Physics of molecular machines: Joining theory and experiments

Final report.

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Schedule: One week workshop, 22-26 May 2006 at the Les Houches School of Physics (France)

Important note on the expenditures: The daily rate of the Les Houches Physics School (65 €/day) includes accomodation and meals. In the form this actual expenditure is listed as accomodation, and this is why there is no cost for meals.

Summary

The modelling of molecular motors has strongly stimulated stochastic dynamics theory. But we thought that the very large body of experimental results on molecular machines, which has been gathered in the last 5 years, had not been fully exploited by the theoretical analysis. This is why this workshop, co-organised by theoreticians and experimentalists, intended to improve the contacts between the two viewpoints.

It took place as planned at the Les Houches Physics School, where all participants were hosted from Sunday May 21st (afternoon) to Friday May 26th (afternoon).

The workshop gathered 49 participants (including the 3 organisers) from UK (12), Japan (12), France (6), USA (5), Germany (4), Spain (2), Switzerland (2), Netherland(1), Israel (1), Sweden (1), Hungary (1), Ukraine (1), Belgium (1).

The large representation from Japan was stimulated by the the Japanese organiser, a top-level Japanese lecturer (T. Yanagida) and support from the "Service pour la Science et la Technologie" of the French Embassy in Japan, which supported to young Japanese scientists besides the Japanese organiser and lecturer.

As expected the audience was approximately equally split between theoreticians and experimentalists, and the program was mixing, on purpose, experimental and theoretical talks during the same session, in order to avoid any splitting of the audience into two groups, and to promote discussions.

A poster session was organised on Monday afternoon, but the posters stayed displayed during the whole meeting, in several small discussion rooms, so that they have been extensively used during the whole meeting as a base for discussions among the participants.

The core of the meeting was organised around long lectures (2×1h or 2×1.5h) on the basic experimental and theoretical aspects of Molecular Machines. The organisers noticed with interest that some lecturers adapted their presentation to the questions of the audience (for their second talk) or to the presentations of other participants, making the discussions much more efficient and the lectures better adapted to the interest of the audience.

Besides the lectures, many participants gave talks (30mn) and the poster session has also been even more lively than expected because we allowed participants to display posters even if they had not been planned at the registration time. This was possible for a fairly small meeting like that one because we could adjust the organisation to participants requests rather easily, and also thanks to the good facilities of the Les Houches school.

Finally we think that the facilities of the Les Houches Physics School played a large role in the success and the good atmosphere of this meeting. As all participants were sharing accommodation and restaurant (for breakfast, lunch, dinner) the discussions could take place at any time of the day. The beautiful scenery and the hike organised in one afternoon helped to put the participants in an ambiance that was not traditional for a scientific conference, and stimulated personal contacts.

The help of the staff of the Les Houches school to handle the administrative tasks and the reimbursements of the participant travel expenses has been greatly appreciated.

Scientific content.

Proteins are ubiquitous molecules in biological cells. They perform a huge variety of function. The most fascinating role of proteins is their activity as "molecular machines" which convert energy into some mechanical motion at the molecular scale. The process by which molecular motors operate appears as an extreme example of the ability of proteins to exhibit very large, concerted, conformational changes for a well defined biological purpose. Because it is extreme this case is particularly challenging to understand, but, on another hand it can also give us very useful hints on the means by which proteins operate because it magnifies some properties of the proteins. This is why understanding the physics of molecular machines is not only a tantalising goal by itself, but also a possible pathway to understand how many proteins perform their function.

In the last few years, studies of molecular motors have progressed in two directions. The development of experimental methods to manipulate and visualise single molecules has been remarkable and it has allowed a precise exploration of some of their properties. On the other hand theory has developed various tools for these systems which are operating on a scale where the thermal fluctuations cannot be ignored, and are even an integral part of the process.

