CHEMICAL REVIEWS

Editorial

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Introduction: Molecular Motors

Molecular motors, an important class of molecular machines, harness various energy sources to generate unidirectional mechanical motion. The operational principles of these motors, whether biological or synthetic, are distinct from those of man-made macroscopic motors. Molecular motors have nanoscale dimensions and generally work in a solution environment where viscosity is dominant. Under these low Reynolds number, overdamped conditions, they cannot rely on inertia to sustain motion.[1] Furthermore, they are continually agitated by random Brownian motion, which provides both challenges and opportunities for energy conversion mechanisms.[2] Researchers have long been fascinated by the question of how biological molecular motors can work so well under these unique conditions.

In biological systems, molecular motors made of proteins and nucleic acids are ubiquitous, and commonly use the chemical energy of ATP or the electrochemical potential of protons across the cell membrane (the so-called proton-motive force) as an energy source. Well-studied examples of ATP-driven linear molecular motors include myosins,[3] kinesins,[4] and dyneins[5] responsible for cellular activities such as muscle contraction and intracellular vesicle transport. ATP-driven and/or proton-motive force-driven rotary motors are found in ATP synthase,[6] V-ATPase,[7] and the bacterial flagellar motor.[8] ATP synthase and V-ATPase also act as energy converters, in which ATP chemical energy and proton electrochemical potential are reversibly converted via mechanical rotation.[9] The macromolecular machines underlying the central dogma of molecular biology, such as RNA polymerase[10] and the ribosome,[11] are also linear molecular motors that move unidirectionally along nucleic acid tracks to read and write genetic information.

Biological molecular motors can often exhibit highly sophisticated performance such as nearly perfect unidirectionality, high velocity,[8,12] and efficient energy conversion.[2] Fueled by available energy reserves under nonequilibrium conditions maintained by the cell, these motors can cycle autonomously and continuously, without requiring external clocking. At the same time, they are often also subject to exquisite control by cellular signals.[13] In a further level of complexity, large collections of motors can form ordered assemblies to achieve coordinated mesoscale or macroscale functions such as force generation in muscle.[14] There are however a number of limitations of biological molecular motors, which work only in aqueous environments under narrowly defined conditions, have poor stability, and are thus often challenging to deploy for applications outside of living organisms.[15]

In the field of chemistry and nanotechnology, synthetic or artificial molecular machines and motors have been one of the ultimate goals since Richard Feynman first advocated the concept.[16] After half a century, the 2016 Nobel Prize in Chemistry has been awarded for "Design and synthesis of molecular machines", and mechanical motions in synthetic molecular machines have been realized.[17] However, many synthetic molecular machines are designed only for switch-like behaviors that respond to changes in equilibrium conditions and do not move autonomously.[18] Only a few autonomous synthetic motors have been reported so far, such as overcrowded alkene-based rotary molecular motors driven by light and rotaxane- or catenane-based linear molecular motors driven by chemical catalysis.[19] DNA-based synthetic molecular walkers can also move unidirectionally and autonomously, but they generally show very low velocities.[20] Synthetic molecular motors are thus in some ways still at an early stage in terms of performance. However, synthetic motors have significant advantages over biological counterparts: flexibility and physical insight made possible by molecular design from scratch, utilization of a broad range of energy sources including light and electrical energy in addition to varied chemical fuels, and often high thermal and physical stabilities. Therefore, synthetic molecular motors have great potential to realize novel functions beyond the capabilities of biological molecules.

Over the past decades, biological and synthetic molecular motors have each been the subject of intense study, but the two research fields have largely advanced independently in parallel. Cross-pollination and integration of the two fields has clear potential benefits, considering both the complementary advantages described above and the common operational and design principles, dictated by physics, needed to attain autonomy and highly coordinated collective behaviors under nonequilibrium conditions.[21] There is now a ripe opportunity for collaboration across the disciplines of biology, chemistry, and physics toward understanding, engineering, and creation of molecular motors and molecular motor systems that are robust and versatile.[22] In Japan, as a concrete action toward this goal, a government-funded "Molecular Engine" project led by Kinbara, one of the authors of this editorial, has been launched recently (http://www.molecular-engine.bio.titech.ac.jp/eng/) (Figure 1).

For this thematic issue, we invited experts in the fields of biology, chemistry, and physics to showcase cutting-edge research on molecular motors. The issue begins with two review articles on biological molecular motors, covering both natural motors and biological motors that have been modified for desired functions through protein engineering. Houdusse and co-workers review myosin, an ATP-driven linear molecular motor which moves on actin filaments and generates force. The actomyosin system was the first biological track-motor system discovered in nature, and many classes of specialized myosin motors supporting diverse cellular processes have now been identified. The authors focus on the structural basis of actomyosin function informed by X-ray crystallography, fiber diffraction, and cryo-electron microscopy, and they discuss what is understood and what remains unanswered about the force generation mechanism

