–enabled systems, and finally, a short review of the technical advances in the field.

2. FOUNDATIONS

2.1. Force Generation and Energy Conversion by Molecular Motors

A wealth of biochemical, biophysical, and structural data contributed to the formation of current views about the operation of linear motors such as myosins and kinesins (8, 19) as well as of rotary motors such as ATP synthase (20). In linear motors, which are the primary interest here, the biochemical cycle of ATP binding, hydrolysis, and ADP/phosphate release is closely coupled to a cycle of conformational changes as well as to a cycle of binding affinities to the cytoskeletal filaments (**Figure 1**). Supporting the notion of a molecular machine, the coupling between these three cycles is achieved by mechanical communication between distinct elements in the protein structure (19). Interestingly, the extraction of mechanical work from the motor is primarily achieved not during the hydrolysis step converting ATP and water to ADP and phosphate but rather during the binding and release of substrate and product. This demonstrates the enzymatic nature of these protein machines, which tailor the chemical reaction pathway by providing specific interactions between the protein and the substrates/products. Recent reviews have aimed to transfer insights from the functioning of biomolecular motors to the design of synthetic molecular motors (9, 21).

2.2. Scaling of Motor Force

Marden & Allen (22) discovered a scaling relationship between the maximum force output of a linear motor and its mass (**Figure 2**), which holds over more than 25 orders of magnitude in mass and can be written as

$$F = (m \times 26{,}600\,\mathrm{N}^{3/2}\,\mathrm{kg}^{-1})^{2/3} = (M \times 1.4\,\mathrm{fN}^{3/2}\,\mathrm{Da}^{-1})^{2/3}.$$

Although there is substantial overlap at the macroscale between biological motors (e.g., muscles) and synthetic motors (e.g., winches), data points at the molecular scale stem entirely from linear

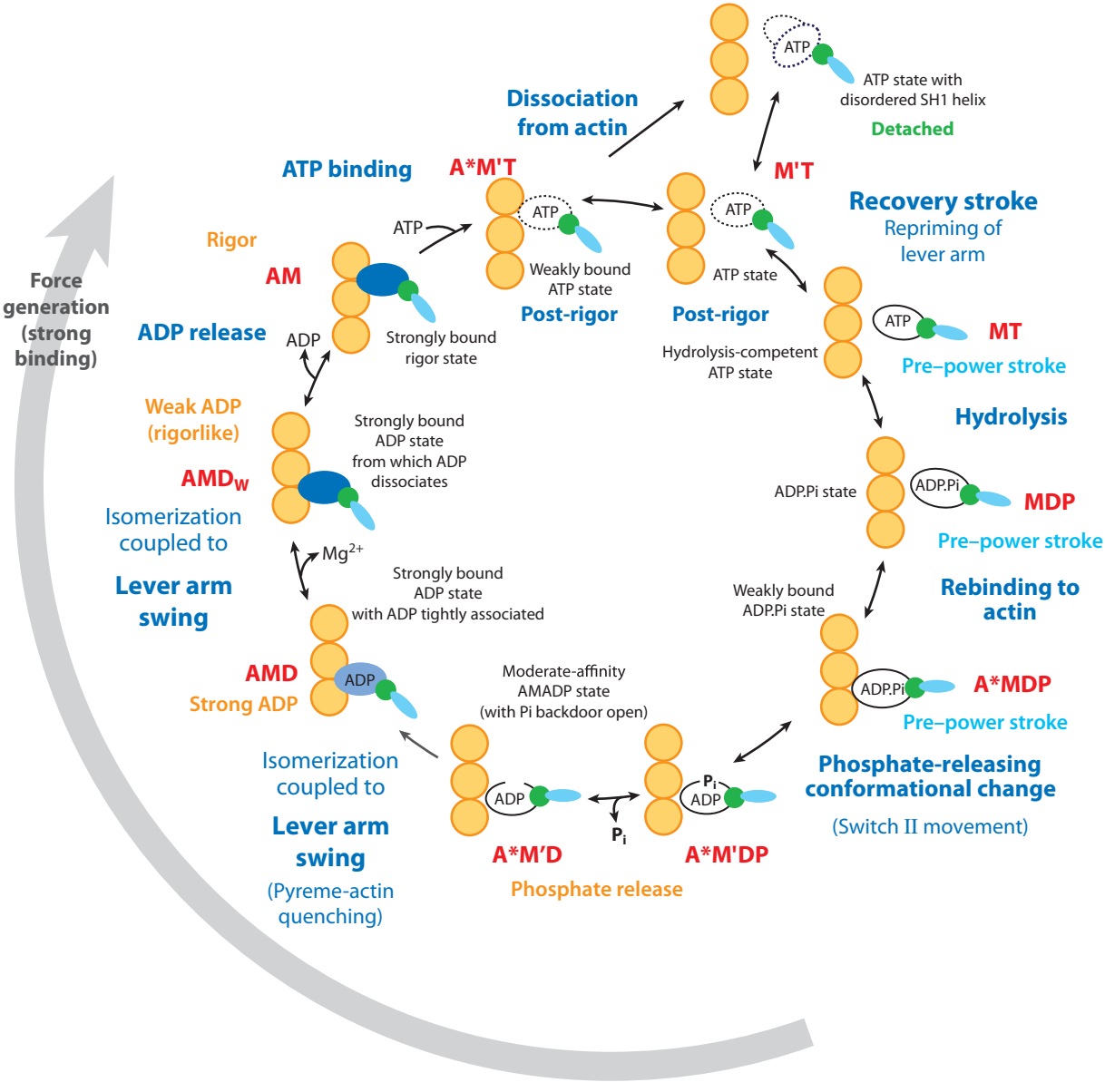

Figure 1

The movement of myosin motors along actin filaments involves a complex cycle of changes in conformation, nucleotide-binding state, and actin affinity. Reprinted with permission from the *Annual Review of Biophysics* (12).

motor proteins. Recent advances by the Stoddart group enable a comparison with synthetic molecular motors. Rotaxanes, photo-activated synthetic molecular motors that have been successfully assembled into artificial muscles (23), theoretically can exert forces of up to approximately 30 pN (24). In practice, an initial average contractile force of 10 pN per motor decreased to less than half after only 25 activation cycles, implying that a significant number of motors lose their activity in

