NANOROBOTS

The force has limits: Molecular motors in robotics

Henry Hess[1]*, Parag Katira[2]*, Juan B. Rodriguez III[1]

Molecular motors generate force to individually power molecular machines or collectively drive macroscopic actuators. The force output of molecular and macroscale motors appears to be constrained by the same scaling law relating motor force and mass. Here, potential origins of these universal performance characteristics are discussed and the implications examined.

INTRODUCTION

Molecular motors are specialized molecular machines that convert energy into mechanical work (Fig. 1A). Prominent examples from nature are myosin motor proteins, which drive muscle contraction by linking adenosine 5′-triphosphate (ATP) hydrolysis to force exertion on actin filaments, and ATP synthase, which couples proton flow across membranes to ATP production via rotary motion. The successful synthesis of artificial molecular motors, recognized by the 2016 Nobel Prize in Chemistry to Feringa, Sauvage, and Stoddart, has created small organic molecules that are driven by chemical energy or light to contract or rotate. The motor operation occurs in the presence of thermal fluctuations, which can be integral to their functioning (*1*). The coupling of the movement of a molecular motor to an external load is critical, and mechanisms range from the simple exploitation of shape changes of the motor to displace surrounding molecules (*2*) to sophisticated designs with complex elastic elements, such as the protein titin, in muscle (*3*).

Molecular motors are the logical end point of a historical trend toward miniaturization in technology (Fig. 1B). Over the course of the 20th century, commercial engines and motors underwent dramatic reductions in size: from 100-kg engines in the 1908 Ford Model T to 10-kg motors in 1920s washing machines, 1-kg motors in 1930s kitchen mixers, 100-g motors in 1960s record players, 10-g motors in the 1979 Sony Walkman, and finally, 1-g motors in 1980s hard disk drives. Advances in microelectromechanical systems (MEMS) technology promise a route toward further miniaturization all the way to the nanoscale and begin to make their way into applications (*4*). The tools of organic chemistry and biotechnology complement micro- and nanoelectromechanical systems (MEMS/NEMS) technology and allow the fabrication of molecular motors in large numbers. This provides the opportunity to follow nature in using molecular motors in teams of vastly different sizes to produce forces from the piconewton to the kilonewton scale.

The integration of molecular motors into technological systems faces several challenges. Promising applications, such as mechanical computing (*5*) or robotic synthesis (*6*), have to be validated, and new applications have to be identified. Energy conversion efficiencies above 1% need to be achieved, at both the individual motor level and the integrated device level, because otherwise the widespread application of molecular motors with low efficiency [as low as 10^{-9} (*7*)] would consume a disproportionate slice of our energy budget. Our own work is one instance of successfully performing molecular scale manipulations using highly efficient biological molecular motors in a tremendously inefficient system (*8*), but there are other examples where molecular scale motion has been achieved via synthetic molecular motors at a prohibitive energetic cost (*7*). Celebrated nano- and micromotor designs often incorporate macroscopic components (electrodes, magnets, and lasers) as essential components that are largely kept out of sight. In some ways, imprecise language in the field impedes conceptual clarity (*9*). An example is that a machine that moves reliably without pushing a load is more a clock than a motor (*10*). Extracting macroscale motion using molecular motors also requires scaling up the action of molecular motors by placing them into arrays. Although efforts in this direction are promising, they still fall short of what nature has achieved in muscle. Currently, synthetic organic chemistry, biotechnology, and NEMS technology compete to enable efficient, self-actuated, self-assembled and packaged molecular motor assemblies. Artificial intelligence may provide new tools and ideas to overcome roadblocks along these distinct approaches.

Here, we wish to highlight another challenge, which is that the force generated by molecular motors may be fundamentally limited. The force output of biological molecular motors and their coupled arrays (also known as muscles) has been found to scale with their mass raised to the power of 2/3 (*11*), implying a roughly constant stress on the order of 100 kPa across their cross section (*12*). Surprisingly, macroscale human-made motors of widely varying designs fall on the same trend line (Fig. 1C). We aim to explore in this Viewpoint whether synthetic molecular motors may be able to greatly exceed the force production of their biological counterparts and how this may affect the integration of molecular motors with robotics and technology in general.