Special Issue: Molecular Motors

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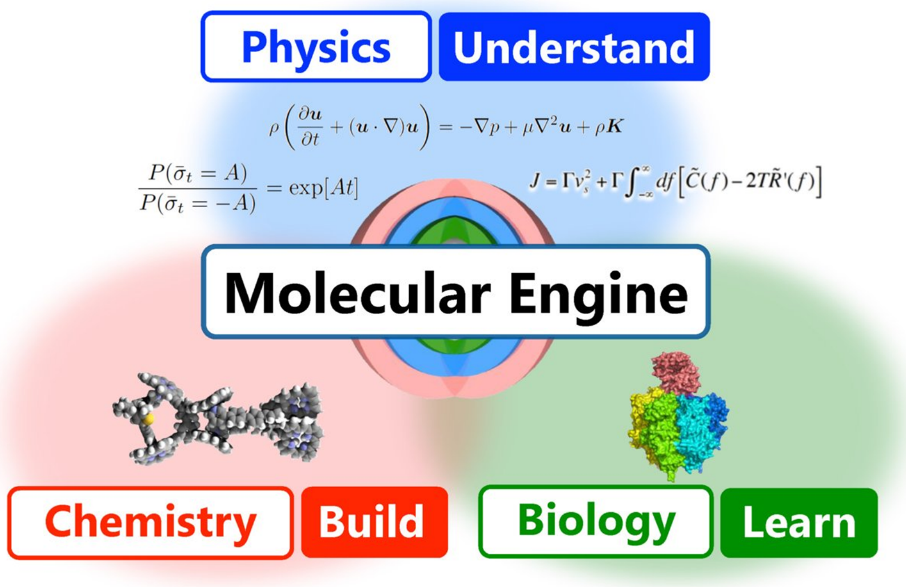

Figure 1. "Molecular Engine" project launched in Japan (2018–2022).

of myosin. Ha and co-workers begin their review with an overview of single-molecule imaging and manipulation techniques, such as single-molecule fluorescence (or Förster) resonance energy transfer, optical and magnetic tweezers, and hybrid methods, which are powerful tools to elucidate mechanisms of molecular motors. Then they discuss mechanisms of biological molecular motors and machines working on DNA, including helicases, DNA and RNA polymerases, and the supercoiling motor DNA gyrase. They also introduce engineering approaches such as mutagenesis, chemical modifications, and optogenetics to impart new functions to these molecular motors.

The next four review articles describe synthetic motors consisting of organic molecules, organometallic compounds, and inorganic materials from different viewpoints. Tour and co-workers focus on synthetic rotary molecular motors driven by photochemical and thermal isomerization reactions. Most of these motors consist of overcrowded alkenes and imines. The authors describe elementary reaction cycles driving unidirectional rotary motion and discuss strategies for molecular design to modulate and optimize properties such as activation wavelength and rotation speed. They also overview interesting applications of molecular motors on surfaces and in self-assembled or macromolecular systems enabling modulation of macroscopic properties of materials. In addition, advanced applications such as catalysis and modulation of biological events are also outlined. Schmittel and co-workers focus on the use of metal ions for construction and regulation of organometallic molecular motors—which undergo machine-like motions such as wing-flapping, flipping, contraction-extension, and rotation—through redox and exchange of metal ions. They then review a variety of synthetic molecular machines made of organometallic compounds—including shuttles, turnstiles, gears, cranks, motors, and complex systems involving catalytic cycles and multiple states—and discuss applications of these machineries to achieve functions such as host–guest recognition and catalysis. Baroncini, Silvi, and Credi focus on the energy sources for molecular motors, and review photo- and redox-driven synthetic molecular motors, especially highlighting progress over the past 5 years. They discuss how autonomous, unidirectional motion and active pumping can be achieved with synthetic molecular machines such as rotaxane, catenane, overcrowded alkene, hemithioindigo, and imine derivatives operated under redox and photochemically triggered switching processes. They then overview the functions achieved by these synthetic molecular motors including chirality switching, catalysis, transmission of directed motions, locomotion, transportation and amplification of motions, from molecular to macroscopic scales. Šípová-Jungová, Käll, and co-workers focus on manipulation of nanosized objects by light to allow these materials to behave like motors (not strictly speaking "molecular" motors but "nano" motors nevertheless). They discuss basic light–matter interactions such as optical momentum transfer, photothermal heating, and photocatalysis, and how these interactions can be used to drive the motions of inorganic nanomotors. They also discuss how random and stochastic forces affect active motions of nanomotors depending on their sizes and shapes, and they review examples of nanomotors based on self-thermophoresis, self-electrophoresis, and bubble propulsion.