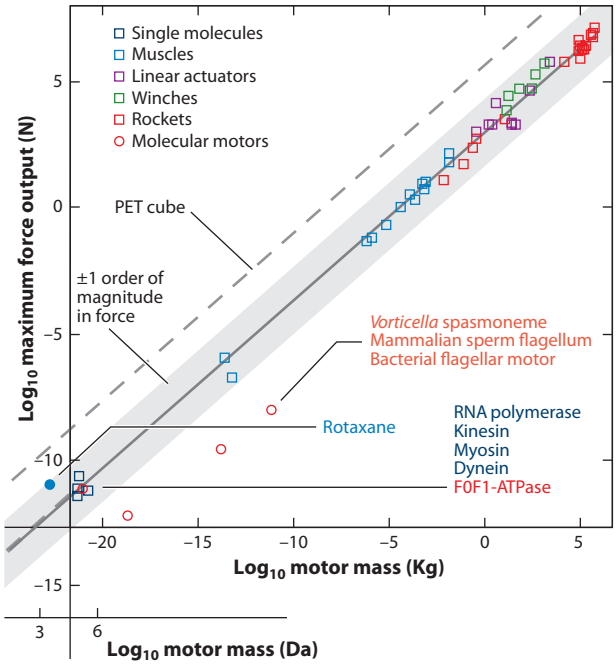

Figure 2

Maximum force of motors as a function of their mass. The motor force output falls into a narrow band around a regression line for biological and man-made linear motors spanning more than 25 orders of magnitude. Some rotary biological motors have a substantially lower force output (adapted from Reference 22). The data point for a synthetic linear motor (Rotaxane) has been added based on Reference 23. The tensile force that can be withstood by a poly(ethylene terephthalate) (PET) cube of given mass is shown as a dashed line.

each cycle (23). **Figure 2** suggests that a functional motor with a mass of 4 kDa should be designed for a maximum force of 0.3 pN.

Neither the existence nor the exponent of this scaling relationship is entirely surprising. The exponent of 2/3 arises from the fact that the cross section of a structure that is scaled linearly in mass will scale with an exponent of 2/3, which enables the supported forces to increase with an exponent of 2/3 without a change in stress. Given the relatively narrow distribution of materials around a line in an Ashby diagram plotting strength versus density (25), the disparate materials employed in constructing molecular motors and ship engines have a minor effect.

However, the coefficient relating force and mass is unexpected. Even a mechanically unremarkable polymer such as poly(ethylene terephthalate) has a tensile strength of more than 50 MPa, which means that a cube of this material with a density of 1.4 g/cm^3 can support a tensile force of

$$F = \sigma \left(\frac{m}{\rho}\right)^{2/3} = (m \times 2.5 \times 10^8\ \mathrm{N}^{3/2}\,\mathrm{kg}^{-1})^{2/3} = (M \times 13{,}000\ \mathrm{fN}^{3/2}\,\mathrm{Da}^{-1})^{2/3}.$$

In other words, the stress averaged over the whole cross section of the motors is 500-fold smaller than the strength of a typical engineering material. This output gap likely originated from a safety factor to account for fatigue as well as from the fact that only a small fraction of the motor cross section is available to support the generated force at certain internal locations, such as the connecting rod in a piston engine.

Designs for synthetic molecular motors will likely have to consider this engineering rule of thumb that connects force and mass in order to create reliable nanoscale devices. The identification of force-limiting weak elements in molecular motor designs will be critical for substantial improvements. A revolutionary design would substantially reduce the output gap without a compromise in lifetime.

2.3. Efficiency

The efficiency in converting chemical (or electrical) energy into mechanical work is a central figure of merit for motors. The rotary molecular motor F1-ATPase reportedly has an efficiency of nearly 100% (26, 27). Similarly, the ability of kinesin-1 to generate a force of up to 7 pN (28) with a step size of 8 nm from the hydrolysis of a single ATP (29) implies a maximal efficiency exceeding 50%. In contrast, heat engines operate with efficiencies of less than 60%, and generally the efficiency decreases as the size of the engine decreases due to higher thermal losses. Large electric motors achieve efficiencies of close to 100%, but the efficiency drops to below 20% for electric micromotors (30). Efforts to exploit phase transitions in polymer gels for force generation scalable to the molecular scale achieved an efficiency on the order of 10^{-6} (31). Therefore, the high efficiency of biomolecular motors is one of their most intriguing attributes from an engineering viewpoint, especially if the efficiency of individual molecular motors can be maintained in macroscopic arrays of such motors.

The high efficiencies of molecular motors can only be achieved when the chemical and mechanical cycles of the motors are suitably designed (32). Of particular interest is the motor efficiency at maximum power, rather than the maximum efficiency at vanishing velocity (33). Some interesting results are that power stroke mechanisms are preferred (34) and that a large free-energy change per fuel molecule expended enables higher efficiencies (35) (see **Figure 3**).

An alternative perspective on the maximum possible efficiency is given by Schneider (36, 37), who notes that a transition to a new state (e.g., a forward step) by a molecular motor constitutes a choice between alternative states. Associated with this choice is an increase in information

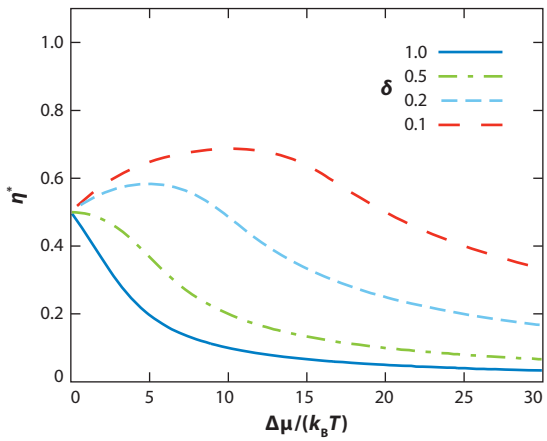

Figure 3

Motor efficiency at maximum power η^* as a function of the chemical potential difference $\Delta\mu$ of the fuel for different relative positions of the transition state δ along the reaction step for a general model of a linear molecular motor. A pure power stroke mechanism corresponds to $\delta = 0$. From Reference 35. Reprinted with permission.

in the system, which is equivalent to a reduction in entropy. According to the Second Law of Thermodynamics, this entropy change requires a minimum amount—$k_B T \ln(2)$ per bit—of heat dissipation. This requirement limits the fraction of the free-energy change associated with the chemical reaction that is available for mechanical work.

