Moving forward noisily

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INSPIRED by biological systems or motivated by biological applications, physicists are currently creating and studying new devices acting on submicrometre scales. The latest example is the microscopic structure presented by Rousselet, Salome, Ajdari and Prost on page 446 of this issue[1]. It consists of an array of 'sawtooth'-shaped electrodes which can be made to propel small charged colloidal particles by alternately switching on and off the electric potential. This structure can be viewed either as a device inspired by the action of motor enzymes, such as kinesin or myosin, or as a first step towards new separation methods for biological macromolecules, chromosomes or viruses.

Let us take the possible applications first. This and similar devices are fabricated by the microlithography techniques developed mainly for semiconductor electronics, which allow one to create well defined structures with submicrometre dimensions. Particles fitting in and moving inside structures of such small sizes are inevitably subject to thermal noise: they are 'brownian particles'. To master their behaviour one has to understand the stochastic processes involved in the movement. Rousselet *et al.* show that not only can one successfully deal with the noisy thermal environment on submicrometre scales, but also, by adding to it some extra component, possibly accomplish useful tasks.

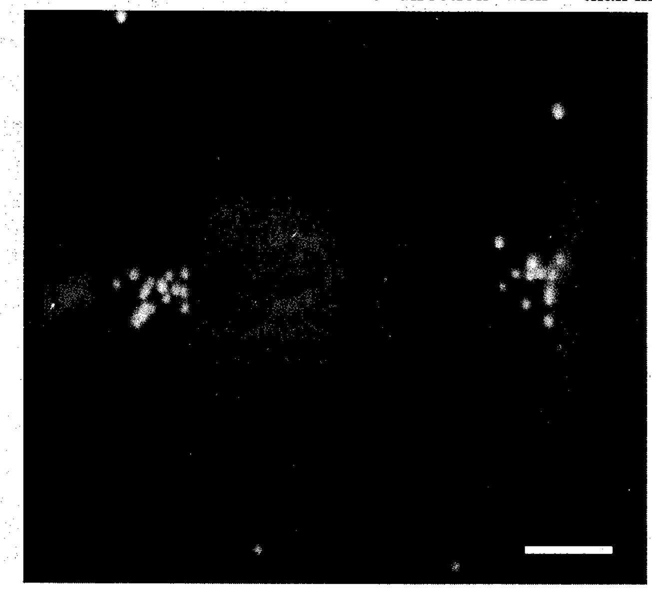
Although the techniques allowing the creation of the present device are relatively new, the underlying ideas are old. A hundred years ago Pierre Curie defined[2] the symmetry principle on which this device is based. It implies that periodic structures with spatial asymmetry may act as 'ratchets' for brownian particles in the presence of dissipation or other source of time-reversal symmetry breaking. By a ratchet we mean here a system which moves the particles with non-zero macroscopic velocity without any macroscopic forces or field gradients. Such a ratchet is thus different from, for instance, a simple electrophoretic machine in which the moving particles are subject to a macroscopic electric force.

Two years ago, Ajdari and Prost[3], working in Pierre Curie's old institution in Paris, pushed his ideas further, showing in theory how a simple microstructure could act as a ratchet or a separation device. Imagine brownian particles moving in a sawtooth potential, $U(x)$, whose 'teeth' are periodic but asymmetric. If the particles are subject only to thermal equilibrium noise, then their movement is not macroscopically biased in one of the directions along the x-axis and the sawtooth potential cannot act as a ratchet for brownian particles[4].

But if one now constantly switches the potential $U(x)$ on and off, then the particles can move in one direction with non-zero macroscopic velocity. During the period in which the potential is switched off, the particles diffuse freely and their distribution spreads along the x-axis. Although the diffusion is symmetrical, the potential U is not, so when it is switched back on it pulls more particles in one direction than in the other.

The calculation shows that in the simplest case, in which the potential is switched periodically, the macroscopic flux depends exponentially on the diffusion coefficient D of the particle (at least in the case of slow diffusion and thus low D). This is particularly promising from the point of view of using such systems to separate particles of different diffusion constant, for instance because of differences in size.

Ajdari and Prost have now gone beyond this purely theoretical work: together with their colleagues from Bordeaux[1] they have built a microelectrode system based on exactly the same principle of periodically appearing and disappearing sawtooth electrostatic potential, and they have demonstrated that it does indeed move forward small colloidal particles of sizes varying between 0.1 and 5 μm (see figure). Although inevitable complications of the real system, such as sticking of the particles and non-isotropic diffusion, prevent quantitative comparison with theoretical predictions, the data agree at least semi-quantitatively with the simple theory.



Trickle down — tiny colloidal spheres trapped at the narrow necks between 'Christmas tree' electrodes. Each on–off cycle of electric field produces a net particle motion from left to right. Scale bar, 10 μm. (Photo courtesy of J. Prost.)