THE UNIVERSAL PERFORMANCE CHARACTERISTICS OF MOTORS

Marden and Allen (*11*) discovered a scaling relationship between the force generated by a motor and its mass by plotting the parameters of macro- to microscale biological and artificial motors and referred to it as the "universal performance characteristics of motors" (Fig. 1C). This scaling relationship appears to be universal in the sense that it applies to motors of different types using a wide range of fuels and that it applies to

[1]Department of Biomedical Engineering, Columbia University, New York, NY, USA. [2]Department of Mechanical Engineering, San Diego State University, San Diego, CA, USA.
*Corresponding author. Email: hh2374@columbia.edu (H.H.); pkatira@sdsu.edu (P.K.)

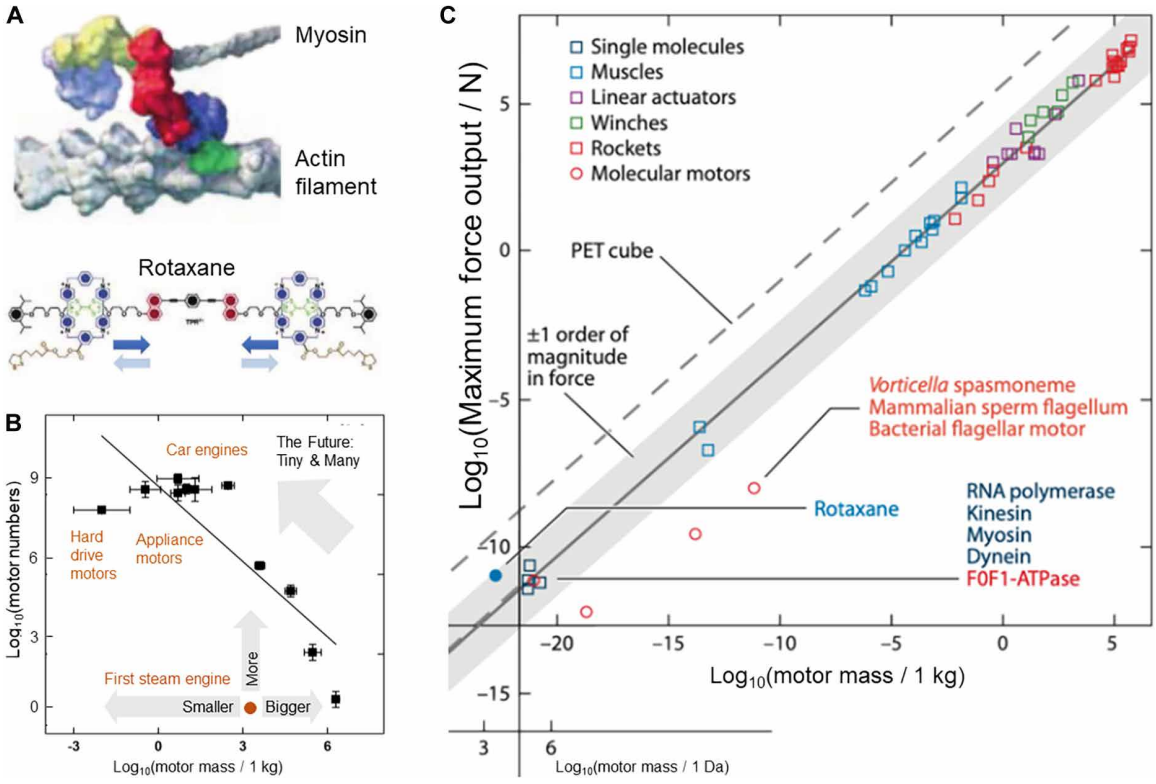

Fig. 1. Molecular motors, motor abundance, and force output as a function of mass for different motors. (**A**) Myosin II is a biomolecular motor exerting force on actin filaments, and a rotaxane is a synthetic molecular motor generating contractile forces. (**B**) The number of human-made motors has increased over time, resulting in a size distribution where numbers are roughly inversely correlated with mass above a certain minimum size. (**C**) The motor force output falls into a narrow band around a regression line for linear biological and human-made linear motors spanning more than 25 orders of magnitude. The tensile force that can be withstood by a poly(ethylene terephthalate) (PET) cube of given mass is shown as a dashed line.