Although kinesin (11), myosin (12), and F1-ATPase (26) use a power stroke mechanism to at least some degree, designs of synthetic molecular motors often do not, which compromises their efficiency. For example, DNA motors (38) or the Tumbleweed (39) rely on a diffusive motion to the new binding site, which represents the antithesis of a power stroke (34). Rotaxanes utilize a power stroke mechanism; however, the theoretical efficiency of a cycle is on the order of 10% in the design used by Liu et al. (23). Synthetic motors often use large free-energy changes, e.g., the 100–200 $k_B T$ provided by photons, which is in principle desirable for high efficiency. However, the extraction of correspondingly large amounts of mechanical work relies on large forces on the order of hundreds of piconewtons, which are difficult to handle, as described in Section 2.2. This is in part due to the increasing number of alternative reaction pathways that become accessible with increasing thermodynamic driving forces.

The efficiency of the individual motor is of little use if the efficiency cannot be maintained at the systems level, where motors often have to act collectively. Muscle tissue demonstrates the feasibility of a system that effectively combines the output of many molecular motors. The efficiency of muscle ranges from 20% to 40% (40, 41), which proves that a macroscopic array of 10^{20} molecular motors can operate with an efficiency close to the efficiency of individual motors. However, the design of the molecular motor has to be adapted to this collective mode of operation to minimize losses (42).

2.4. Biological Applications of Molecular Motors

Molecular motors are employed in biology for a wide variety of functions that often have macroscopic equivalents in engineering. In this section, the applications of motors in intracellular transport, in cellular motility, and as key elements of muscle tissue are briefly discussed (see **Figure 4**).

Intracellular transport comprises a range of motor-driven mechanisms, including, for example, anterograde and retrograde transport in neurons (43) and cytoplasmic streaming in algae (44).

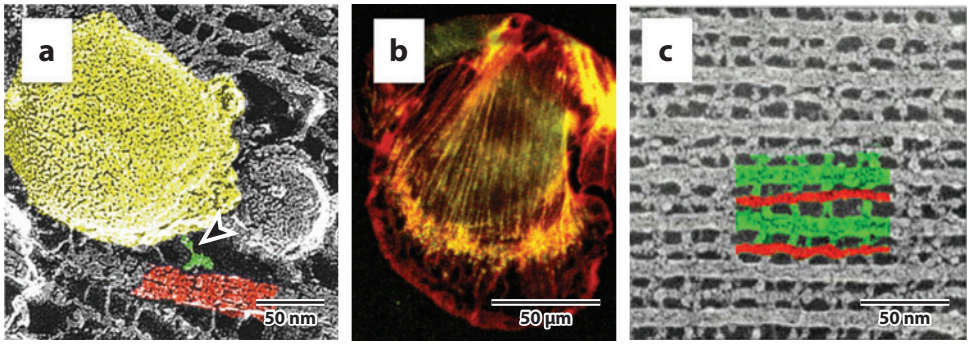

Figure 4

Biological functions of biomolecular motors. (*a*) A vesicle-carrying kinesin bound to a microtubule; adapted from Reference 43. Reprinted with permission from AAAS. (*b*) Myosin II (*green*) colocalizes with actin filaments (*red*) in stress fibers of spreading cells; from Reference 47. © Rockefeller University Press. (*c*) Myosin II organized into thick filaments (*green*) and actin (thin) filaments (*red*) in insect muscle; from Reference 48. Reprinted with permission.

The neuronal anterograde and retrograde transport mechanisms rely on the active movement of kinesins and dyneins, respectively, to shuttle a variety of cargoes along the microtubule network inside axons and thereby enable the cell to greatly extend its physical size. The advantages of motor-driven transport over diffusion are the abilities to cover long distances, transport molecules against concentration gradients, and force cargo through crowded environments. Cytoplasmic streaming occurs in the giant intermodal cells of characean algae, where organelle-bound myosins propel themselves along an actin network at the periphery of the cell to stir the cytosol and thereby improve mixing. Again, this transport mechanism is an adaptation to a large cell size.

Cellular motility is a complex process that relies on forces generated by polymerizing actin filaments and forces generated by myosin motors. The contraction of the actomyosin machinery generates the traction force at focal adhesions and induces the retraction at the rear of the cell (45). Disassembly of actin filaments at the rear end of the moving cell is a newly discovered role of myosin II motors (46). The utilization of the mechanical work generated by molecular motors to accelerate the disassembly of a molecular structure is conceptually interesting because the motor takes on the role of a shredder rather than that of a transporter.

The evolution of specialized muscle tissue whose primary function is the amplification of molecular motor output creates fascinating applications beyond the obvious roles as skeletal muscle and heart muscle. For example, the ciliary muscle alters the shape of the ocular lens and thereby changes its focal length. The muscle cells in the media layer of arterial walls can dynamically change the mechanical properties of the wall and enable complex responses of the cardiovascular system. The demonstrated microscale integration of sensing, energy harvesting, and mechanical adaptation motivates the pursuit of synthetic functional materials.

3. APPLICATIONS

The biological applications of molecular motors as well as motor applications in macroscale engineering can act as guides toward identifying engineering applications of molecular motors. For example, biomolecular motors can in principle be used to construct a microscopic displacement pump (49) for the purpose of moving analyte molecules through a microfluidic system. However, biomolecular motors can also act orthogonally to fluid flow, for example by capturing analytes and extracting them from a fluid stream molecule by molecule (50). In other cases, entirely new ideas have been demonstrated such as the use of biomolecular motors to construct actively moving surface probes. This section provides an overview of these application concepts.

