# Design and Synthesis of Molecular Machines: Progress and Challenges

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The Nobel Prize in Chemistry 2016 was awarded jointly to Jean-Pierre Sauvage, Sir J. Fraser Stoddart and Bernard (Ben) L. Feringa for the design and synthesis of molecular machines. They have developed molecules and machines with controllable movements which can perform work when energy is supplied to them. We hope that these tiny molecular machines will most likely revolutionize the development of various new materials and technologies in the twenty first century, in a manner similar to the Industrial Revolution in the nineteenth century brought about by their macroscopic counterparts such as steam and internal combustion engines. This article summarizes the groundbreaking work done by them, as well as some challenges ahead from a physicist's perspective, and how they can be handled.

Professor Ambarish Kunwar has been working on problems related to transport and forces generation by molecular motor proteins inside living cells since the last ten years. He did his M.Sc. (Physics) from BHU and Ph.D. (Physics) from IIT Kanpur. He worked as a postdoctoral scholar at the University of California Irvine and University of California Davis before joining IIT Gandhinagar as assistant professor in Physics in 2011. He moved to the Department of Biosciences and Bioengineering at IIT Bombay in 2012. Khushnandan Rai is a Ph.D. student in the Department of Biosciences and Bioengineering working under the joint supervision of Professor Ambarish Kunwar and Professor Dulal Panda.

## Molecular Machines: Dream turning into reality

Macroscopic machines in our day to day life are devices that can replace/augment/accelerate human effort in accomplishing a physical task. The operation of most of the machines in our life involves a transformation of chemical/thermal/electrical energy into physical force that produces movement or other structural changes i.e. mechanical work. One of the most prominent examples of a machine in day to day life is an internal combustion engine which converts chemical energy into mechanical force required to drive the vehicle.

The problem of manipulating and controlling things on a small scale was first discussed by the famous Nobel laureate Richard Feynman who gave a lecture talk on December 29, 1959 at the American Physical Society, titled *"There's plenty of room at the bottom"*, in which he posed a question: "Computing machines are very large, they fill rooms," he said. "Why can't we make them very small, make them of little wires, little elements — and by little, I mean little" [1]. Twenty five years later, on October 25, 1984 Richard Feynman again gave that lecture during a week-long experimental seminar called idiosyncratic thinking, where he presented his philosophy on thinking in conventional and different ways in his lecture titled *"Tiny Machine"*.

Richard Feynman turned to the audience and said: "Now let us talk about the possibility of making machines with movable parts, which are very tiny" [2]. Thus, Feynman was convinced that it is possible to build machines with dimensions of the nanometer scale. Feynman shared his ideas of making machines constructed of single atoms, and had some ideas about how that might take place. However, things did not go exactly the way Richard Feynman had thought, but his dreams now seem to be turning into reality with the gallery of molecular machines i.e. molecules with controllable movements developed by Jean-Pierre Sauvage of the University of Strasbourg, Sir J. Fraser Stoddart of Northwestern University, and Bernard L. Feringa of the University of Groningen (Figure 1). Molecular machines might be in the same stage as steam and internal combustion engines which catalyzed the Industrial Revolution in the nineteen century [3], but they have been exciting enough to have attracted the attention of the Nobel committee. Jean-Pierre Sauvage, J. Fraser Stoddart, and Bernard (Ben) L. Feringa have been awarded the 2016 Nobel Prize in Chemistry "for the design and synthesis of molecular machines". Hence, it is conceivable that molecular machines will play a prominent role in the nano technological revolution of the twenty first century as their macroscopic counterparts such as steam and internal combustion engines.

Figure 1: Jean-Pierre Sauvage, Sir J. Fraser Stoddart and Bernard (Ben) L. Feringa (left to right)

## Molecular Machines developed by 2016 chemistry Nobel laureates

The Royal Academy of Sciences awarded the 2016 Nobel Prize in Chemistry to Jean-Pierre Sauvage, and Bernard L. Feringa as they developed molecules with controllable movements, which can perform a task when energy is added.

A molecular machine has to consist of many moving parts. Ring shaped molecules are ideal for making moving parts, however one of the major challenges in making molecular machines was to mechanically interlock the moving parts i.e. ring shaped molecules. A French research group led by the chemist Jean-Pierre Sauvage was the first to be able to create a mechanical bond where two ring shaped molecules were interlocked without any direct interaction between their atoms [4]. This was done using a copper ion which attracts the molecules which form chain and leads to their interlocking. The copper ion can be removed once the molecules are interlocked and the resulting structures are called *catenanes* (Figure 2). In 1994, Jean-Pierre Sauvage also took the first step to create a molecular machine using *catenanes* where one ring rotated with respect to another when energy was added (Figure 3) [5].

