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физики им. Б. П. Константинова,
Санкт-Петербург*

**Нобелевская премия за 2016 год
в области химии
«Разработка и синтез
молекулярных машин»**

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Институт химической физики им. Н. Н. Семенова, Москва

Нобелевские лауреаты



фото: Университет им. Луи Пастра (Страсбург).

**Жан-Пьер Соваж
(Франция)**

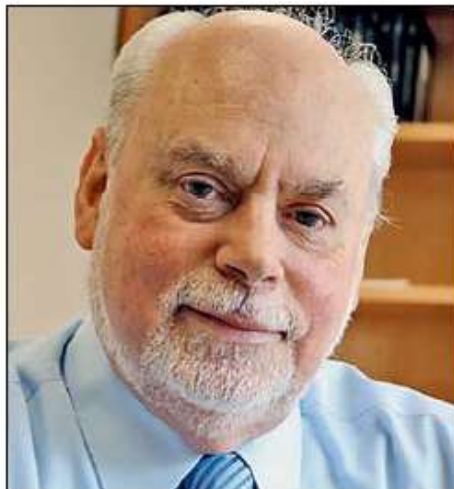


фото: Northwestern University.

**Джеймс Стоддарт
(США)**



фото: Wybe/CC-BY-SA/Wikimedia Commons.

**Бернард Феринга
(Нидерланды)**

The Royal Swedish Academy of Sciences has decided to award ***Jean-Pierre Sauvage, Sir James Fraser Stoddart and Bernard (Ben) L. Feringa*** the Nobel Prize in Chemistry 2016 “for the design and synthesis of molecular machines” .

Although development towards highly complex and useful molecular machines is still in its infancy, the laureates have successfully demonstrated that the rational design and synthesis of molecular machines are indeed possible.

"молекулярная машина" (в понимании Нобелевским комитетом, и лауреатами, конечно)

A molecular-level machine can be defined as “an assembly of a distinct number of molecular components that are designed to perform **machinelike movements** (output) as a result of an appropriate external stimulation (input)”.

"... машина – это то, что совершает машино-подобные движения ... " — замечательное определение!

две принципиальные, по мнению Нобелевского комитета, разработки

Two major technology advances have proven particularly useful in addressing the complex challenge of constructing machines at the molecular scale. The first of these involves topological entanglement and so-called **mechanical bonds**, while the second is based on **isomerisable (unsaturated) bonds**, and both advances have resulted in large ranges of complex structures with **machine-like functions**.

I. Mechanical bonds

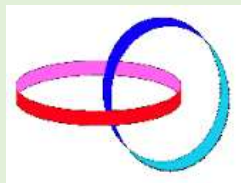
A substantial part of the progress made towards molecular machinery has its roots in the emergence of **interlocked molecular assemblies based on mechanical bonds**. In such assemblies, the individual parts are not directly connected and held together by covalent bonds, but **inseparably entangled through, for example, loops and stoppers**.

катенаны и ротаксаны

Catenane –

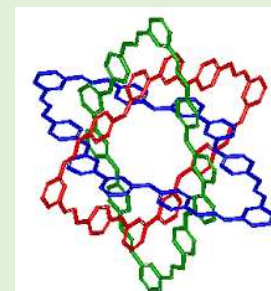
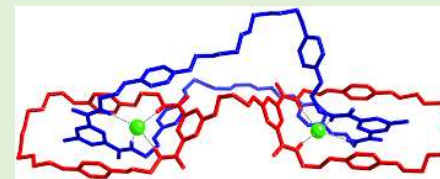
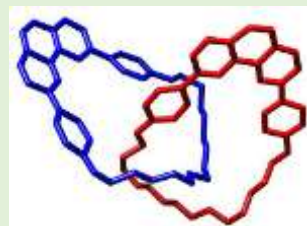
two interlocked rings

Латынь : Catena – неразделяемая последовательность, цепь



Первые публикации:

Wasserman, E. The Preparation of Interlocking Rings: A Catenane. *J. Am. Chem. Soc.* **1960**, 82 (16), 4433



Rotaxane –

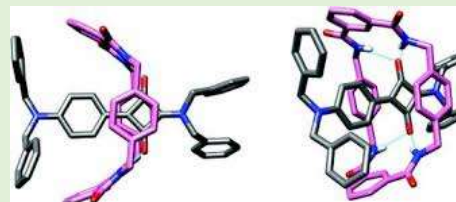
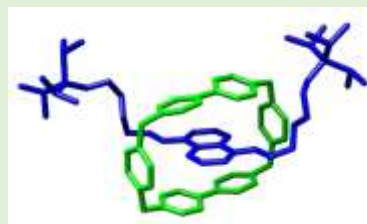
a ring threaded over an axle with stoppers at each end.



Латынь: Rota + axle – колесо + ось

Первые публикации:

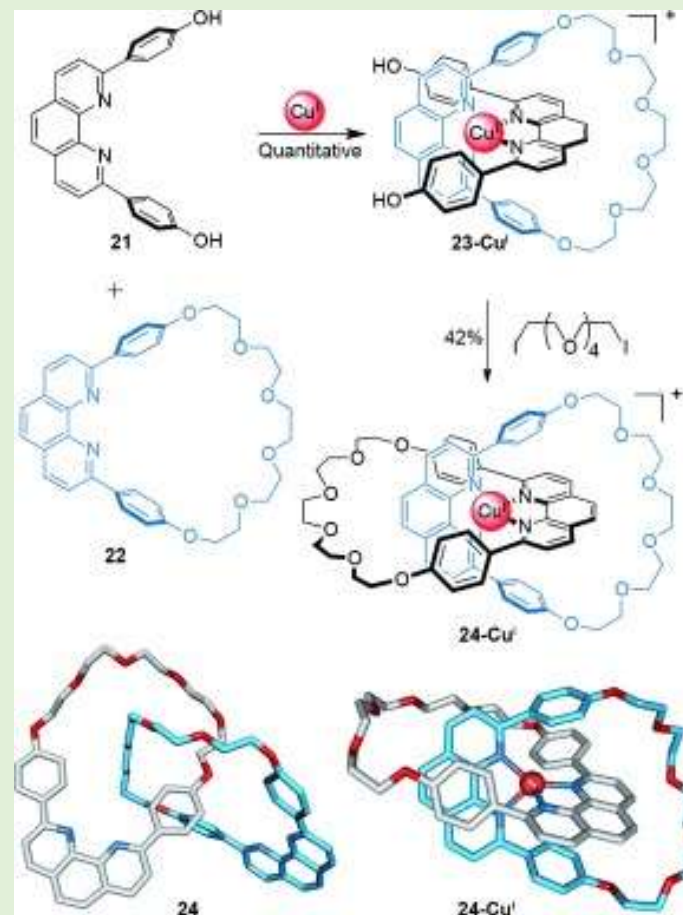
T. Harrison and S. Harrison "Synthesis of a stable complex of a macrocycle and a threaded chain". *J. Am. Chem. Soc.* **1967**, 89 (22): 5723–5724.



Ж-П. Соваж придумал как эффективно синтезировать катенаны и ротаксаны

In 1983 the field took a giant leap forward when Jean-Pierre Sauvage and his co-workers introduced **template synthesis** as a straightforward route to catenanes and rotaxanes. Using metal coordination, the threading of the chains could easily be accomplished, with much higher overall yields as a consequence.

This discovery marked a true breakthrough that dramatically invigorated the field of topological chemistry and subsequently led to molecular machinery. As a consequence, the scientific community gained access to substantial amounts of these complex entities, and the methodology has resulted in a vast range of structures of differing topology.