In spite of these remarkable progress, we still do not know how energy is converted from one form to another, from chemical energy to motion. Some experiments show that chemical energy is not used in a single step of a molecular motor, but may be stored and used in several steps. How is the storage made is another challenging question.

In his paper on *Brownian motors* (Physics Reports, 2002) Peter Reimann notices: While initially the modelling of molecular motors has served as one of the main motivations, the scope of Brownian motor studies has subsequently been extended [...] a much broader and unified conceptual basis has been achieved, new theoretical tools have been developed, which lead to the discovery of many interesting and quite astonishing effects ...

Clearly the motivation to study molecular motors has efficiently pushed forward the theory of stochastic dynamics. In our opinion the richness of this motivation has not been fully exploited. One reason is that the is large "cultural gap" between the experimentalists and the specialists of stochastic dynamics. One aim of this workshop was to transfer the very large body of detailed experimental results on molecular machines, obtained in the last few years, to the domain of stochastic dynamics. We are convinced that, first it can provide some accurate tests for the experimental tools which are mentioned in P. Reimann's remark, but also stimulate new theoretical ideas.

None of the two approaches, experimental or theoretical, is sufficient by itself to explain how molecular machines work, and the dialogue between the two is necessary. But a dialogue requires a minimum common language. A theoretician must understand what experiments actually see, and what they can measure, in order to propose models which have some usefulness to analyse actual phenomena, and to suggest experiments that can discriminate between competitive explanations. An experimentalist must be aware of the ideas that theoreticians have in mind to design experiments which can test them, or to make new suggestions for alternative approaches.

Therefore, the first point of the workshop has been to teach the basic ideas and knowledge of a community to the other, in order to contribute to set up a common language and provide a

suitable framework for the discussion, that will be the second goal of the meeting. Therefore, contrary to a standard workshop, the meeting has been structured around a few courses, completed by shorter talks and discussion in a more traditional workshop style.

Experimental Lectures.

The first lecture was given by Jim Sellers who gave a pedagogical view of Myosins, a superfamily of Actin-Dependent molecular motors. This was very useful to set the frame of the meeting, particularly for theoreticians who had a very formal view of molecular motors. This presentation was completed by the lectures of Justin Molly who showed how studies go from muscles to single molecules. Christoph Schmidt discussed in details some experimental methods, in particular the optical tweezers. This is important because it allows theoreticians to better appreciate what can be expected from measurements. Toshio Yanagida gave a broad view of experiments that are able to monitor the operation of molecular motors at a very microscopic scale and to correlate it with the ATP consumption, another point very important for the development of models.

The talk given by Rob Cross completed the experimental lectures very usefully because, besides showing results and images of the molecular motors at work, Rob Cross explained how these images are precisely obtained, which is essential to understand what they really mean.

Theoretical Lectures.

Theoretical lectures tried to show to the experimentalists the main view point of the statistical physics of molecular motors. Scientists who have not been exposed to this view tend to consider a molecular motor as a "mechanistic" device, like macroscopic motors. If one considers a molecule in a fluid, the situation is completely different and is well summarised by the titles of the first lecture of Dean Astumian: Swimming in molasses and walking in a hurricane! Due to the very low velocities involved, inertial affects are negligible, as if, at a macroscopic scale, one was moving in a highly viscous fluid. On the other hand the molecule is constantly bombarded by small molecules that give it strong impulses leading to very large fluctuations. Another view of the role of fluctuations was provided by the lectures of Ken Sekimoto: Pedagogical Introduction to the thermally fluctuating world.

Felix Ritort focused his lectures on non-equilibrium effects and showed how theory can be used to extract useful information from experimental results.

Talks

The short talks covered various aspects of the theory and experiments, at different scales, from single molecule studies to the motion of muscles. One session focused on some fundamental problems of statistical physics, in particular microscopic mechanisms to control heat transfer, by showing how microscopic systems can act as heat pumps.

Assessment of the results.