3.1. Molecular Transport

The transport of molecules, supramolecular complexes, and nano- or microparticles is a prime application for molecular motors because demand and supply are well matched. On the demand side, there is an extensive effort in nanotechnology to master the fast and precise positioning of nanoscale objects, for example by using scanning force probes (51) or templated self-assembly (52). However, trade-offs between throughput, precision, cost, and other process metrics exist and create a need for improved technologies. On the supply side, biomolecular motors such as kinesin-1 or myosin V evolved for the specific purpose of intracellular transport (8).

This opportunity has been addressed by the design of molecular shuttles: nanoscale transport systems powered by biomolecular motors (53). In a typical design (**Figure 5*a***), the motor proteins are adhered to a patterned surface and propel the complementary cytoskeletal filaments (microtubules or actin filaments). Patterns on the surface create topographical or chemical cues to guide

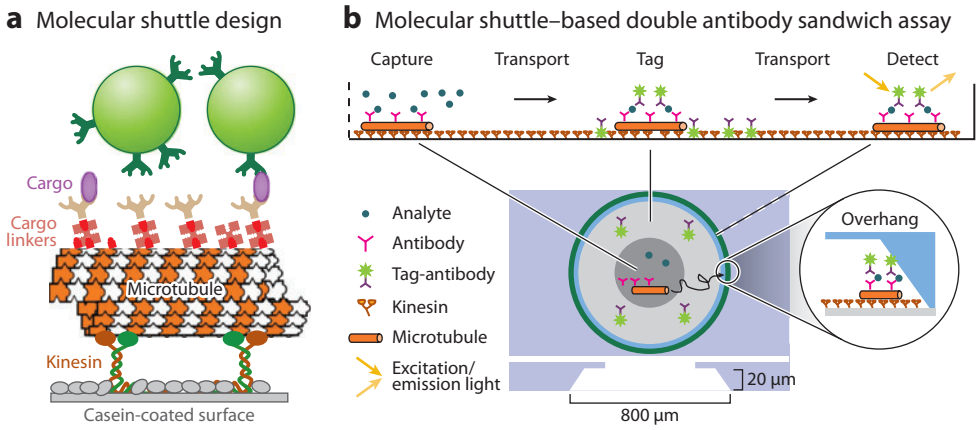

Figure 5

(*a*) A typical molecular shuttle design relies on surface-adhered kinesin motors to transport functionalized microtubules that carry different types of cargo. (*b*) Molecular shuttles enable a double antibody sandwich assay where analytes are captured, tagged, and delivered to a detection site. In the present design, capture and tagging occur inside a circular well, and the tagged analytes are delivered to the deposition site at the periphery of the well. An overhang prevents the unintended presence of tags in the deposition zone.

the movement of the shuttles, linkers on the gliding filaments enable cargo loading, and control molecules in the solution modulate the motor activity.

Molecular shuttles outrun diffusive transport only over long times or for large cargo particles. A rough estimate shows that the product of transport time and particle diameter has to exceed 1,000 s·nm in order for the average displacement of a cargo particle by a shuttle to exceed the average displacement of the particle by free diffusion (assuming the viscosity of water and the speed of kinesin). However, the directed nature of the transport that can take cargo without detour from location A to location B can provide a major boost to cargo delivery speed, depending on the size of the cargo loading and unloading areas (54).

The path chosen by a molecular shuttle depends on its internal mechanics and can be constrained by tracks (55–58) or controlled by external forces (59–62). Thermal fluctuations of the advancing tip of the cytoskeletal filament cause the deviations from a straight path, and, as a result, the trajectory can be described by a persistence length (63, 64). In principle, the trajectory persistence length should be equal to the filament persistence length (65), but the length dependency of the microtubule persistence length (66) reduces the trajectory persistence length to the persistence length of the tip segment of the gliding microtubule (63, 67, 68). Using the statistical description of the shuttle movement, one can accurately predict average shuttle behavior in Monte Carlo simulations that include the effect of physical barriers (69) and external forces (70).

The state of the art in controlling the movement of molecular shuttles and in loading/unloading of cargo is reviewed in Reference 17. The most recent developments include the autonomous delivery of lipid vesicles (71) and the integration of cargo loading and unloading into one device (72). Kinesin-powered molecular shuttles have enabled the design of a double antibody sandwich biosensor (73), where antibody-functionalized molecular shuttles capture protein analytes, pick up antibody-functionalized optical tags, and deliver the tags to a detection zone (**Figure 5*b***). Investigators envision that the integration of molecular transport enables smart dust biosensors (74). Efforts to create fully synthetic cargo transporters based on catalytic nanoparticles have also yielded initial successes (75, 76).

3.2. Analyte Concentration

The detection of chemical and biological entities is a complex process that often requires the capture, aggregation, and identification of the target molecules. Active transport of captured analyte molecules and particles can be exploited to enhance the mass transport to a sensor under specific conditions (54). In particular, advantages can be obtained for sensors of submicrometer size because diffusive transport to such a small target is particularly inefficient. In this situation, a significant benefit is already realized from reducing the dimensionality of the search for the sensor from three dimensions for purely diffusive transport to a two-step process where diffusion to a surface and capture by a molecular shuttle is followed by a two-dimensional search of the shuttle for the sensor (77). The mass transport can be further accelerated if the shuttle is guided toward the sensor. An experimental realization of the concept of analyte capture and aggregation is shown in **Figure 6** (78). A second approach is to exploit the orthogonality of active transport by molecular motors to transport via fluid flow and utilize molecular shuttles to remove captured molecules from an analyte stream (50).

In general, the comparison of competing sensor device designs with and without active transport driven by molecular motors is complex because the optimal design depends so much on the interaction between the sample properties, the aggregation process, and the detector characteristics. The ongoing research into nanoscale sensors, such as semiconducting nanowires (79), may provide the ideal detector as partner for an active aggregation step.