II. Translational isomerism:

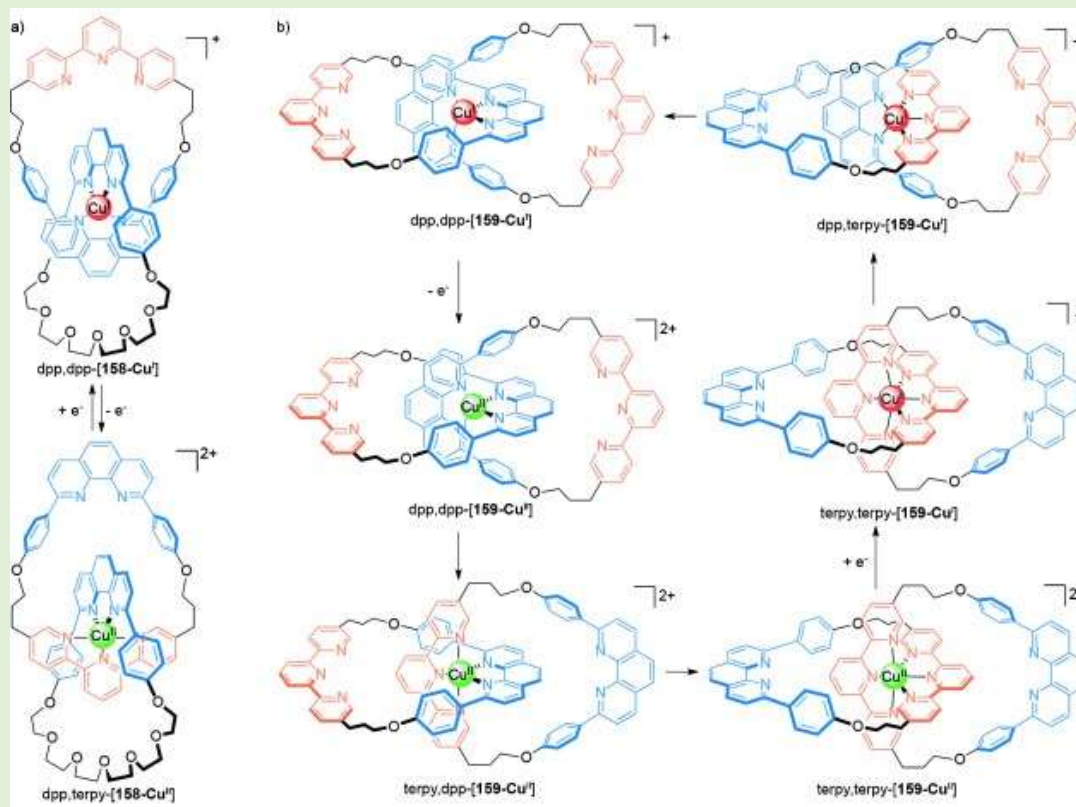
**“machine-like movements” of catenanes and rotaxanes
designed by J-P. Sauvage and D. Stoddart**

Unidirectional rotation in a catenane

Cesario, M.; Dietrich-Buchecker, C.; Guilhem, J.; Pascard, C.; Sauvage, J.-P. Molecular Structure of a Catenane and Its Copper(I) Catenate: Complete Rearrangement of the Interlocked Macrocyclic Ligands by Complexation. *J. Chem. Soc. Chem. Commun.* **1985**, 244–247.

Based on the catenanes developed, Sauvage and co-workers were subsequently able to demonstrate the potential of the structures for **translational isomerism**.

Dramatic, reversible changes in the catenanes' molecular shape were thus observed upon decomplexation and recomplexation of the metal coordination entities with Cu(I).



molecular shuttle

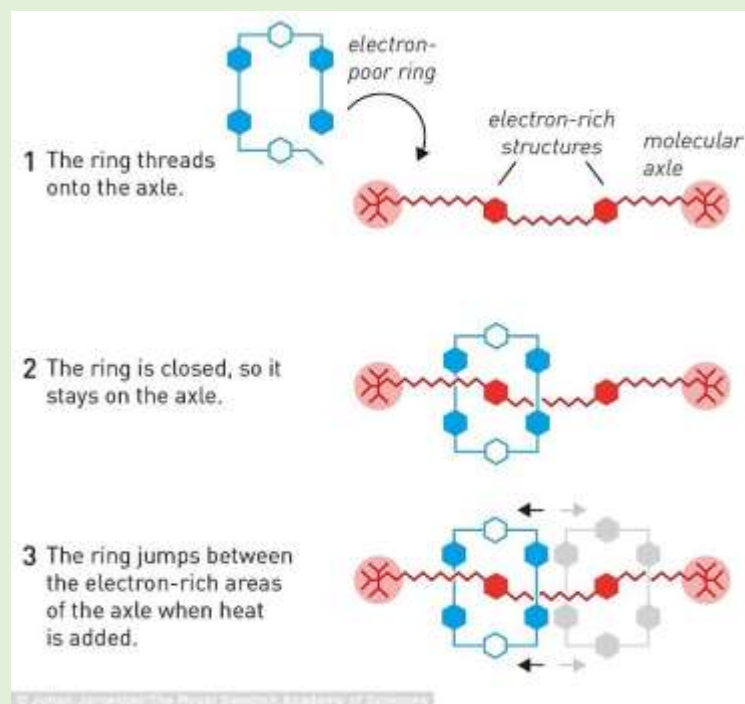
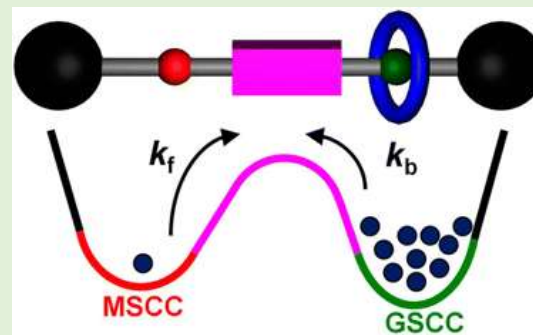
Anelli, P. L.; Spencer, N.; Stoddart, J. F. A Molecular Shuttle. *J. Am. Chem. Soc.* **1991**, *113* (13), 5131–5133.

The field took another big leap forward in **1991**, when a clear demonstration of **translational isomerism** was reported by the group of Sir James Fraser Stoddart ...

Stoddart and co-workers had been working in the 1980s <...> in the development of a <rotaxane ring>, which could be “clipped” around an axle containing two hydroquinol units separated by a linker.

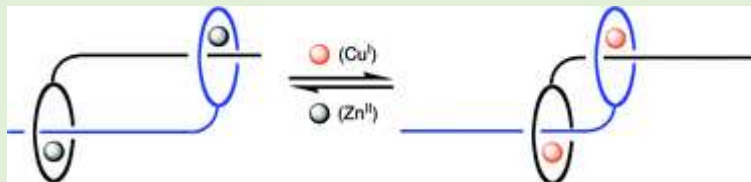
The resulting rotaxane ring could be shown to act as a molecular shuttle, able to move between the two hydroquinol stations on the axle.