motors weighing more than 100 tons as well as to motors weighing as little as 100 kDa (~10^{-25} tons). Forces generated by biomolecular motors, such as the motor proteins myosin II and kinesin-1, and the forces generated by rotaxanes have been measured to be in the piconewton range (*13*). The production of a few piconewtons of force by biomolecular motors weighing about 100 kDa is exactly what one would expect from extrapolating the trend of the force-to-mass ratio of macroscopic motors. This is surprising given that the principles of operation of these biomolecular motors are dramatically different from those of macroscopic motors and their performance is limited by different factors. For example, force generation by macroscale electric motors is supposedly limited by the heat production in their coils because of the electrical resistance of the wires (*14*). In contrast, biomolecular motors operate essentially isothermally because waste heat is rapidly distributed to the solution (*13*). Although stronger and more durable materials greatly advanced the performance of heat engines, biomolecular motors are proteins relying on much weaker noncovalent interactions for their integrity. It is an open question as to why molecular motors and macroscale motors appear to follow the same force-versus-mass relationship.

EXPLORING THE ORIGINS OF MASS CONSTRAINT ON MOTOR FORCE PRODUCTION

So why do motor designs by humans and nature cluster around the same ratio of force to mass raised to the power 2/3 of about 1 kN/1 $kg^{2/3}$? The scaling exponent of 2/3 is intuitive to the mechanical engineer because the force required to produce the same relative amount of stretching, bending, or twisting (e.g., of a beam) scales with the square of the linear dimensions of the structure, and the linear dimensions scale with the third root of the volume (Fig. 2A). In combination, this yields the observed 2/3 exponent (*11*).

This explains the origin of the slope of the scaling relationship, but it does not explain why motors constructed from different types of materials (e.g., steel or amino acids) do not fall on parallel lines shifted relative to each other. Parts made from materials with higher strength, which is often quantified by the yield strength σ_y or ultimate strength σ_{UTS}, can support higher forces before plastically deforming or fracturing. Somewhat counterintuitively, though, the σ_y of engineering materials increases approximately linearly with their density ρ ($\sigma_y \approx \rho \times 3 \times 10^4$ m^2/s^2; Fig. 2B). So, although steel is 100-fold stiffer than plastic as measured by the elastic modulus, the yield strength increases only about 10-fold; this means that on a per mass basis, little is gained by exchanging soft for stiff elastic materials. Moreover, one has to appreciate that many proteins that make up biological motors have the mechanical properties of hard plastics (*13*), whereas the viscoelasticity of biological tissues arises from special rubber-like proteins, such as collagen, and their foam-like character. Therefore, motors built from different materials, be it biological or synthetic, may achieve a similar ratio of force to mass raised to the power 2/3.