An alternative approach to make molecular machine was started in 1991 by Sir J. Fraser Stoddart by using *rotaxane,* which is a molecular ring mechanically locked to a dumbbell-shaped molecular axle (Figure 4). This ring could slide back and forth along

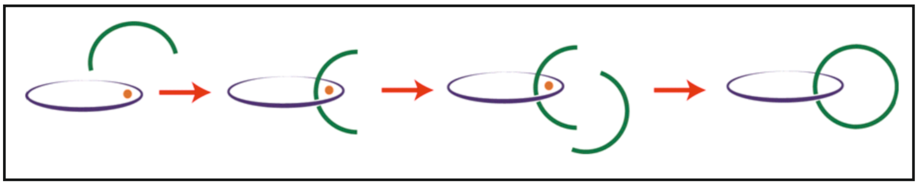

Figure 2: Jean-Pierre Sauvage's research group synthesized one ring shaped (blue) and one crescent shaped molecule (green) that were attracted to a copper ion (brown). Subsequently, they used chemistry to link together the crescent-shaped molecules with a another crescent-shaped molecule to form a new ring shaped molecule which resulted in mechanical interlocking of molecules. The copper ion can be removed after interlocking and resulting structures are called catenanes.

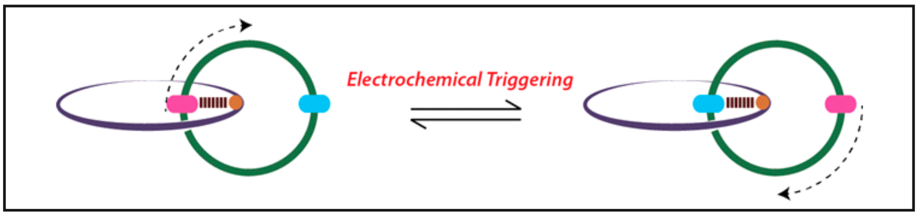


Figure 3: An electrochemically triggered sliding motion of one ring within other in catenanes leads to rotation of one ring with respect to the other.

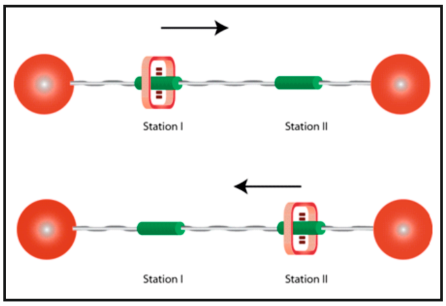


Figure 4: A molecular shuttle in which a tetracationic ring slides back and forth like a shuttle between two identical stations in the form of hydroquinol ring grafted symmetrically into an polyether axle which were terminated at the ends by large triisopropylsilyl groups that act as stoppers, resulting in a dumbbell-shaped geometry for the molecular assembly on which the ring shaped shuttle travels.