Together with Sauvage’s demonstration of reversible catenane shape-shifting, **this work marked the start of applying topological entanglement in the development of molecular machinery.**

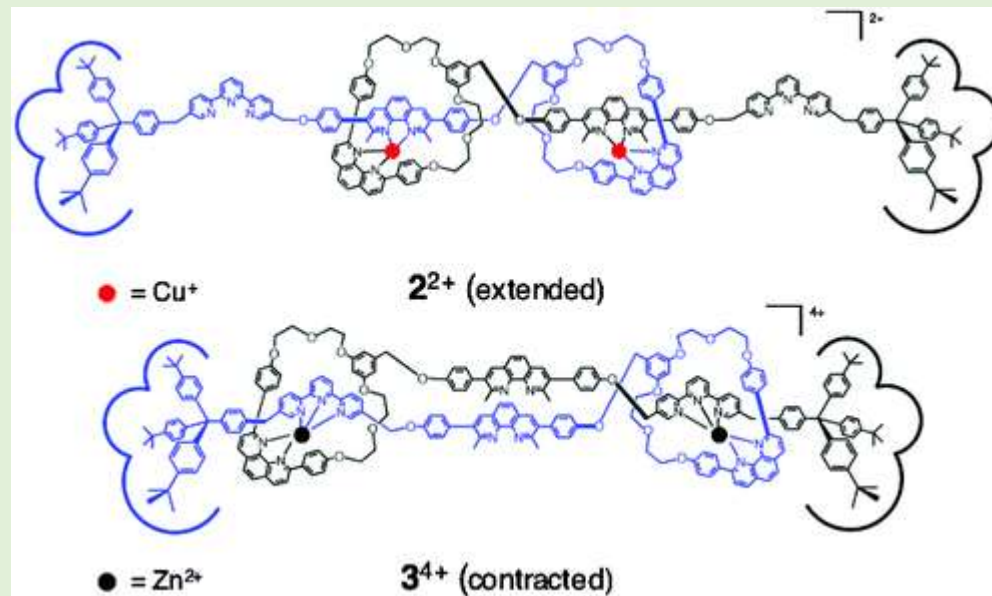


contraxiton/extention (“muscle-like”) molecular machine (J-P Sauvage, since the late of 1990s...)

For review, see [Jean-Pierre Sauvage](#)
Chem. Commun., 2005, 1507-1510



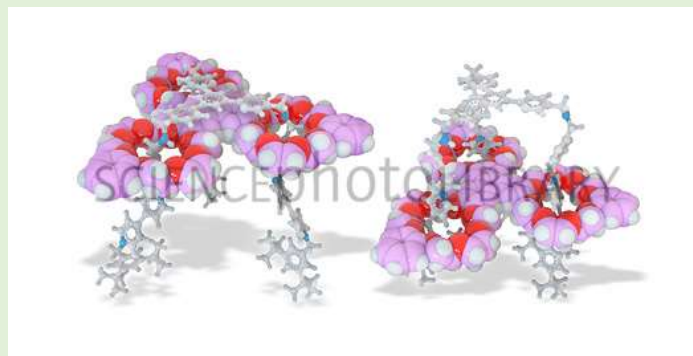
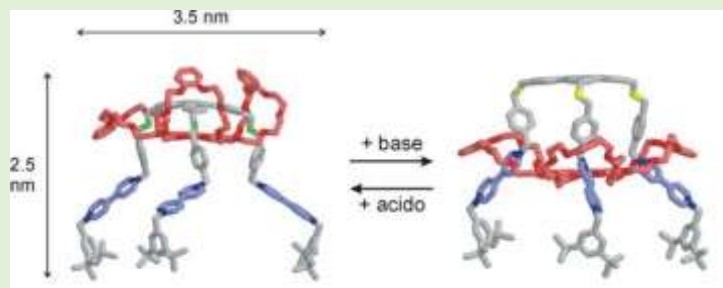
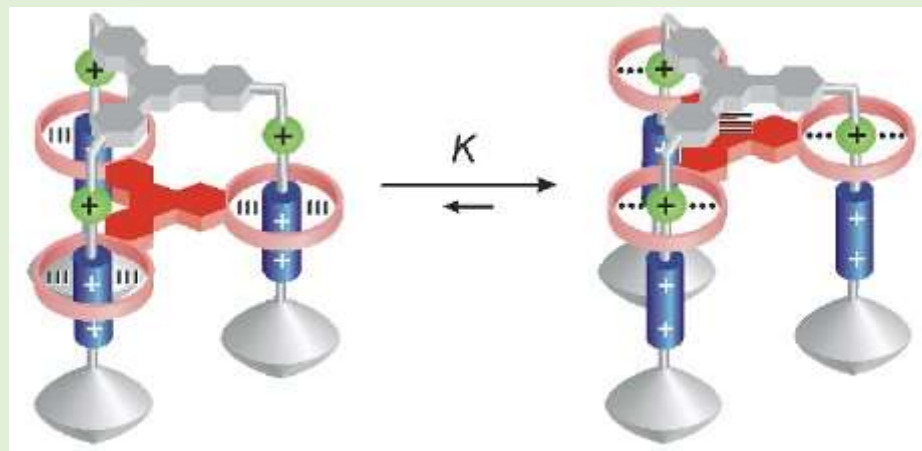
Since the late 1990s, the application part of the field has increasingly been addressed by the groups, and also pursued by many other researchers. **Chemical control of molecular contraction/extension, resembling the action of muscles in living systems, was for example demonstrated in a topologically challenging daisy-chain structure by the Sauvage group in 2000 .** By integrating two mutually entangled rotaxane functionalities, they were able to achieve high control of translational contraction and extension of ca. 2 nm under chemical stimulus.



Stoddart's molecular elevator

Badjić, J. D.; Balzani, V.; Credi, A.; Silvi, S.; Stoddart, J. F. A Molecular Elevator. *Science* **2004**, 303 (5665), 1845–1849.

Similarly, the Stoddart group developed a complex rotaxane device called a “**molecular elevator**” in 2004, where high control of the motion of a moving plane between two “floors” separated by a distance of **0.7 nm** could be achieved



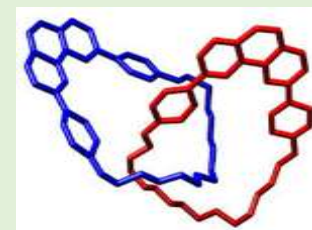
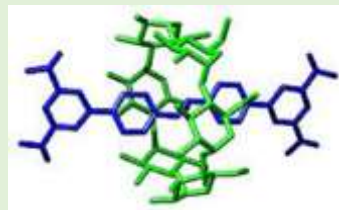
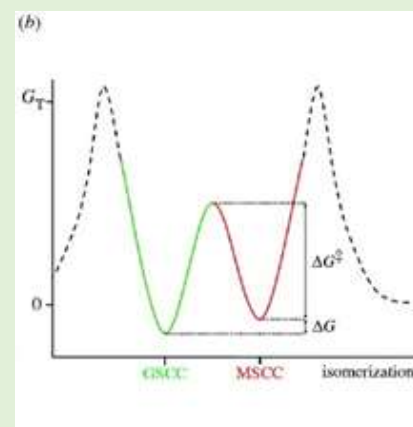
Logic gates and electronic devices based on two-state (Boolean) translational isomerism

Collier, C. P.; Wong, E. W.; Belohradský, M.; Raymo, F. M.; Stoddart, J. F.; Kuekes, P. J.; Williams, R. S.; Heath, J. R. Electronically Configurable Molecular-Based Logic Gates. *Science* **1999**, *285* (5426), 391–394

Together with colleagues, the Stoddart group has in addition pursued the development of **molecular-scale electronic devices** based on rotaxanes and catenanes, with the intention of fabricating **molecular logic gates and memories**.

The rotaxanes were mounted between electrodes in a microelectronic device and could be shown to respond to writing potentials, resulting in closed and opened states that could be read at a non-perturbing potential.

160 kbit memories, composed of a few hundred rotaxanes/bit and a density of **ca. 100 Gbit/cm²**, could be fabricated using this methodology.