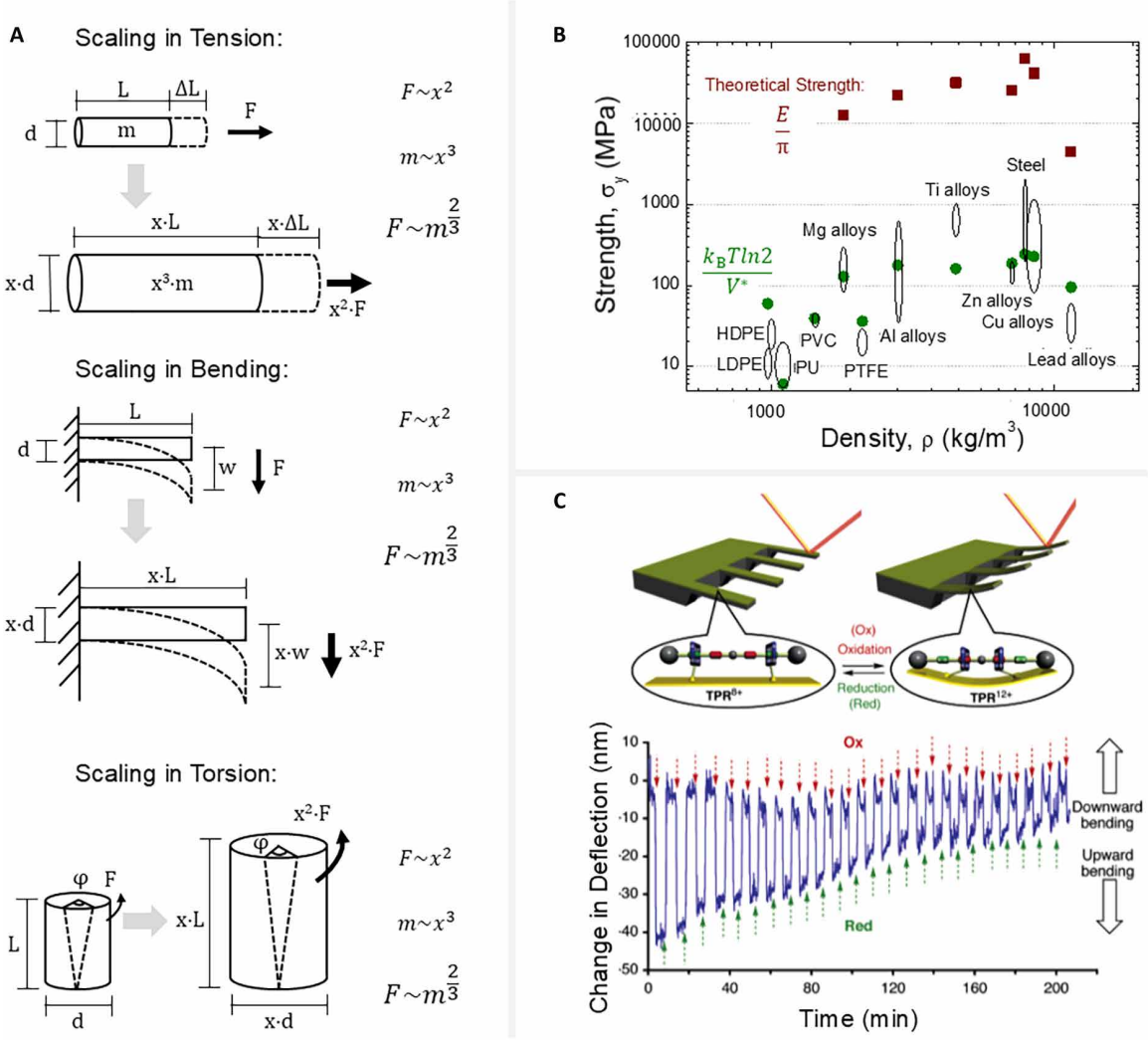

Fig. 2. Force scaling with geometry and material strength. (**A**) If geometric similarity is maintained, then as a stretched, bent, or twisted rod is scaled up by a factor *x*, the force varies proportional to the mass raised to the 2/3. (**B**) Ashby plot of yield strength as function of density for a variety of materials. The range of yield strengths, σ_y, of typical materials, their entropic yield strength (green circles), and their theoretical strength estimated by E/π (red squares), where E is the elastic modulus. k_B, Boltzmann's constant; T, temperature; V^*, molecular volume. (**C**) The contractility of a layer of rotaxanes diminishes rapidly.

As it turns out, the specific value of the force-to-mass-raised-to-power-2/3 ratio produced by a typical motor (~1 kN/1 $kg^{2/3}$) is 300-fold lower than the force that can be sustained by a simple cube made of plastic (Fig. 1) following the yield strength argument presented above. The reason for this dramatically lower ratio is likely again simple geometry: In a motor, generated forces have to be transmitted by parts, such as the nozzle in a rocket or the neck-linker region in a kinesin motor protein, whose cross section is limited to only a small fraction of the cross section of the overall motor. For example, the cross-sectional area of the crankshaft in a Dodge 426 Hemi automotive piston engine is less than 1% of the cross-sectional area of the entire engine. The art of engineering (by design or evolution) is to reinforce these choke points as much as possible and distribute stresses evenly throughout the structure. However, even in supremely evolved muscle tissue, the cross-sectional area of the actin filaments transmitting the tensile forces is less than 3% of the entire cross section (*15*).