The success of this exemplary interplay between theory and experiment does not yet imply the success of future applications. Although the present work clearly shows that biased movement and separation can be achieved, it remains to be seen whether the method can give better results than more traditional techniques, such as electrophoresis, in which macroscopic gradients or forces are directly applied, especially as a new class of such techniques has been introduced which also takes advantage of the microlithographic technology. For instance, one can perform electrophoresis of DNA molecules in a submicrometre 'maze' structured in a silicon wafer[5]. Further development of electrophoresis in such well controlled geometries might lead to separation of relatively large brownian particles (megabase pieces of DNA or even whole cells) for which the usual gel methods are inefficient.

Periodic switching of the sawtooth potential is not the only way of introducing the time correlations necessary for macroscopic movement — a series of theoretical papers has more recently explored other possible ratchets. Magnasco[6] looked at the case in which the particles are subject to a periodically varying macroscopic force, $\mathbf{F}(t)$. Strictly speaking this is not a ratchet in the sense defined above, but it is analogous to it, provided that the time average of $\mathbf{F}(t)$ is zero. Analysis of this model showed that macroscopic movement takes place for various functional forms of $\mathbf{F}(t)$.

Similar results can be obtained if one simply modulates the height of the teeth of the potential. This can be done, as before[3], by switching between two different 'sawtooth' potentials[7], or equivalently, by assuming that a brownian particle can be in two different internal states, each of which feels a different sawtooth potential (ref. 8; and G. Oster, C. S. Peskin and G. B. Ermentrout, personal communication). Instead of introducing the time correlations in the potential $U(x)$ itself, one introduces them in the transitions between two internal states of the particle. Out-of-equilibrium, correlated noise (so-called 'coloured noise') is again necessary: if the transition rates correspond to thermal equilibrium ('white noise') then the particle cannot move on average in one direction[9]. In the presence of coloured noise the average flux depends strongly on the noise amplitude, in some cases showing a maximum for a well defined value[7].

Earlier this year Doering *et al.*[10] investigated how the average velocity of the particles depends on the characteristics of the out-of-equilibrium noise. Their combination of numerical and analytical results shows that not only the magnitude of the flux but also its sign depends on the nature of the noise. This means that for a given sawtooth potential the particles may be moved in either direction by simply changing the characteristics of time correlations in the nonthermal component of the noise.

Most of this theoretical activity was inspired not by Curie's old results but by developments in the study of motor enzymes[11]. Molecular motors, such as kinesins or myosins, move on protein fibres many micrometres long, and can transport objects such as vesicles or chromosomes within the cell, participate in cell locomotion or accomplish other types of useful mechanical work. The energetics of the action of molecular motors has long been known[12]: hydrolysis of bound nucleotides such as ATP provides the necessary energy. But the dynamics of this process is less well understood, although the crystal structure of muscle myosin has now been established[13] and the action of single motors has been observed with impressive nanometre resolution[14,15]. Not surprisingly, experimental data like these have inspired theorists to new efforts.

Motor enzymes and ratchets are indeed analogous in many respects. Both work in the presence of thermal noise and transport brownian particles; the ATP hydrolysis which drives a molecular motor is local, not involving gradients or forces on micrometre scales; the fibre on which a motor enzyme moves shows periodicity and spatial asymmetry because of the nature of its protein components; the binding sites for a motor on a fibre are analogous to the minima of a sawtooth potential; and the movement of a motor is directional, but different motors may move in different directions on the same fibre.

It is tempting to take the extra step and argue that a ratchet and a motor enzyme work in exactly the same way. Then one can try to compare quantitatively their characteristics[7]. Unfortunately, one cannot then get anything beyond a simple dimensional analysis. The immediate problem is which of the ratchet models is the most appropriate. For instance, can the hydrolysis of ATP be considered as a source of a 'coloured', out-of-equilibrium noise which moves the motor in a fixed fibre potential? Or is it better to say that the motor enzyme can be found in two different states and ATP hydrolysis introduces nonthermal transitions between these states? One could also imagine a motor locally modifying the fibre on which it moves and thus changing the sawtooth potential, or some still more complicated situation.

The point is that all these questions are of microscopic nature and will be answered only by further experimental studies of the details of molecular motors. It is useful to know that simple physical devices can perform tasks analogous to those of biological systems, but this does not mean that the latter are as simple as the former.

Should we even try quantitatively to model the motor enzymes? Well, the effort might be worthwhile provided that one stays on the phenomenological rather than the microscopic level. For instance, *in vitro* motility assays [16] characterizing the action of molecular motors tell us that the average motor velocity depends on ATP concentration, or on the load acting on the motors. Similarly, more quantitative motility assays might establish the relation between the mean hydrolysis rate and motor velocity, or correlations between the statistics of hydrolysis events and fluctuations in their movement. Phenomenological models explaining all these relations could also give some testable predictions, point to the differences in the action of different motors[17] or even suggest some molecular (genetic) modifications which could alter the action of the motors.