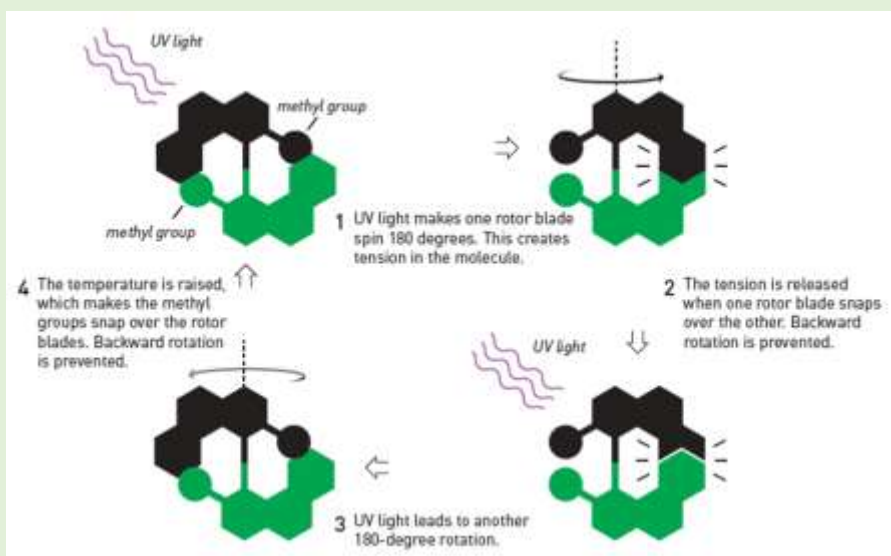


III. Isomerisable unsaturated bonds: Feringa's molecular rotor

The first example of **controlled unidirectional rotation** <...> was reported by Bernard L. Feringa. Koumura, N.; Zijlstra, R. W. J.; Delden, R. A. van; Harada, N.; Feringa, B. L. Light-Driven Monodirectional Molecular Rotor. *Nature* **1999**, *401* (6749), 152–155.

In parallel with the advances based on mechanically interlocked structures, **isomerisable unsaturated bonds** have also been at **the core of progress on molecular machines**.

This pathway has witnessed a number of important contributions, in which different entities have been designed, synthesised and applied to rotation. **The major challenge of achieving controlled unidirectional rotation, however, marks the most fundamental breakthrough in this development.**



Using so-called overcrowded alkenes, and engineering asymmetries in the molecules, it was possible to obtain unidirectional rotation through cycles of light irradiation and thermal relaxation.

Feringa's molecular motor

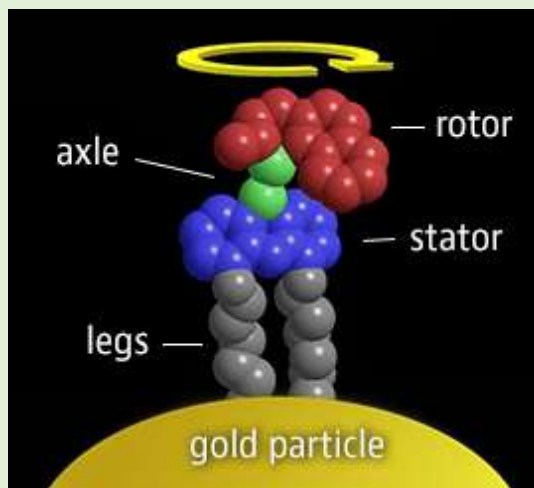
Delden, R. A. van; Wiel, M. K. J. ter; Pollard, M. M.; Vicario, J.; Koumura, N.; Feringa, B. L. Unidirectional Molecular Motor on a Gold Surface. *Nature* **2005**, *437* (7063), 1337–1340.

Eelkema, R.; Pollard, M. M.; Vicario, J.; Katsonis, N.; Ramon, B. S.; Bastiaansen, C. W. M.; Broer, D. J.; Feringa, B. L. Molecular Machines: Nanomotor Rotates Microscale Objects. *Nature* **2006**, *440* (7081), 163–163.

Vachon, J.; Carroll, G. T.; Pollard, M. M.; Mes, E. M.; Brouwer, A. M.; Feringa, B. L. An Ultrafast Surface-Bound Photo-Active Molecular Motor. *Photochem. Photobiol. Sci* **2014**, *13*, 241–246.

Following the original breakthrough, several major advances were made. For example, the motor construct was mounted on a gold surface, **anchoring the stator part of the device**, leading to a surface-mounted, light-driven propeller-type function.

In 2005, another motor system was developed, in this case driven by selective protection/deprotection of phenolic groups < ... >, thus allowing for **chemical fuelling of the rotational molecular motion**. It could also be shown that motor components can be made to controllably rotate in either direction upon addition of a base.

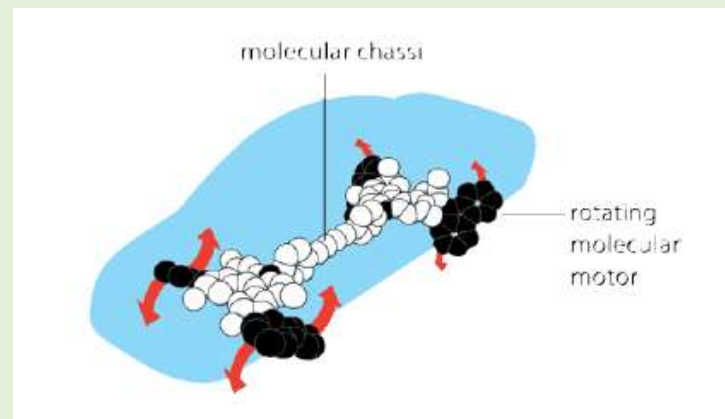
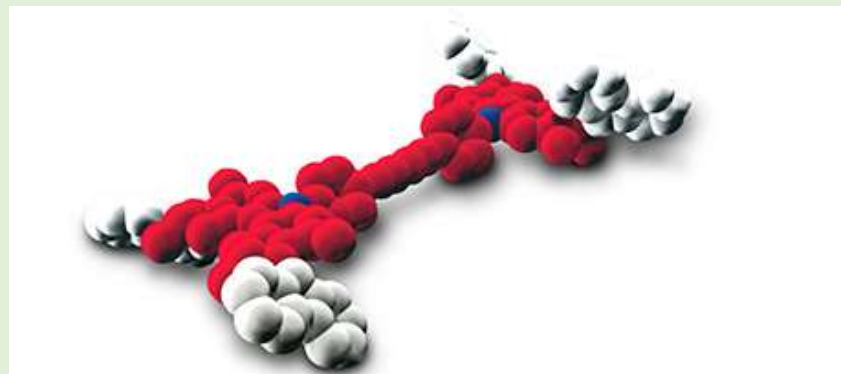
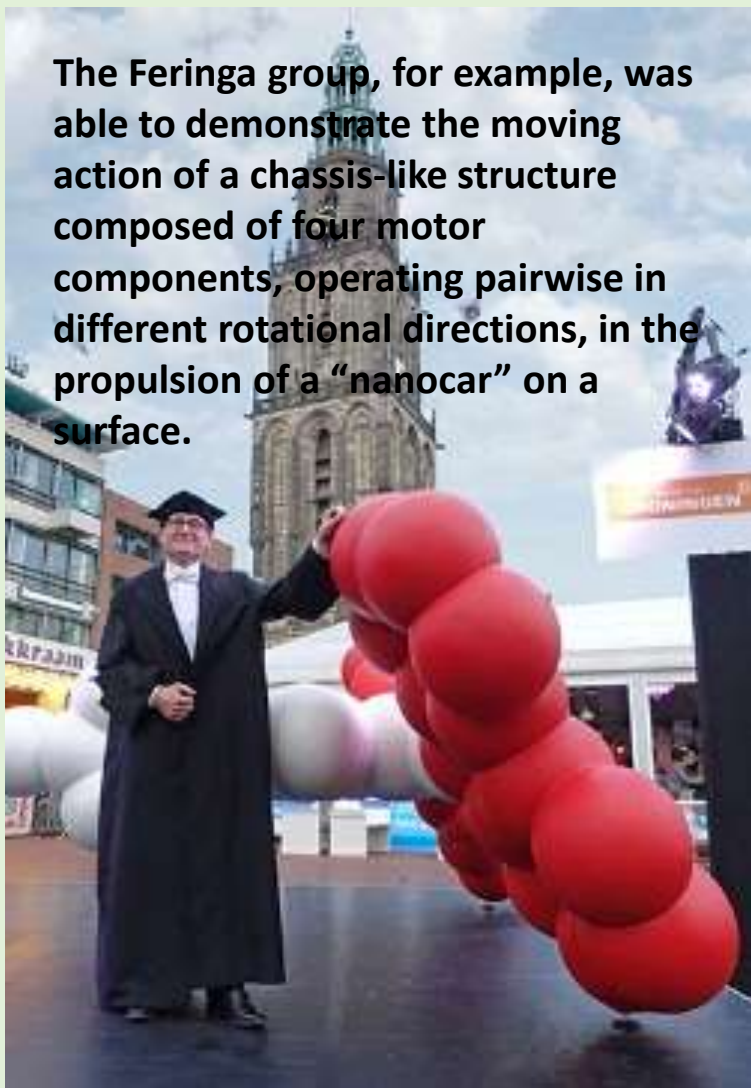


In 2014, for example, an optimised motor structure was demonstrated to rotate with a frequency of over **12 MHz**.

