

Making models of muscle contraction

Models of even the simplest biological systems madden bench biologists by what seems naivety and pretension, but some of them deserve attention for their more general attributes.

The industry for making models of biological processes may not be nearly as productive as present circumstances require. Part of the trouble is evidently the huge gap that still persists between models that are simple enough to be calculated with reasonable accuracy and the reality of the problems in biology on which they are expected to throw some light. The model-makers may spend endless time (and even other people's Cray time) solving problems only to be told by biologists that the models are either hopelessly oversimplified or, worse, are "unhelpful".

A little charity is called for. Sometimes, even the most rarefied models can provide a way of looking at a real problem that would not otherwise be available. Who, for example, would claim that the simple molecular orbital model of benzene is an accurate representation of the electrons in the molecule? And who would be without it?

The eager band of physicists busily adapting classical models in physics to problems in biology may need extra indulgence. One of the latest of their products is an adaptation to the case of muscle contraction of a model originally introduced by Kramers for explaining the exponential dependence of chemical reaction rates on free energy differences, the Arrhenius effect as chemists sometimes call it.

The crude model for this problem is that of a particle trapped in a potential well. Usually, the problem is one in classical mechanics. The question does not arise of whether the particle can tunnel through the potential barrier as an α -particle does (through the confining barrier of the strong nuclear force) in radioactivity, but is that of whether, and with what probability, it will acquire from its surroundings the thermal kinetic energy to escape. Over the years, this simple model has been found illuminating in a variety of unexpected fields; the motion of impurity atoms in solids is one example.

To repeat, what follows needs charitable reading. Marcelo O. Magnasco, who divides his time between the NEC research laboratory at Princeton and the Rockefeller University in New York, has devised an elaboration of the Kramers model to deal not just with muscle, but also with molecular motors generally, notably those by which the transport of chemicals is effected in eukaryotic cells (*Phys. Rev. Lett.* **71**, 1477; 6 September 1993). Magnasco's purpose is to plead the case for the unintuitive behaviour of objects such as molecules in the

"Brownian domain". He puts it vividly like this:

In the macroscopic world, energy need not be spent to support a force; any object resting on a table is an obvious example. But in the Brownian domain, a hypothetical microscopic object on a microscopic table will not rest but rather dance around until it reaches the end of the table and falls off. If we wish to confine the object to the table top, we are obliged to pick it up from the floor and place it again on the table, thereby spending some energy. This is of course not a permanent solution: the object will keep falling. In order to expend a force, energy needs to be spent constantly.

Magnasco's model is that of a ratchet on a molecular scale, best visualized in one dimension as a periodic potential energy in whose profile the repetitive units are asymmetrical; they might, for example, be 'V'-shaped, but with one arm making a different angle from the other to the vertical. Macroscopically, such a ratchet behaves unsymmetrically; less force is needed to pull an object over it in the direction of the arm with the smaller gradient than in the opposite direction. A generation of Victorian gadget-makers knew that.

What happens in the Brownian domain? Suppose that Kramers' model of a particle in a single box is replaced by that of a particle in a periodic box, each unit of which has the asymmetrical profile of a ratchet. The particle, being molecular, is also immersed in a thermal bath. Then strange things happen. For one thing, Newton's Second Law no longer applies in its simple form. The faster the particle is moving, the faster it will lose energy to its surroundings.

If one insists on describing only the motion of the particle that defines the state of the ratchet, and not that of the uncounted molecules in the surroundings with which it interacts, then the situation is more like that of the motion of a particle in a viscous liquid. In particular, the gradient of the potential energy determines the *velocity* rather than the *acceleration* of the particle. But only partly. Brownian exchange of energy between the particle and its surroundings must also be counted, which means a time-dependent force of necessity comparable with the forces generated by the ratchet and whose properties can be described only statistically as those of 'white noise', whose magnitude is necessarily an increasing function of the temperature.

There is a flourishing if minor industry in the handling of equations of the type

thrown up by these statements, which are known as Langevin equations. The interest of the present case is when the velocity of the particle representing the state of the ratchet is determined not only by the gradient of the potential energy and the white noise forces but also by a third force, which may at one extreme be a constant and, at the other, 'coloured' noise — white noise with some parts of the spectrum missing.

Marvellously, Magnasco is able explicitly to solve the simplest case of a ratchet (with a repetitive 'V'-shape with straight-line arms) and with a variety of third forces. He confirms the expectation that the ratchet begins to move before the temperature of the surrounding heat-bath responsible for the white noise reaches that equivalent to the height of the potential barrier in the ratchet. It is more interesting, and not intuitive, that there should be a temperature at which the movement of the ratchet in the general direction of the third forcing influence is a maximum. At too low a temperature, the chance that the ratchet will be lifted over the potential barrier by external noise is too small to matter. But if the temperature is too great, the ratchet goes into 'overdrive', and is more likely to slip backwards, even against the influence of the third force.

More complicated cases are dealt with by numerical simulation, largely with the objective of showing that the rate at which the ratchet on the average moves generally increases with the intensity of the forcing influence. The importance of that is to demonstrate that different forcing influences have similar effects. The general conclusion, on which purists may demand further proof, is that it is a sufficient condition for a molecular ratchet to move in the preferred direction, that the third force even if it can be described only statistically, should have longish time correlations built into it.

What does that say about the molecular motors in cells, muscle cells in particular? Magnasco himself says that the question "is still under investigation". Others may take a more optimistic view on two scores. For one thing, the general idea that there may be an optimum temperature for the operation of molecular ratchets will bring modest rejoicing. And some may even go looking for some system in a real cell in which the description of a real ratchet can be pinned down. They may even find substance in the guess that time-correlation follows from linkage with molecules of ATP followed by their hydrolysis.

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