3.3. Nanoscale Assembly

The assembly of nanoscale and microscale parts into larger structures is an application of molecular motors with significant promise. Although robotic assembly can manipulate individual atoms (51), the assembly speed drops steadily from tens of thousands of parts per hour for millimeter-scale parts to one atom per hour (80). Self-assembly, in contrast, is a highly parallel and therefore fast process; however, diffusion slows with increasing part size, and the increasing mismatch between interaction energies and thermal energies limits the accuracy of the assembly process. Active self-assembly by molecular motors has advantages of both self-assembly and robotic assembly. It is highly parallel, like self-assembly, and it can utilize external energy supplies to move parts, resolve mismatched connections, and create nonequilibrium structures (81).

These properties of active self-assembly are on display when sticky microtubules gliding on kinesin collide to form wires and, ultimately, spools (82–84) (see **Figure 7**). Within less than an hour, more than 10,000 microtubule spools with an average diameter of 5 μm form in a single experiment, each spool requiring more than 1,000 $k_B T$ of energy input to bend the constituent microtubules into a circular shape. Bifunctional kinesin constructs can also organize microtubules into aster-shaped structures reminiscent of mitotic spindles (85). However, the efficient assembly of functional photonic or electronic nanostructures by molecular motors, which is the ultimate goal, has not yet been demonstrated.

At the molecular scale, the controlled translocation of chemical building blocks by molecular motors can also facilitate organic synthesis by increasing speed and yield (86), or it could facilitate the transcription or translation of a molecular template, as demonstrated by DNA polymerase, RNA polymerase, and ribosomes (16).

3.4. Self-Propelled Probes

Microscopic probes are widely used to obtain information about the local environment. In particular, scanning probe microscopy with its wide range of measurable surface properties exemplifies

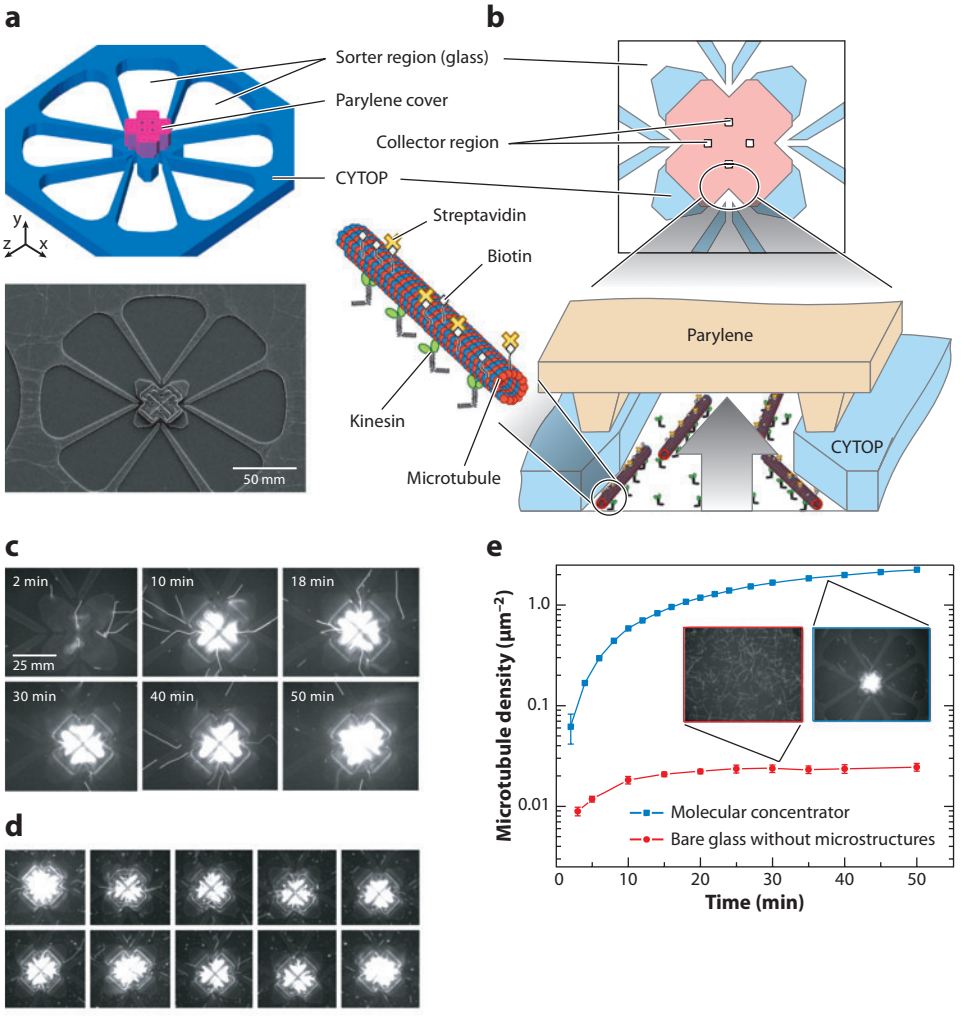

Figure 6

A concentrator device relying on kinesin-driven transport of biotinylated microtubules to deliver fluorescent streptavidin to a central collection site. (*a*,*b*) Schematic of the device. (*c*,*d*) Fluorescence microscopy images of the aggregation process. (*e*) Hundred-fold enhancement of the microtubule density in the collector region relative to a bare glass surface. Reproduced with permission from *Nano Lett.* 2008, Vol. 8, No. 4, the American Chemical Society.

the utility of a nanoscale probe (the scanning tip) that is manipulated to examine a surface. Autonomous, self-propelled probes may overcome the inherently serial nature of the scanning process and its preference for planar surfaces. A biological example of an alternative approach to a surface detection process is the random movement of T cells as they search for antigen-presenting dendritic cells within lymph nodes (87). Similarly, autonomous probes for surface imaging do not necessarily require the ability to sample along a straight path and turn on command; instead, a locomotive behavior that leads to random sampling of the surface can be sufficient to generate an image. This process is reminiscent of the Monte Carlo method (88) and is particularly well suited to nonplanar surfaces that are difficult to access. Kinesin-powered molecular shuttles have been