Feringa proposed nanocar

Kudernac, T.; Ruangsapapichat, N.; Parschau, M.; Maci. Electrically Driven Directional Motion of a Four-Wheeled Molecule on a Metal Surface. *Nature* **2011**, 479 (7372), 208–211.

The Feringa group, for example, was able to demonstrate the moving action of a chassis-like structure composed of four motor components, operating pairwise in different rotational directions, in the propulsion of a “nanocar” on a surface.



Обзоры:

Richard Feynman.

<http://calteches.library.caltech.edu/47/2/1960Bottom.pdf>

There's Plenty of Room at the Bottom

An invitation to enter a new field of physics.

by Richard P. Feynman

I imagine experimental physicists must often look with envy at men like Kamerlingh Onnes, who discovered a field like low temperature, which seems to be bottomless and in which one can go down and down. Such a man is then a leader and has some temporary monopoly in a scientific adventure. Percy Bridgman, in designing a way to obtain higher pressures, opened up another new field and was able to move into it and to lead on all along. The development of ever higher vacuum was a continuing development of the same kind.

I would like to describe a field, in which little has been done, but in which an enormous amount can be done in principle. This field is not quite the same as the others in that it will not tell us much of fundamental physics (in the sense of, "What are the strange particles?") but it is more like solid-state physics in the sense that it might tell us much of great interest about the strange phenomena that occur in complex situations. Furthermore, a point that is most important is that it would have an enormous number of technical applications.

What I want to talk about is the problem of manipulating and controlling things on a small scale.

As soon as I mention this, people tell me about miniaturization, and how far it has progressed today. They tell me about electric motors that are the size of the nail on your small finger. And there is a device in the market, they tell me, by which you can write the Lord's Prayer on the head of a pin. But that's

nothing; that's the most primitive, halting step in the direction I intend to discuss. It is a staggeringly small world that is below. In the year 2000, when they look back at this age, they will wonder why it was not until the year 1900 that anybody began seriously to move in this direction.

Why cannot we write the entire 24 volumes of the *Encyclopaedia Britannica* on the head of a pin?

Let's see what would be involved. The head of a pin is a sixteenth of an inch across. If you magnify it by 25,000 diameters, the area of the head of the pin is then equal to the area of all the pages of the *Encyclopaedia Britannica*. Therefore, all it is necessary to do is to reduce in size all the writing in the *Encyclopaedia* by 25,000 times. Is that possible? The resolving power of the eye is about 1/120 of an inch—that is roughly the diameter of one of the little dots on the fine half-tono reproductions in the *Encyclopaedia*. This, when you demagnify it by 25,000 times, is still 80 angstroms in diameter—32 atoms across, in an ordinary metal. In other words, one of these dots still would contain in its area 1,000 atoms. So, each dot can easily be adjusted in size as required by the photoengraving, and there is no question that there is enough room on the head of a pin to put all of the *Encyclopaedia Britannica*.

Furthermore, it can be read if it is so written. Let's imagine that it is written in raised letters of metal, that is, where the black in the *Encyclopaedia*, we have raised letters of metal that are actually 1/25,000

"There's Plenty of Room at the Bottom" is a reprinted of a talk given by Dr. Feynman on December 29 at the annual meeting of the American Physical Society at Colloid.

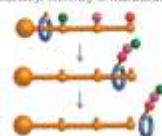
S. Erbas-Cakmak, D. A. Leigh, C.T. McTernan, and A. L. Nussbaumer . Artificial Molecular Machines. *Chem. Rev.* 2015, 115, 10081–10206

CHEMICAL REVIEWS

Artificial Molecular Machines

Sunil Erbas-Cakmak, David A. Leigh,* Charlie T. McTernan, and Alina L. Nussbaumer

School of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, United Kingdom



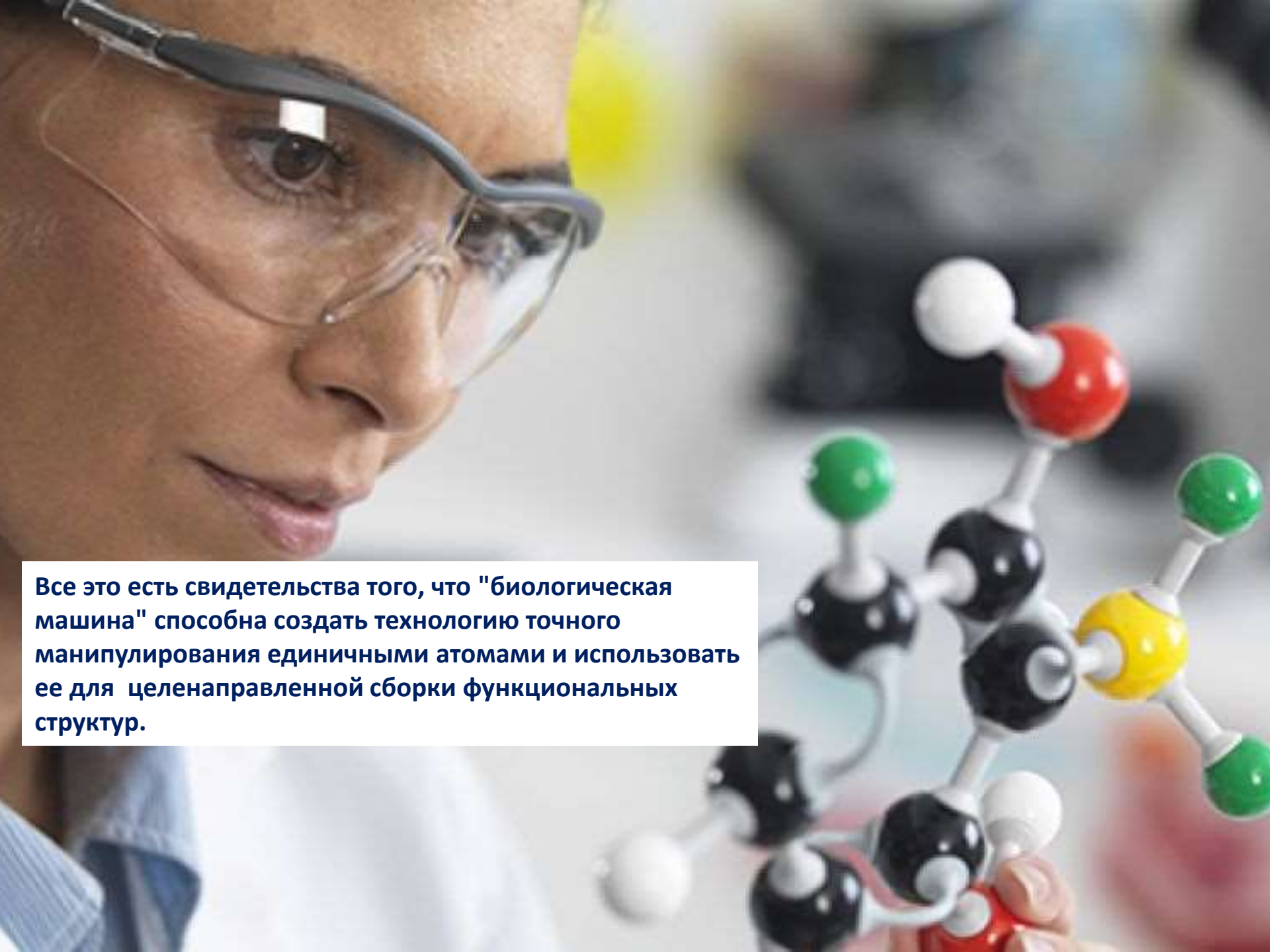
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or arion binding, allosteric effects, temperature, reversible covalent bond formation, etc.). Finally, we discuss the latest generations of sophisticated synthetic molecular machine systems in which the controlled motion of subcomponents is used to perform complex tasks, paving the way to applications and the realization of a new era of "molecular nanotechnology".