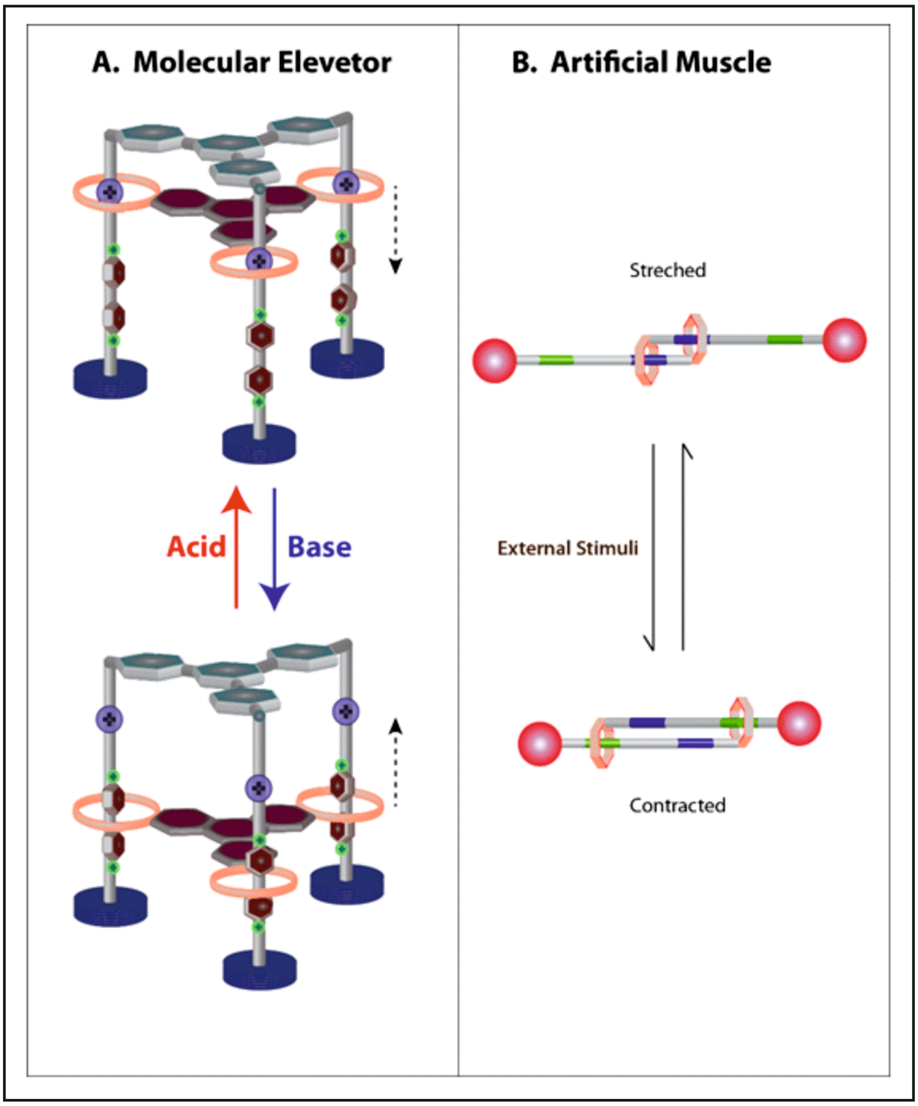


Figure 5: (A) Schematic of a Molecular Elevator and (B) schematic of an artificial muscle developed by the group of J. Fraser Stoddart.

the axle on addition of heat like a tiny shuttle travelling between two stations [6]. He could completely control the motion of the molecular shuttles chemically and electrochemically by 1994. Stoddart's research group further used various rotaxanes to construct numerous molecular machines such as a molecular elevetor [7] and an artificial muscle [8] (Figure 5).

Another important goal towards the designing of molecular machines was making rotary motors (similar to wheel on an axle) that can continuously spin in one direction. This was achieved by Bernard L. Feringa in 1999, who designed a molecule that was mechanically constructed to spin monodirectionally. Each monodirectional spinning of 360 degree of rotor blade around a central carbon-carbon double bond in a chiral, helical alkene involving four discrete isomerization steps was activated by ultraviolet light or a change in the temperature (Figure 6) [9]. The speed of their first monodirectional motor was not very fast; however, they were able to make rotory motors that could spin with a speed of 12 million revolutions per second by 2014. In 2011, his group built a four-wheel-drive molecular car in which a molecular chassis held together four rotory motors that functioned as wheels (Figure 7). The molecular car was propelled unidirectionally across a metal surface when the wheels spun [10]. In another remarkable experiment, Ben Feringa's research group used molecular motors to spin a 28 micrometer long glass cylinder which was 10000 times bigger than molecular motors [11].

Thus, the groundbreaking work by Jean-Pierre Sauvage, Sir J. Fraser Stoddart and Benard L. Feringa in designing molecules with controlled motion has resulted in a toolbox of molecular motors that can be used by scientists around the world to build increasingly advanced molecular machines. One of the notable examples in this direction is a molecular robot that picks and connects amino acids similar to a ribosome [12].

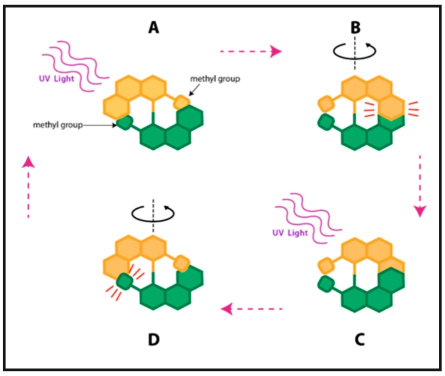


Figure 6: A monodirectional rotory motor developed by the group of Benard L. Feringa. (A) Exposure to UV light causes one rotor blade to spin by 180 degree causing development of tension in the molecule. (B) Snapping of one blade over the other causes the release of tension and, backward rotation of the blade is prevented. (C) Another exposure to UV light leads to a further rotation of 180 degree (D) Snapping of a methyl group over the rotor blade again happens when temperature is raised and, backward rotation is prevented.