ROUTES TO OVERCOMING THE MASS CONSTRAINT ON FORCE PRODUCTION

The limit placed by motor mass on the maximal force generated by a motor can put severe restrictions on the design and function of machines powered by the motor, especially for the case of molecular motors. When the force output of the motor is limited but large forces are required, gearboxes, lever arms, and pulleys have to be used to multiply the forces. The design and accurate assembly of such systems at the molecular scale presents unique challenges beyond just engineering the molecular motor. Additionally, force multiplication comes at the cost of reduced displacement and speed.

Accessing the ultimate strength of a material instead of the yield strength

The transition to the molecular scale may offer unique opportunities to increase the force output of synthetic molecular motors above the trend line defined by macroscale and

biomolecular motors. Nanoscale structures formed with strong covalent and ionic bonds can more closely approach the theoretical strength of solids, as has been demonstrated for single crystal nanostructures (*16*) as well as nano-architectured materials (*17*). Stronger structures would allow us to approach the theoretical limit for the generated force given by the free energy change of the driving reaction (or the energy of the absorbed photon) divided by the distance of mechanical movement. Using exothermic reactions or photons providing energies on the order of several hundred zeptojoules and a motor stroke of a few angstroms, the generated force can theoretically exceed a nanonewton. However, a molecular motor relies on funneling the flow of energy into one mechanical degree of freedom (e.g., a rotation in the case of F_1 ATPase). This is achieved by creating a path along deep valleys across the potential energy surface (*18*). If the motor were capable of generating nanonewton forces for sub-nanometer movements, the potential energy of the initial state would have to exceed the potential energy of the final state by a large amount. With such a high starting energy, it would be difficult to prevent movements in other degrees of freedom, because the energy barriers to these movements would be barely higher than the energy of the starting state. This was essentially the problem faced by the builders of the first steam engines, when the energy of the steam was occasionally released in explosions rather than the intended motions. It is also a challenge to couple such (on the molecular scale) tremendous force to an external load.

Design of better force transmission mechanisms at the nanoscale

The transmission of force across intra- and intermolecular bonds is in itself an interesting optimization problem, where the optimal load is given by the ratio of the thermal energy and the distance between the ground and transition state of the bond (*19*). An example demonstrating this argument is in the form of human-made molecular motors, such as rotaxanes, that can theoretically generate forces of up to 30 pN (*20*), much higher than the 0.2 pN expected from extending the force-versus-mass trend line down to a molecular weight of 2000 daltons. Because each rotaxane is essentially an individual molecule with molecular subunits connected by covalent and Stoddart's mechanical bonds (*21*), one could expect that its mechanical strength approaches the limit defined by the theoretical strength of solids that greatly exceeds the yield strength of the actual materials because of the absence of defects (Fig. 2B). However, when rotaxanes were assembled into a two-dimensional array, an initial average contractile force of 10 pN per motor decreased to less than half after only 25 activation cycles (Fig. 2C), potentially because of rapid failure of the coupling between the motors and the gold surface, a soft and highly malleable material. Other synthetic rotary molecular motors have been connected to a network of polymer chains to create gel-like materials that contract because of the winding action of the motors (*11*). The contractile force exerted by the centimeter-scale gel is again surprisingly close to the trend line in Fig. 1. Both of these systems demonstrate the need and opportunity to optimally engineer the coupling between molecular motors and external loads, either via the use of catch bonds or load-dependent reinforcement of the couplings, which are strategies commonly observed in natural systems (*22*).