1.1. The Language Used to Describe Molecular Machines

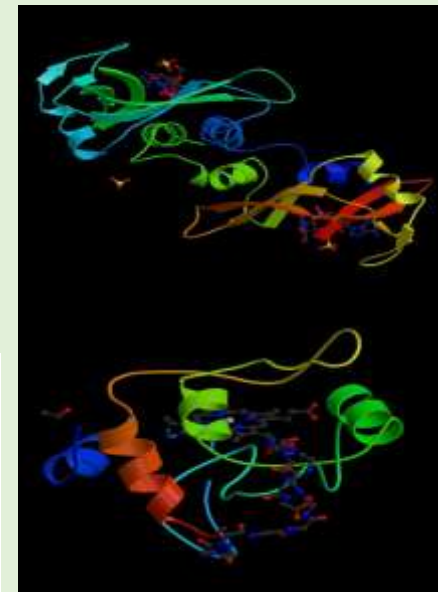
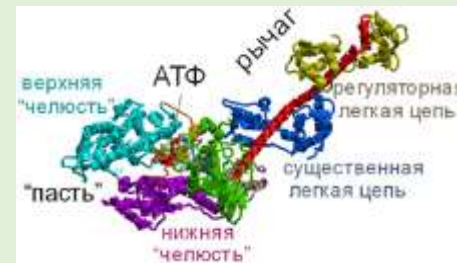
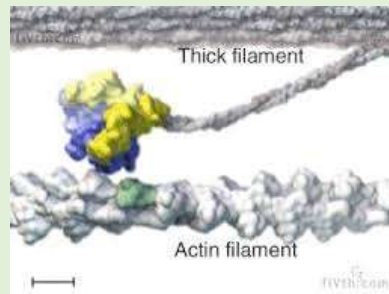
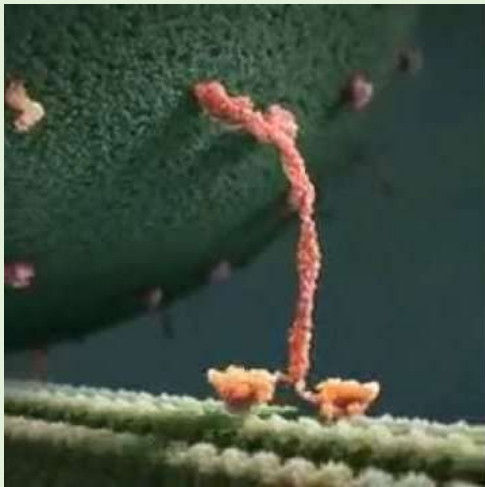
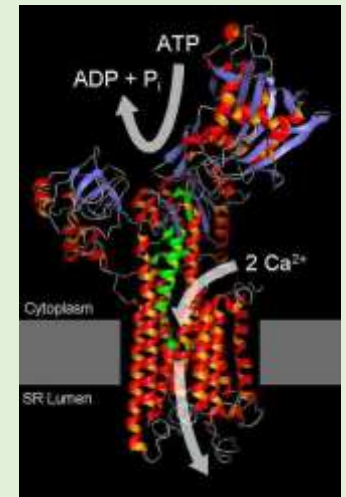
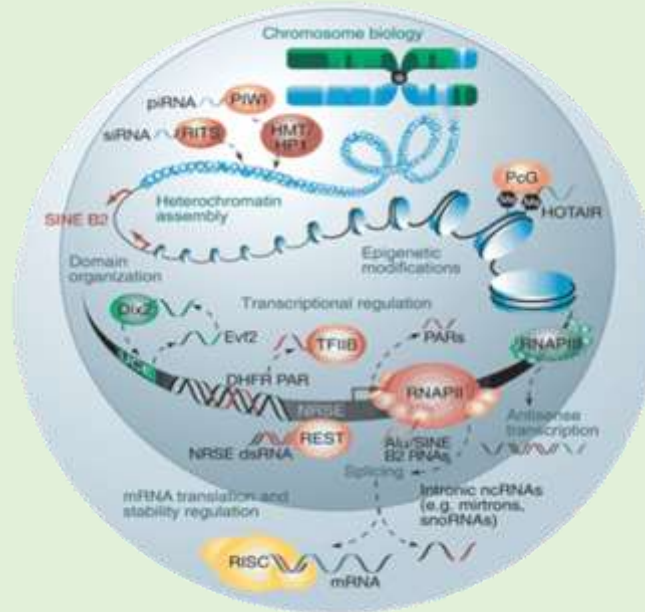
Terminology needs to be properly and appropriately defined and these meanings used consistently to effectively convey scientific concepts. Moreover it is the need for accurate scientific language more apparent than in the field of molecular machines. Much of the terminology used to describe molecular level machines has its origins in observations made by biologists and physicists, and these findings and descriptions have often been misinterpreted

A close-up photograph of a scientist with a focused expression, wearing clear safety glasses. The scientist is looking towards a molecular model in the foreground. The model consists of white, black, red, yellow, and green spheres connected by white rods, representing atoms and their bonds. The background is blurred, showing a laboratory setting with a yellow safety cone.

Все это есть свидетельства того, что "биологическая машина" способна создать технологию точного манипулирования единичными атомами и использовать ее для целенаправленной сборки функциональных структур.

Аналогичная технология есть и в природе, и возникла она "самопроизвольно", без всякого участия человека.

Цель у Природы была та же – точная сборка сложных молекулярных структур с помощью молекулярных машин, но машины она сделала принципиально другие, основанные не на трансляционном или поворотном изомеризме, а на **конформационной динамике** полимеров.

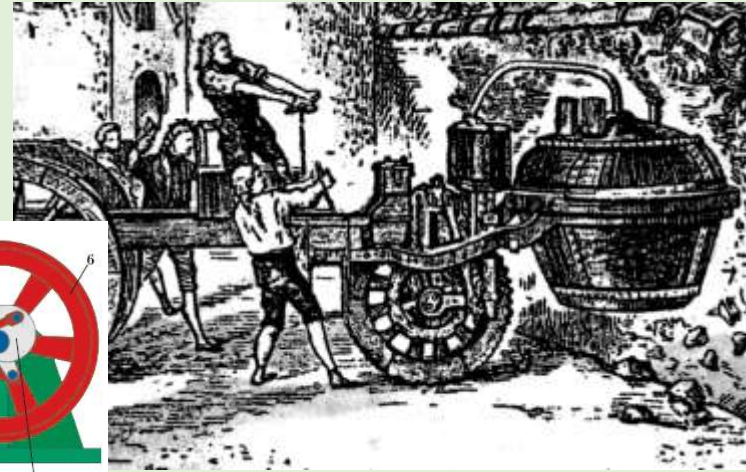
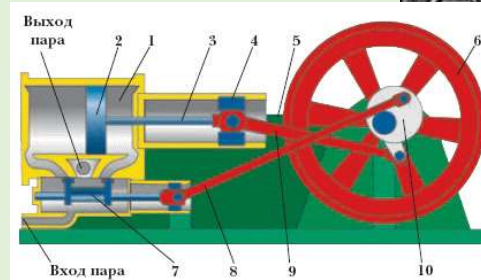


Природные (биологические) молекулярные машины — это динамические системы, и создавая такие системы следует, в первую очередь, смотреть на их физические свойства.