The goal of this meeting was to bring together theory and experiments. This was a challenge because the cultures of scientists working in these two domains are very different.

We think that it was successful for two reasons:

- The audience was really mixed, with approximately equal numbers of theoreticians and experimentalists,
- The lecturers made a real effort to bridge the knowledge gap, and to speak to non-specialists. For them it was not obvious to spend time on some aspects that they consider as the basic points, and they could have been afraid of looking too "trivial" for the members of their community. They nevertheless played their role, and it turned to be interesting even for those participants who were supposed to already know the domain of the lecturers. It appeared that lectures often gave rise to lively discussions even within a community. It is also remarkable that the lecturers, who were giving two lectures on different days, adapted their presentation to the reactions of their audience. For instance Ken Sekimoto, theoretical lecturers, developed some points in his second lecture after listening to the experimentalists in the previous days.

However it should be recognised that some of the experimentalists found that some theoretical lectures were difficult, essentially due to notation problems or lack mathematical culture. From the discussions we had with the participants after the meeting, this has been limited by the efforts of the lecturers but not completely avoided.

The main outcome of the meeting is probably that many participants left with a renewed view of their field. For theoreticians, the complexity of the actual mechanisms, often overlooked has been emphasised. For experimentalists one important message was probably the important role of fluctuations and Brownian motion, which precludes a too mechanistic view of the molecular motors.

One issue which appears as still fully open after the workshop is the basic one: how does ATP hydrolysis act to lead to conformational changes corresponding to the "power stroke". This points out the importance of studies *at the biochemical level*, which were not sufficiently represented in this meeting, perhaps because the community working in this area is disconnected from the main stream of experimentalists who helped us shape the meeting. For future developments or further meetings, this is probably an area on which more attention should be focused.

At the request of the participants the slides of some presentations are now accessible on the web (thanks to the lecturers and speakers who accepted to communicate them) at the address:

`http://perso.ens-lyon.fr/michel.peyrard/HOUCHES2006/houches2006_main.html`

Physics of Molecular Machines 22-26 May 2006 17/05/2006

	Monday May 22	Tuesday May 23	Wednesday May 24	Thursday May 25	Friday May 26
8h					
9h	**9h Opening**	9h-10h (E) Sellers	9h-10h (T) Sekimoto	9h-10h (E) Yanagida	9h-9h30 (E) Jankevics
	9h15-10h15 (E) Sellers				9h30-10h (T) Fleisman
10h		10h-10h30 (E) Knight	10h11h (E) Molloy	10h-11h (E) Yanagida	10h-10h30 (T) Sasaki
11h	10h45-12h (T) Astumian	11h-12h15 Astumian			11h-11h30 (T) Geislinger
			11h30-12h30 (T) Ritort	11h30-12h30 (T) Ritort	11h30-12h (E) Malnasi
12h	12h-12h30 (E) Bagshaw	12h15-12h30 (T) Capello			**Closing**
13h	Lunch	Lunch	Lunch	Lunch	Lunch
14h					Departure (bus to Geneva)
	Posters		Discussion		
15h				Hike - Discussion	
16h		Hike - Discussion	16h30-17h (E) Martin		
17h	17h-18h (T) Sekimoto		17h-17h30 (T) N. Nakagawa	17h-17h30 (E) Cross	
			17h30-18h (T) Van den Broeck	17h30-18h (T) Bolterauer	
18h	18h-19h (E) Molloy		18h-19h (E) Schmidt	18h-19h (E) Schmidt	
19h	Dinner	Dinner	Dinner	Dinner	
20h		20h30-21h (E) Robert	20h30-21h(T) Linden	20h30-21h (E) Sleep	
21h		21h-21h30 (T) Sanejouand	21h-21h30 (E) Ferenczi	21h-21h30 (T) Harada	
		21h30-22h (E) Diez	21h30-22h (T) Ciudad	21h30-22h (T) Kagawa	