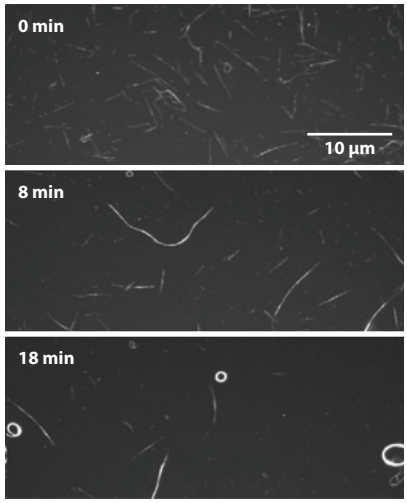

Figure 7

Sticky microtubules (biotinylated microtubules partially coated with streptavidin) gliding on motor-coated surfaces self-assemble into linear and circular structures. Reproduced with permission from *Nano Lett.* 2005, 5:629–33, the American Chemical Society.

used experimentally to demonstrate such an imaging procedure (89). A further refinement of the process (**Figure 8**) collects positional information from the molecular shuttles with nanometer resolution in three dimensions (90). Again, the promise of Monte Carlo imaging by self-propelled probes relative to other imaging modalities depends critically on the exact problem statement (e.g., if "at least one" or "all" of specific sites of interest need to be detected).

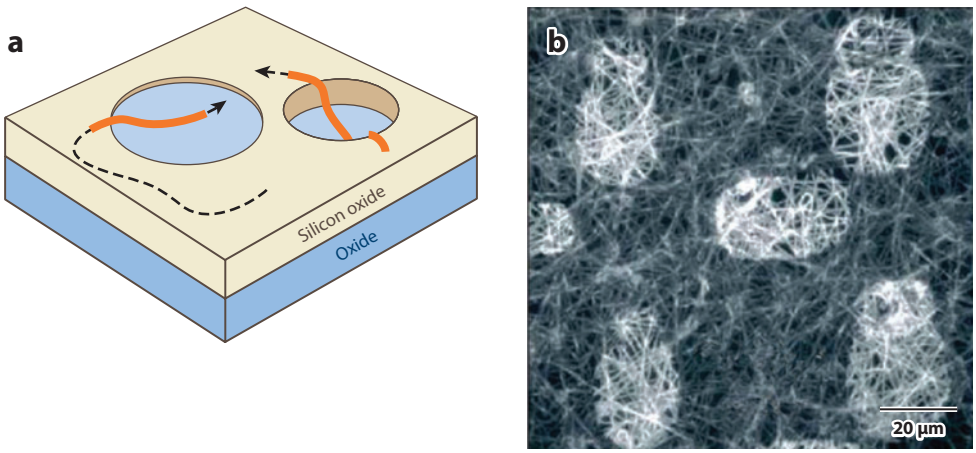

Figure 8

(*a*) The positions of microtubules gliding on kinesin-coated surfaces can be determined in three dimensions by encoding the *z*-position in the microtubule brightness, which predictably varies if the microtubule is located within 100 nm of a reflecting surface. (*b*) By tracing the positions of a large number of moving microtubules and overlaying the images, a topographical map of a surface can be created. From Reference 90, © Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

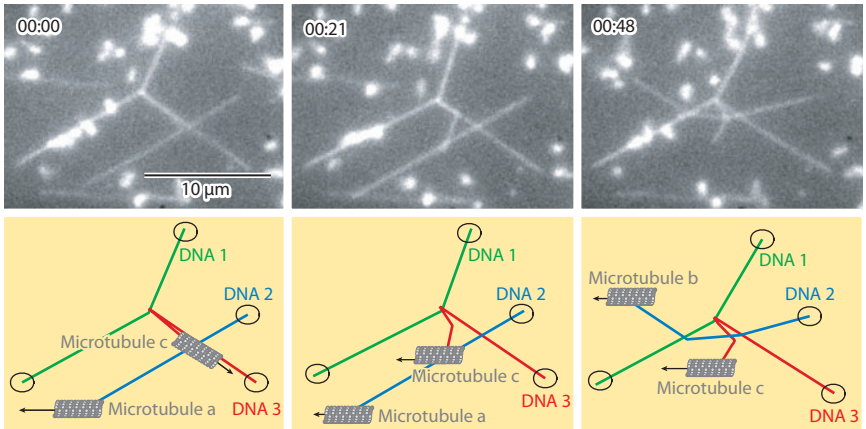

Figure 9

Microtubules gliding on a kinesin-coated surface can bind λ-DNA via biotin-streptavidin linkages and manipulate multiple fluorescently labeled DNA strands simultaneously and independently. Unattached λ-DNA coils up and is visible as bright dots. Attached λ-DNA is stretched by the moving microtubules and visible as straight lines. From Reference 92, © Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

3.5. Stretching and Bending

The generation of mechanical work by molecular motors can be used to stretch and bend molecular structures. For example (see **Figure 9**), kinesin-powered molecular shuttles have been used to stretch λ-DNA (91) and subsequently to assemble the stretched DNA strands (92). This is made possible by the parallel but independent force generation of molecular motors. In contrast, DNA combing by flow fields achieves parallel manipulation of DNA, but the identical direction and magnitude of the applied force makes assembly of complex structures impossible. This is not a small difference: It is relatively straightforward to apply external fields to a single micro- or nanoscale entity and manipulate it in space (93) or to multiplex the process and perform an identical operation on many identical entities (94). However, molecular robots should be autonomous and able to operate in parallel on different programs (95). Although molecular motors provide autonomous movement, an ongoing challenge is to program a sequence of actions (96) beyond prescribing a hard-wired pattern of tracks to follow (97) or controlling individual molecular shuttles by external fields (60).

By bending beams of known stiffness, investigators can calibrate the force exerted by molecular motors and determine rupture forces of linkages connecting beams and motors. Hess et al. (98) demonstrated such a force meter by using a microtubule as a reference beam bent by a gliding microtubule connected to the reference beam via biotin-streptavidin linkages. However, subsequent studies showed that microtubules are beam structures with a particularly complex elastic behavior (66, 99–101), which makes them poorly suited for this application.