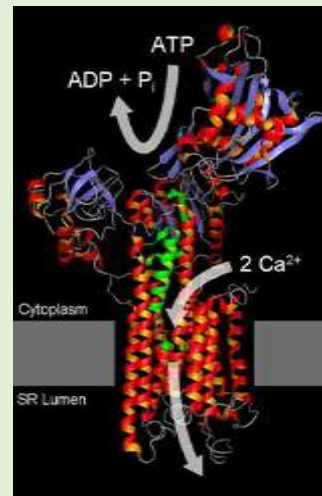
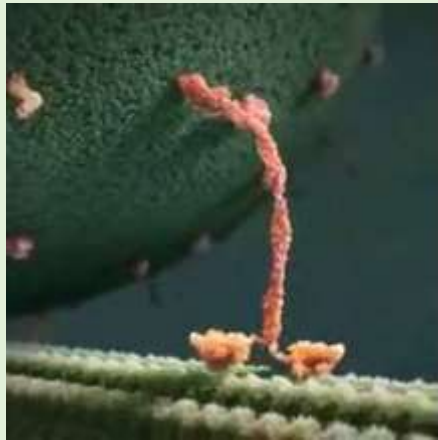
Какие?

Машины и молекулярные машины.

Машина (тепловая) есть устройство, преобразующее тепловую энергию в механическое движение, ...

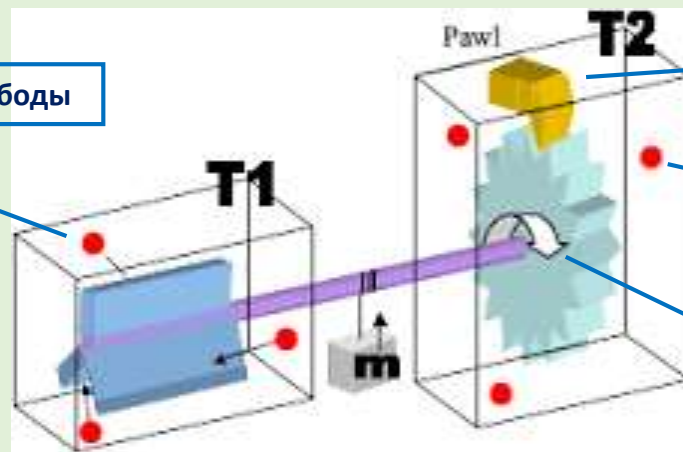


молекулярная машина – это такое же устройство, только нанометрового масштаба.



физика:

Молекулярная машина - система наноразмерного масштаба, преобразующая возмущение **большого числа быстрых степеней свободы** в направленное движение вдоль **одной-двух медленных** (квазимеханических) **степеней свободы**.



быстрые степени свободы

выделенное направление

тепловые флуктуации

медленная (механическая) степень свободы

Если не забывать про то, на наномасштабах все "трясется и прыгает", и про то, что механика – это когда масштаб флуктуаций конструкции существенно меньше масштаба движения конструкции, то "броуновская машина" Фейнмана является замечательной моделью молекулярной машины. Ее (машину Фейнмана) цитируют все, и Нобелевский комитет тоже.

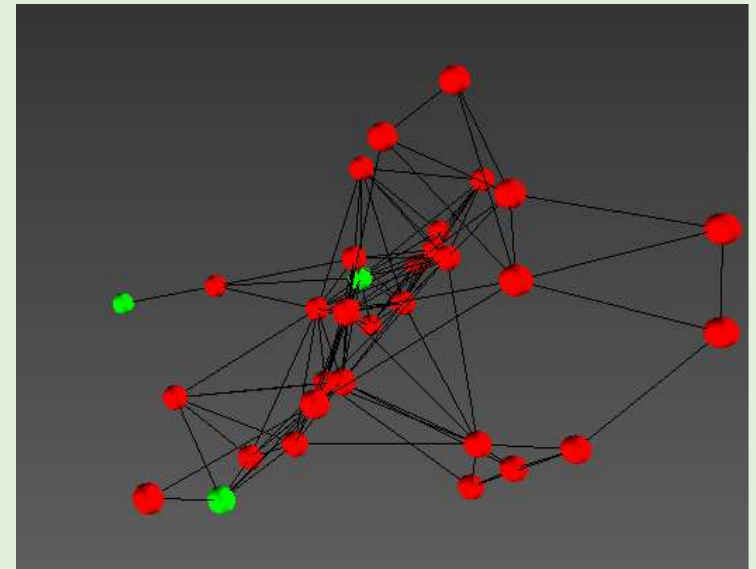
физическая модель

молекулярная структура как эластичная (динамическая) сеть

Уравнения для движения узлов под действием упругих сил (в сильно демпфированном приближении):

$$\frac{d\mathbf{R}_i}{dt} = \sum_{j=1}^N a_{ij} \frac{\mathbf{R}_j - \mathbf{R}_i}{|\mathbf{R}_j - \mathbf{R}_i|} (|\mathbf{R}_j - \mathbf{R}_i| - |\mathbf{R}_j^{(0)} - \mathbf{R}_i^{(0)}|)$$

\mathbf{R}_i - положение i -ого узла сети, $\mathbf{R}_i^{(0)}$ - его равновесное положение, a_{ij} - элемент матрицы смежности (связей) сети.



Для малых отклонений $\mathbf{r}_i = |\mathbf{R}_i - \mathbf{R}_i^{(0)}|$, ($|\mathbf{R}_i - \mathbf{R}_i^{(0)}| / \max\{|\mathbf{R}_i^{(0)} - \mathbf{R}_j^{(0)}|\} \ll 1$):

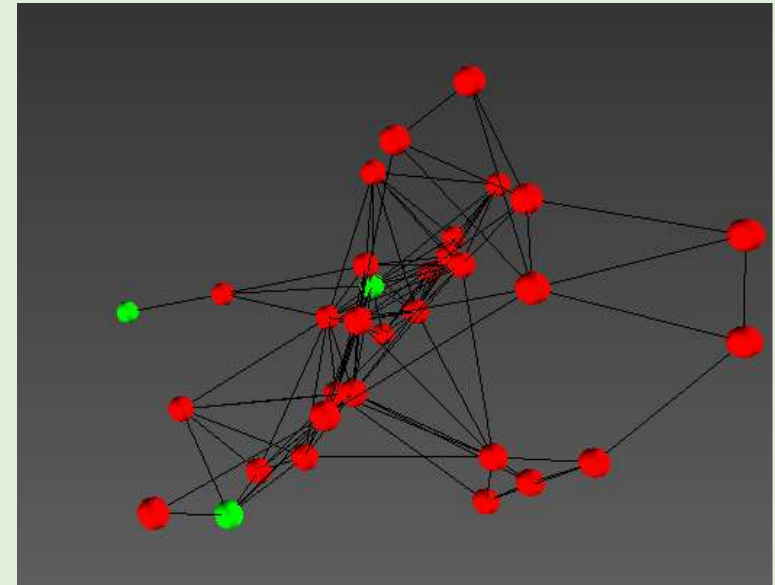
$$\frac{d\mathbf{r}_i}{dt} = -\sum_j \Lambda_{ij} \mathbf{r}_j \quad ;$$

Спектр собственных значений матрицы линеаризации Λ есть спектр нормальных релаксационных мод структуры.