Meanwhile, the work of Rousselet and her colleagues provides us with a beautiful example of biologically inspired physics and, in addition, a device with possible applications in biological research. □

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1. Rousselet, J., Salome, L., Ajdari, A. & Prost, J. *Nature* **370**, 446–448 (1994).
2. Curie, P. *J. Phys.* **III**, 383 (1894).
3. Ajdari, A. & Prost, J. *C.R. Acad. Sci. Paris* **315**, 1635–1639 (1992).
4. Feynman, R. P., Leighton, R. B. & Sands, M. in *The Feynman Lectures in Physics* (Addison-Wesley, Reading, Massachusetts, 1966).
5. Volkmuth, W. D. & Austin, R. H. *Nature* **358**, 600 (1992).
6. Magnasco, M. *Phys. Rev. Lett.* **71**, 1477–1481 (1993).
7. Astumian, R. D. & Bier, M. *Phys. Rev. Lett.* **72**, 1766–1769 (1994).
8. Prost, J., Chauwin, J.-F., Peliti, L. & Ajdari, A. *Phys. Rev. Lett.* **72**, 2652–2655 (1994).
9. Vale, R. & Oosawa, F. *Adv. Biophys.* **26**, 97–134 (1990).
10. Doering, C. R., Horsthemke, W. & Riodan, J. *Phys. Rev. Lett.* **72**, 2984–2987 (1994).
11. Maddox, J. *Nature* **369**, 181 (1994).
12. Hill, T. L. *Thermodynamics for Chemists and Biologists* (Addison-Wesley, Reading, Massachusetts, 1968).
13. Rayment, I. *et al. Science* **261**, 50–58 (1993).
14. Svoboda, K., Schmidt, C. F., Schnapp, B. J. & Block, S. M. *Nature* **365**, 721–727 (1993).
15. Finer, J. T., Simmons, R. M. & Spudich, J. A. *Nature* **368**, 113 (1994).
16. Scholey, J. M. *Motility Assays for Motor Proteins* (Academic, New York, 1993).
17. Leibler, S. & Huse, D. A. *J. Cell Biol.* **121**, 1357 (1993).

RÉSUMÉ

Radical solution

At last, some cheering news for smokers. Dosing-up with vitamin C can protect against one of smoking's nastier side effects — the clumping of white blood cells on vessel walls, which can trigger cardiovascular and pulmonary disease (H. A. Lehr, B. Frei and K. E. Arfors, *Proc. natn. Acad. Sci. U.S.A.* **91**, 7688–7692; 1994). Vitamin C, which is a water-soluble vitamin, acts as an antioxidant, disarming poisonous oxygen radicals from cigarette smoke that cause the white blood cells to become sticky. But the water-insoluble vitamin E, another antioxidant that works by a different mechanism, does not confer the same protection. The secret is probably that the oxygen species responsible for the effect on a smoker's leukocytes are more soluble in blood plasma.

Old crocs

Crocodiles today like their climate balmy — 25 to 35 °C is their preference, and anything above 39 °C or below about 4 °C is inhospitable. So P. J. Markwick has been comparing the distributions of ancient crocodilians with their modern counterpart *Alligator mississippiensis* and drawing inferences about continental temperatures across North America in the Cenozoic era (*Geology* **22**, 613–616; 1994). Fossil crocodilians from the Eocene (38–55 million years ago) are widespread, but by the late Oligocene the populations had apparently shrunk to little more than modern-day Florida. The Miocene again was crocodile-friendly, but the Pleistocene and early Holocene were emphatically not. The crocodilian low-down on climate, part of a larger compilation of vertebrate records, thus backs up floral and modelling evidence for climes milder than today's during both Eocene and Miocene.

High charges

The simplest of all atomic systems are those that, like the hydrogen atom, have just one electron and so avoid the complexities of multielectron interactions. And the higher the atomic number of an element, the greater the contributions of quantum electrodynamics and relativity to the atomic energy levels. The ideal testbed for theoretical models, then, is a heavy ion with every electron but one stripped away — such as the high-velocity U^{91+} ions produced in a storage ring last year (T. Stohlker *et al. Phys. Rev. Lett.* **71**, 2184; 1993). Now R. E. Marrs and co-workers have gone further by trapping single-electron U^{91+}, and even a few naked U^{92+} ions, in a compressed electron beam (*Phys. Rev. Lett.* **72**, 4082–4085; 1994). With the ions more or less stationary, they were able to derive cross-sections for electron impact ionization, and suggest that current theoretical estimates are too low.