3.6. Microfluidic Pumps

A key component of many microfluidic systems is a pump, and biomolecular motors with their ability to harvest chemical energy from the fluid and convert it into microscopic mechanical work seem ideally suited to compete with complex microscale pumping schemes involving, for example, optical tweezers to move fluid-displacing particles (102). A theoretical analysis suggests

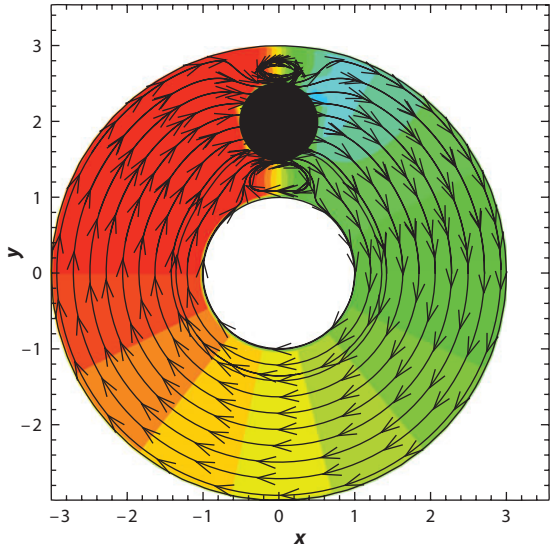

Figure 10

A microsphere propelled by biomolecular motors can act as a displacement pump in a microchannel, as a detailed analysis of the flow characteristics reveals. From Reference 49. Reproduced by permission of the Royal Society of Chemistry.

the feasibility of a pump design relying on a kinesin-coated microsphere moving in a slightly larger microchannel decorated with aligned microtubules (**Figure 10**) (49). The motor-driven transport of the microsphere could deliver flows in the atto- to picoliter per second range.

Of course, biomolecular motors compete with other approaches to combine energy harvesting with pumping, including the use of glucose-consuming motile bacteria (103) or combinations of fuel cells and electroosmotic pumping (104). However, pumping by molecular motors should be feasible in nanofluidic channels with submicron dimensions, where other approaches fail. Because the pumping can originate from motors and filaments moving on the channel surface, and because transport velocities are quite uniform (63), plug-like flow with small sample dispersion could be realized.

3.7. Micro- and Macroscale Actuation

In the context of micro- and nanofluidic devices, actuation is often required to implement valve functions, and biomolecular motors could potentially be employed to actuate valves. The ultimate extension of this concept has been demonstrated with synthetic molecular motors by placing them at the opening of a nanopore (**Figure 11**), where their conformational change can trigger the release of small drug molecules (105). The extension of the concept toward larger cargoes, such as therapeutic antibodies or DNA for gene delivery, may be aided by larger motors such as F1-ATPase (106) or the Phi29 DNA packaging motor of bacteriophages (107).

Multiplication of molecular motor output in terms of force and actuation velocity by hierarchical assembly of motors into arrays is strikingly demonstrated in muscles. The high energy efficiency of individual molecular motors at maximum power (Section 1.3) would make a compelling argument for macroscopic arrays of molecular motors, if bundling of motors into arrays does not introduce significant efficiency losses. Muscle is experimental proof that scaling is possible and that efficiency can be maintained at a level comparable to modern car engines (20–40%) for decades.

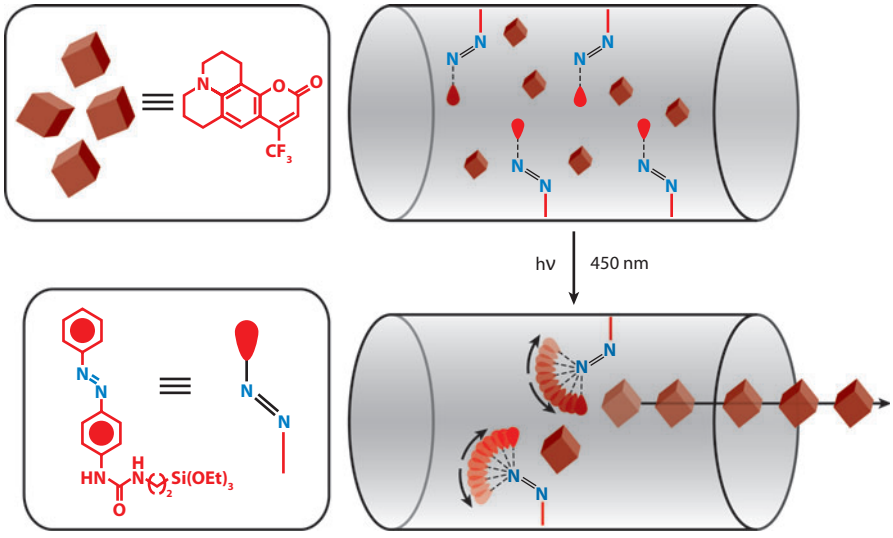

Figure 11

Nanoimpellers can control drug release from mesoporous silica nanoparticles. Continuous excitation of the nanoimpellers at 450 nm induces *trans*-to-*cis* and *cis*-to-*trans* isomerizations of the azobenzenes, generates a nanoimpeller-type motion, and causes the cargo molecules to be propelled out of the mesopores. From Reference 105. Reproduced by permission of the Royal Society of Chemistry.

Initial experiments targeted toward artificial assemblies (as opposed to experiments with muscle or its components) focus on the coupling of motors into one- and two-dimensional arrays. One-dimensional arrays are expected to exhibit rich dynamic behavior, including synchronization, oscillations, phase transitions, and hysteresis (108, 109). In particular, the kinesin/microtubule system has been used experimentally to explore the effects of coupling a defined number of motors (110). In two dimensions, the state of the art is still represented by the gliding of kinesin-coated particles with lateral dimensions of a few micrometers on isopolar arrays of microtubules (111). In contrast, billions of synthetic motors have been successfully assembled to collectively generate millinewton forces (23). Independent of the origin of the motor, the design of three-dimensional macroscopic arrays of molecular motors represents an exciting scientific and engineering challenge.