Two more review articles illustrate biological and synthetic molecular motor systems enabling functions at larger scales, which may involve collective and coordinated behaviors. Saper and Hess review integration of biological molecular motors such as kinesin and dynein into hybrid nano- and microelectromechanical systems (NEMS/MEMS), to power actuators and engines, shuttle cargo to sensors, and enable new computing devices. They then discuss efforts to improve the performance and extend the capabilities of biological molecular motors, including the construction of engineered molecular motors combined with synthetic components. They compare biological molecular motors with synthetic ones such as DNA walkers, discuss how to overcome current limitations for construction of hybrid molecular motor systems, and consider theoretical limits of their performance. Giuseppone and co-workers review collective behaviors of

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synthetic molecular switches based on azobenzene, spiropyran, diarylethene, catenane, and rotaxane, rotors based on double decker porphyrin, and motors based on overcrowded alkene. They especially focus on intermolecular coupling in space and time and how individual molecular machines can be used as elementary modules coupled into large assemblies. They also discuss how collective and synchronized motions of molecular machine assemblies can lead to emerging functions and how these functions can be implemented into mechanically active devices and materials.

A final review article concerns physics of molecular motors relevant to understanding the common principles behind biological and synthetic molecular motors. Brown and Sivak review how molecular motors and machines transduce energy, and they outline theories and models to tackle questions about how they work under isothermal nonequilibrium conditions at low Reynolds number. They outline important concepts and quantities such as nonequilibrium steady states, free energy, microscopic reversibility, and power stroke and Brownian ratchet models to understand behaviors of molecular motors and machines. They then discuss theoretical approaches to identify and improve physical limits of motor performance, including efficiency, output power, and precision. Finally, they introduce emerging concepts such as information machines, predictive machines, and dissipative adaptation.

We wish to express our sincere appreciation to the authors for their dedicated contributions to this thematic issue. We hope that the collection of review articles in this thematic issue sheds light on future directions of molecular motor research, facilitates fruitful collaborations among biologists, chemists, and physicists, and helps stimulate advances that build on accomplishments in both synthetic and biological molecular motors while integrating across these sibling fields.

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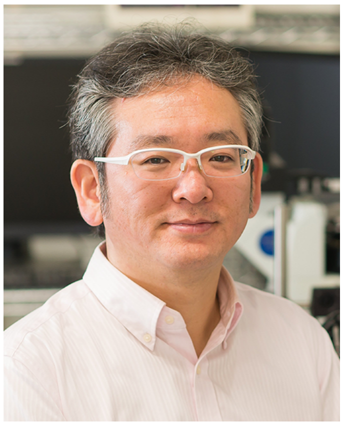

Ryota Iino received his B.E. in polymer chemistry and M.E. in synthetic chemistry and biological chemistry at Kyoto University in 1995 and 1997, respectively, and Ph.D. in biophysics at Nagoya University in 2003. He worked as a research fellow at Japan Science and Technology Agency (2000–2005), a specially appointed assistant professor (2005–2006) and an assistant professor (2006–2011) at Osaka University, and a lecturer (2011–2013) and an associate professor (2013–2014) at the University of Tokyo. In 2014, he began his fully independent academic career as a professor at Institute for Molecular Science (IMS), National Institutes of Natural Sciences (NINS), Japan. From 2018, he has also served as the director of Department of Life and Coordination-Complex Molecular Science, IMS, NINS. His current research interests include operation and design principles of protein molecular motors, engineering of protein molecular motors, and development of single-molecule techniques based on advanced optical microscopy.

Kazushi Kinbara was born in 1967. He received a B.S. degree in Organic Chemistry from the University of Tokyo in 1991 and obtained a Ph.D. in Organic Chemistry in 1996. He then began an academic career at the University of Tokyo and had been involved until 2001 in the development of optical resolution upon crystallization. In 2001, he moved to Professor Takuzo Aida's group at School of Engineering, the University of Tokyo as a lecturer and associate professor. In 2008, he was promoted to Professor of the Institute of Multidisciplinary Research for Advanced Materials, Tohoku University. In 2015, he moved to Tokyo Institute of Technology. His research interests include (1) development of biomimetic molecules, (2) supramolecular chemistry of macromolecules, and (3) protein engineering.

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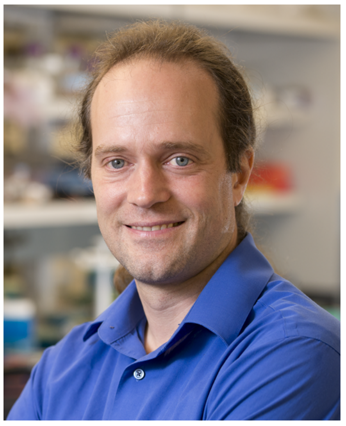

Zev Bryant is a native of Vancouver, Canada, and earned a B.Sc. in 1998 from the University of Washington, Seattle. He received a Ph.D. in 2003 from UC Berkeley, where he studied single-molecule DNA mechanics and topoisomerase function with Prof. Carlos Bustamante. As a postdoctoral researcher with Prof. James Spudich, he investigated structure−function relationships in unconventional myosin motors. Since 2007, he has been on the faculty of Stanford University, where he is an Associate Professor of Bioengineering and (by courtesy) of Structural Biology. His research combines single-molecule measurements and protein engineering to dissect the physical mechanisms of biological molecular motors.

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