Releasing heat dissipated in the operation of motors

Nanoscale structures are able to rapidly dissipate heat because of their high surface-to-volume ratio, thereby preventing the overheating and loss of structural integrity common to insufficiently cooled macroscale motors. In fact, molecular motors in solution operate essentially isothermally because of the ultrafast dissipation of generated heat (*23*). The efficient inter- and intramolecular redistribution of vibrational energy that is responsible for heat dissipation is desirable, because it prevents undesired and potentially destructive chemical reactions from occurring. Interestingly, Riedel *et al.* (*24*) as well as Jee *et al.* (*25*) claimed that enzymes can channel the energy released during their catalytic cycle into directed movement rather than dissipating it as heat as was previously assumed. However, their experimental results and theoretical explanations have been questioned by several groups of researchers (*26*–*28*). Although molecular motors in isolation are efficiently cooled by their environment, molecular motors assembled into dense three-dimensional arrays can elevate the local temperature substantially, a fact exemplified by the warming of muscle tissue during strenuous activity. Nevertheless, the need to dissipate heat is a limitation to the generated power rather than a limitation to the generated force.

Reduction in motor life span or increase in motor replacement rates

The need for durability limits the designed force output as already discussed by Marden (*11*, *29*), with a tradeoff between mass and durability for a given force output. For simple parts, such as axles or microtubules, the fatigue life (Basquin) exponent is typically on the order of −0.012 to −0.05 (*30*), meaning that the life span can be extended by a factor of 1000 to 1 million if the load is cut in half. For more complex machines, such as pairs of gears or turbines, the life span is a complex function of different wear mechanisms and much less affected by a reduction in load. Together, this would suggest that larger forces could be produced if the life span is greatly reduced, but in nature this is not the case. The force output of muscles of different organisms with varying life spans appears to be roughly the same (*12*). Furthermore, the forces generated by a myosin motor and a complex muscle fall on the same trend line in the force-mass diagram even though a cardiac muscle operates over 100 years and one billion cycles (high lifetime through continuous replacement of failing parts), whereas the myosin is replaced every other day after fewer than a million cycles of operation (low lifetime without any replacement) (*31*). Thus, it appears unlikely that significant gains in force output can be simply achieved by a reduced life span or more frequent replacement.

IMPLICATIONS FOR THE APPLICATIONS OF MOLECULAR MOTORS

If molecular motors could be engineered to deliver more than a few piconewtons, new macro- and microscale applications would become accessible to them. Motors with higher force output would obviate the need for gearboxes and other machines used to multiply forces, which are so prominent in current robots. Additionally, molecular motors exerting forces on the order of 100 pN would be able to strongly affect the lifetime of inter- and intramolecular bonds and could be used to reshape commonly used engineering materials and molecules.

If molecular motors are limited to forces of a few piconewtons or less, the design of molecular machines will have to account for the relatively small forces. As demonstrated by biology, these forces are sufficient to move particles against viscous drag forces (e.g., aggregate and disperse chloroplasts in the leaves of plants depending on the intensity of sunlight), to

drive mildly endergonic reactions (such as the synthesis of ATP), and to propel organisms when molecular motors are organized into larger teams. The generation of bond-breaking forces would have to be achieved with clever machines similar to, for example, macroscale pile drivers or wrecking balls, where weak motors are used to lift masses that are released and produce large forces on impact.

CONCLUSION

It still requires some imagination to envision a future where synthetic chemistry prepares artificial molecular motors and integrates them into drug delivery systems and active materials, where biotechnology uses advanced protein engineering to create biomolecular motors that position organelle transplants in human cells and augment the transport systems in aging axons, and where semiconductor nanofabrication methods enable devices that seamlessly merge electronics, photonics, and mechanics. Humans have created motors ranging in size from millimeters to tens of meters to multiply their capability to change the physical world. The miniaturization of macroscale motor designs may have slowed over the past decades, but the potential to build up from the molecular scale is great. However, the trend line identified by Marden and Allen indicates a performance limit for molecular motors that needs to be overcome through either an improvement in motor design or the way these motors are integrated into engineered systems; otherwise, it will limit the applications of molecular scale motors. Although our discussion focused on the attainable force output for molecular motors, equal consideration needs to be paid to power, efficiency, durability and ultimately cost.

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