3.8. Molecular Computation and Communication

The persistent movement of nanoscale agents along branching paths enables new computational architectures (112). For example, actin filaments gliding on a surface with myosin motors could be assembled in a pooling area, enter and traverse a network of channels, and return solutions to questions encoded in the network by reaching different outlets of the network (see **Figure 12**). The appeal of this approach derives primarily from the parallel computations enabled by employing large numbers of nanoscale agents, which can counteract the relatively slow rate of decision making by individual agents.

Similarly, active transport enabled by molecular motors may be exploited for the delivery of molecular messages, enabling a new communication paradigm in engineering (113). The kinship of such an approach with intra- and extracellular communication modes in biology may enable a seamless interface between biological and engineered systems in health applications. The infectious

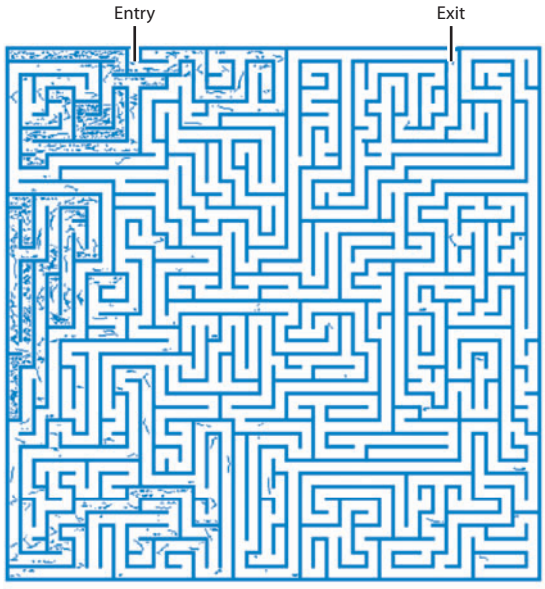

Figure 12

Motile molecular agents exploring mazes can in principle solve graph connectedness problems in a scalable manner. Adapted from Reference 112. Reproduced with permission.

path of herpes viruses, which hijack dyneins to travel from their axonal entry point into the cell to the nucleus, represents the delivery of a potent molecular signal (114).

3.9. Control of Material Properties

Molecular motors distributed throughout a material enable the controlled modulation of optical and mechanical properties. Biological proof-of-principle examples are the modulation of color in melanophores via the aggregation and dispersion of pigment granules by motor proteins (115) and the modulation of the mechanical properties of muscle as a result of contraction.

The demonstration of color tuning of a liquid crystal by activation of synthetic molecular motors has been a major milestone in demonstrating potential applications of molecular motors (116). However, given the advanced state of solid-state photonics, the demands on competing technologies with respect to switching speed and on/off ratios are particularly high. At the same time, photovoltaics may offer applications for relatively slow tuning of optical properties, similar to the optimization of chloroplast position by motor proteins in green leaves (117).

Materials with controllable mechanical properties, such as magnetorheological fluids, find widespread use in engineering. Molecular motors provide the added functionality of converting chemical energy into mechanical work and thereby drive energy-dependent property changes such as shape changes against a load. In vitro experiments using myosin motor proteins and actin gels have demonstrated that motors can modulate stiffness by more than two orders of magnitude (118) (see **Figure 13**). Although the stimulation of phase transitions has successfully modulated mechanical properties of polymeric materials, the energy conversion efficiency is orders of magnitude lower than the efficiency of individual motor proteins or muscle (31, 119, 120). High efficiency is thus the key potential advantage of molecular motors over other approaches, even though efficiency is rarely the focus of discussion in either case. At the same time, the limitations

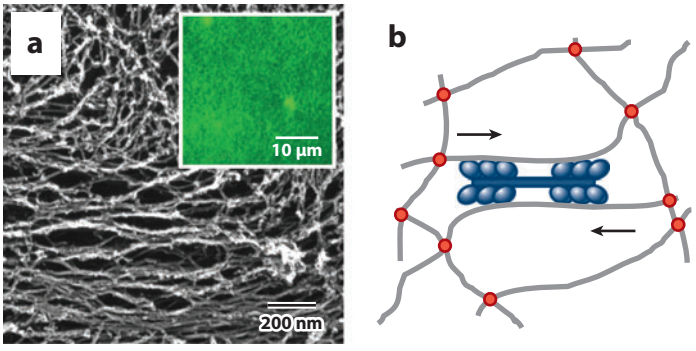

Figure 13

Microstructure of active networks of actin and myosin visualized by electron microscopy and fluorescence microscopy (*a*) and the proposed mechanism of active stiffening (*b*). Reproduced with permission from Reference 118.

on force generation discussed in Section 1.2 are likely to limit the tensile strength of tunable materials integrating molecular motors to less than 1 MPa.

4. SUMMARY AND CONCLUSIONS

The discovery of many motor proteins in addition to myosin has been an exciting development in cell biology in the past decades (121), and the elucidation of their inner workings has stimulated thousands of biophysical studies (11). The role of motor proteins in the normal functioning of the cell, their involvement in various pathologies, and their potential use as drug targets are areas of intense interest in biomedical research.

At the same time, motor proteins serve as a proof of principle, inspiration, and test bed for future engineering applications using molecular motors. Recent research suggests the fundamental potential and also the limitations of molecular motors in terms of force generation, efficiency, and scalability. However, the development of molecular motors, either by modifying biological motors or by creating synthetic motors, is aimless without concurrent development of application concepts. This review has discussed such often bio-inspired applications, including molecular transport, nanoscale assembly, actuators, self-propelled probes, molecular communication and computation systems, and active materials. Ultimately, the success of the field will depend on a convergence between motor capabilities and application requirements.

These engineering efforts, whether successful or unsuccessful, impart lessons about the design of complex supramolecular structures. The lessons may stimulate new approaches to classic problems in biomedical engineering, such as protein adsorption (122–124) or analyte capture (54). They also teach us to integrate biophysical insights obtained using the reductionist approach and appreciate emergent phenomena (81, 125). And finally, our growing understanding of engineered mechanically active nanosystems will translate into an improved appreciation of biological design solutions (2), which in turn has the potential to translate into novel therapeutic concepts (126, 127).

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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