методика исследования

малые возмущения – вычисляем нормальные релаксационные моды, т.е. собственные значения и собственные векторы матрицы линеаризации полной системы динамических уравнений эластичной сети

большие возмущения – изучаем динамические траектории и аттракторы в (многомерном) фазовом пространстве системы.



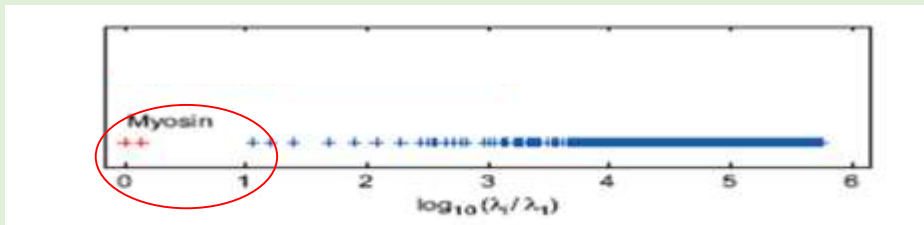
Динамика сети существенно зависит от ее топологических свойств.

Эластичные сети белков

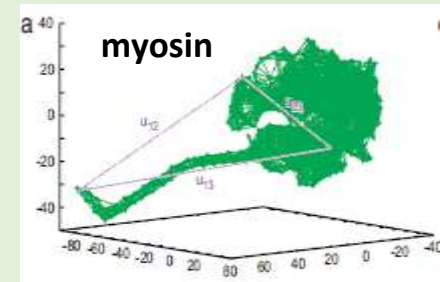
Yuichi Togashi, and Alexander S. Mikhailov

PNAS 2007;104:8697-8702; originally published online May 16, 2007;

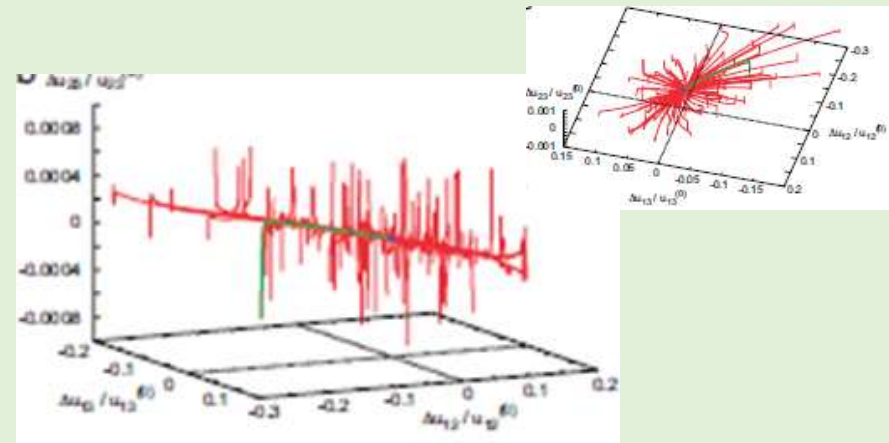
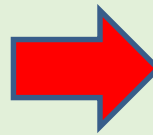
1. Имеется большая **спектральная щель**, отделяющая две самые медленные релаксационные моды от остальных.



эластичная сеть миозина



2. Имеется **низкоразмерное многообразие с большим бассейном притяжения**: - траектории вначале быстро притягиваются к двумерному подпространству двух самых медленных степеней свободы и затем, оставаясь в нем, медленно стягиваются к точке равновесия .

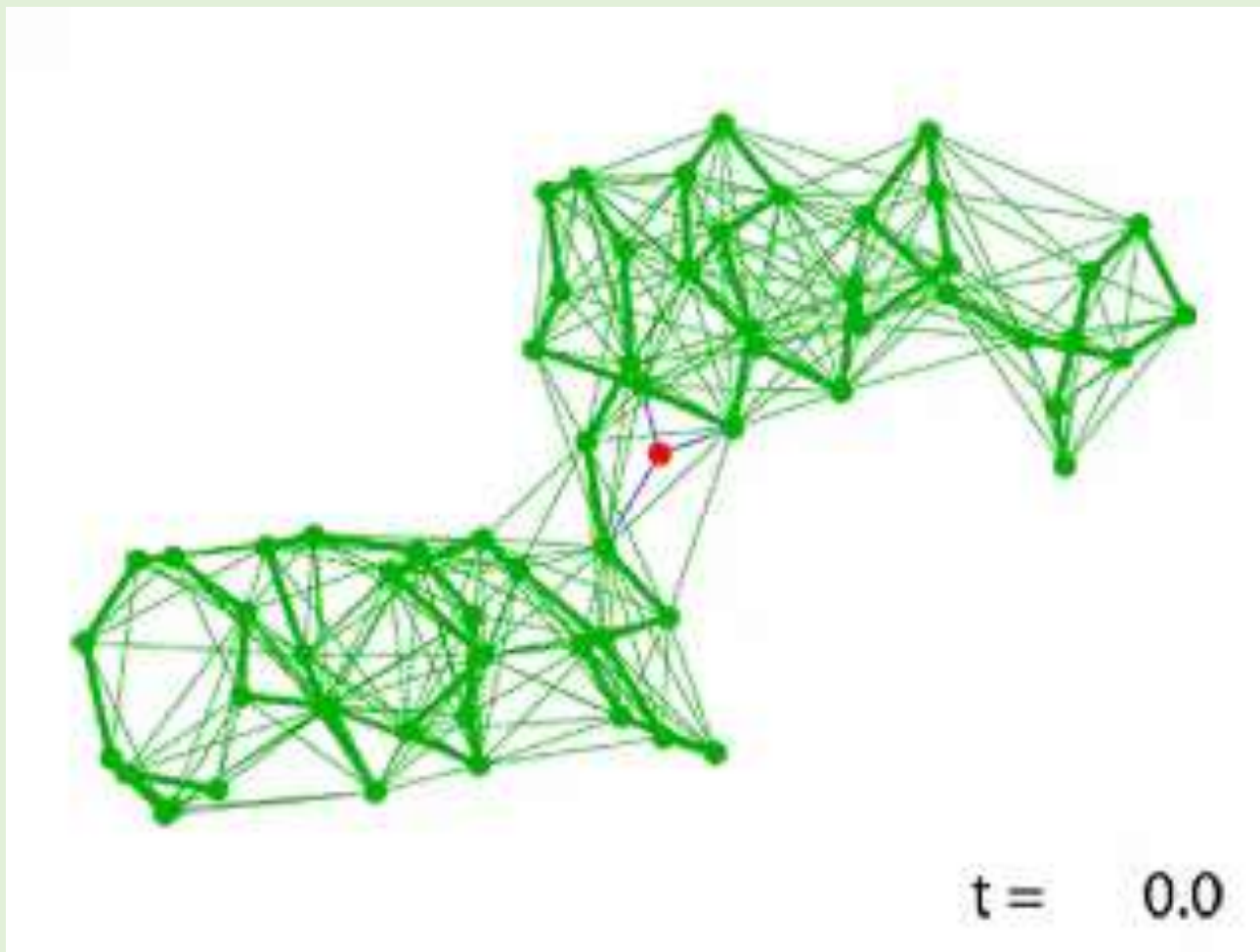


Белки – это действительно молекулярные машины.

Белки преобразуют возмущение быстрых степеней свободы, инициированное химической реакцией в активном центре белка, или поглощением излучения, в движение "механических" субъединиц вдоль одной-двух медленных степеней системы.

Это не совсем то, что сделали Нобелевские лауреаты.

Дизайн молекулярных машин



все только в начале ...



• • •



... а какой путь выбрать – решайте сами.

Успехов вам!