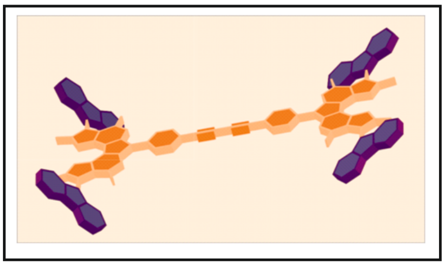

Figure 7: Schematic of a four-wheel-drive molecular car developed by the group of Benard L. Feringa.

Traditionally, all chemical systems strive for equilibrium i.e. a lower energy state. However, these researchers have pushed molecular systems away from equilibrium which is another development which has resulted in the 2016 Nobel Prize in Chemistry. The development of artificial molecular systems by these researchers, similar to the biomolecular machines in our body, which use chemical energy derived from food to perform controlled tasks and always function away from equilibrium, has certainly pushed traditional chemistry into a new dimension [13].

## Molecular Machines versus Macroscopic Machines: There are dramatic differences between them!

Molecular machines cannot be designed by a simple scale down process as one has to start worrying about many things which are not relevant at the macroscopic scale. It is well known that at the length scale of nanometers (i.e. at the length scale of molecules) thermal energy becomes comparable to other forms of determinate energy i.e. mechanical, electrostatic and chemical bonding. Therefore, thermal energy which can be safely ignored for the motion of macroscopic objects should be considered for molecular machines [14]. When comparing a molecular machine and its operation with a daily life macroscopic machine, it should be further noted that the inertial forces that govern the motion of macroscopic objects become irrelevant for molecular machines, as their mass is extremely small and hence, the effect of gravity can be ignored altogether. Thus, what matter in the world of the molecular machine are thermal forces and viscous forces [15]. Thermal energy creates a turbulent environment for molecular machines – an environment which is full of thermally driven random motions or Brownian motion. Thus, to operate in such a turbulent world the molecular machine must either exploit thermally driven random motion/Brownian motion using mechanisms as in ratcheting used by motor proteins [16], or somehow overcome it. Since the viscous forces acting on these molecular machines are much larger than inertial forces, these molecular machines essentially function in a low Reynolds number regime where a geometrically reciprocal motion does not lead to a net movement [17]. Thus, these machines have to somehow execute a non-geometrically reciprocal motion similar to the one used by cilia or flagella [17] or a non-Newtonian fluid as medium for their movement [18]. Thus, looking back at natural molecular machines can be of great help.

## Natural molecular machines can help us to understand the design principles for artificial molecular machines

In living organisms, nature has produced a fascinating inventory of linear and rotary molecular machines. One set of the remarkable natural linear molecular machines is motor proteins that transport materials such as cargos and vesicles inside cells. The other remarkable natural rotary molecular machine is ATP Synthase that synthesizes ATP using proton gradient as an energy source (Figure 8). Other important examples of natural molecular machines are ribosomes that synthesize proteins, DNA helicase which locally unzips double-stranded DNA and, RNA polymerase that synthesize messenger RNA using a single-stranded DNA as template, and Na-K pump that transports ions across the cell membrane [19]. These natural biological molecular machines perform their function with remarkable efficiency and accuracy. Thus, these fascinating biological machines can serve as a guide for scientists to conceptualize, design and fabricate artificial molecular machines, and perhaps the current limitation to their development appears to be only the imagination of scientists.

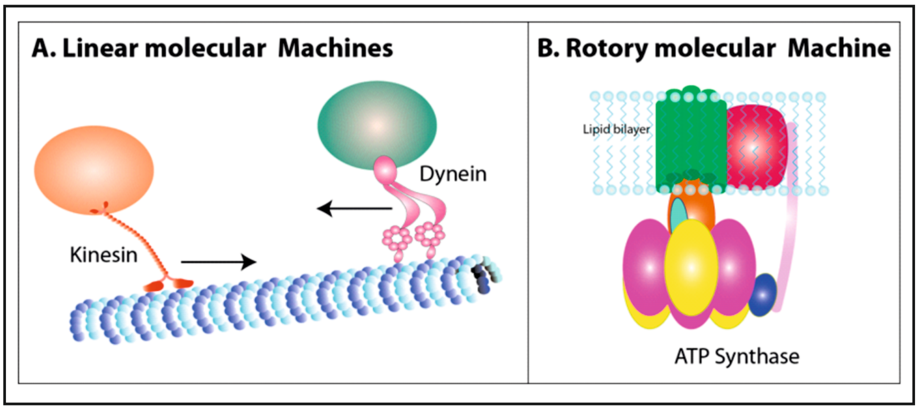


Figure 8: (A) Examples of natural linear molecular machines in nature are motor proteins such as kinesin and dynein which transport cargo and vesicles insides cells. (B) ATP synthase is example a natural rotary motor which synthesizes ATP using proton gradient inside living cells.

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