group, that are concerned with segmental identity, leading to a view of evolution in which most animals evolved from a segmented animal with a relatively complex anatomy. This view has been challenged, however, not least by work on enteropneusts showing that anatomy is no guide to the complexity of gene expression[5]. *Xenoturbella* could be a model of early deuterostome ancestry, if not the ancestry of both deuterostomes and protostomes. Classifying it as a flatworm, therefore, might not have been so far from the truth, as that is what the earliest deuterostomes may have looked like.

However, the fact that Bourlat and colleagues[3] have placed *Xenoturbella* closer to the ambulacraria than to the root of deuterostomes in general raises further problems, for it means that it cannot represent a truly primitive state. Ambulacraria and chordates share anatomical features, such as a body cavity and structures called pharyngeal slits,

that were presumably primitively present in the *Xenoturbella* lineage but have since been lost. This means that *Xenoturbella* is secondarily simplified rather than pristine and primitive, and may not be as reliable a guide to deuterostome evolution as we should like.

As we reflect on *Xenoturbella*'s newly exalted state as a deuterostome, it is worth recalling similar examples. Aristotle classed tunicates with the molluscs, and the amphioxus, when first described, was named *Limax lanceolatus* — a kind of slug. So there is no shame in having once been classed as a mollusc: many of the best deuterostomes started out that way. ■

Henry Gee is a senior editor at Nature.

1. Norén, M. & Jondelius, U. *Nature* **390**, 31–32 (1997).
2. Israelsson, O. *Nature* **390**, 32 (1997).
3. Bourlat, S. J., Nielsen, C., Lockyer, A. E., Littlewood, D. T. J. & Telford, M. J. *Nature* **424**, 925–928 (2003).
4. Shu, D.-G. *et al. Nature* **414**, 419–424 (2001).
5. Lowe, C. J. *et al. Cell* **113**, 853–865 (2003).

the associated thermal energy (equal to the product kT, where k is Boltzmann's constant and T is the temperature in kelvin) is too small to allow relative particle motion, as it does in ordinary liquids. So dynamic collections of grains require a continuous external source of energy to prevent them from getting stuck in a particular configuration.

To complicate matters further, because energy is typically injected through a surface (a stirring rod, shear zone or vibrating wall, for example), steep gradients of kinetic energy are invariably present in the system, caused by the decrease in relative particle motion further from the energy source and by the spatial anisotropies arising from the directional nature of the forcing. These complications make it unclear whether granular liquids can be described by the traditional hydrodynamics derived from equilibrium statistical mechanics[5,7,8]. And they are the major reasons why granular materials remain one of the least well understood classes of matter.

Rather than being deterred by the complications associated with the lack of energy conservation in granular media, D'Anna *et al.*[6] have attacked the problem directly by studying the response of vertically vibrated glass beads (physicists' equivalent of sand), using a beefed-up version of the aforementioned pendulum (pictured on the cover of this issue). Their bead-filled container is driven with band-filtered white noise at a relatively high frequency, which ensures that no single characteristic frequency dominates the forcing, that the natural frequency of the oscillator is far below the driving frequency, and that the beads are condensed. The pendulum probe is operated in two modes: free and forced. In the free mode, a constant barrage of grains bombards the probe and jostles it about in irregular excursions about its equilibrium position. Analysis of this Brownian-like motion gives the 'noise power spectral density' in terms of the driving frequency. In the forced mode, a sinusoidal torque is applied to the oscillator, and measurements of the relative phase and amplitude of the response determine the 'complex susceptibility'.

Interestingly, the group finds that the measured complex susceptibility is well described by the theory developed for equilibrium fluids — one of the two parameters used in the fit to theory being the friction coefficient, which is proportional to the shaken beads' viscosity. Furthermore, the bead viscosity is found to decrease nearly linearly with increasing amplitude of shaking. Ordinary liquids show a similar decrease in viscosity with increasing temperature — nearly a factor of three for water between 0 °C and 45 °C.

Of greater interest is D'Anna and colleagues' finding[6] concerning the so-called fluctuation–dissipation ratio, which is

Shaken sand — a granular fluid?

Paul Umbanhowar

The connection between random grain motion and viscosity in shaken sand — a strongly non-equilibrium system — has been probed. Curiously, the link is similar to that found in an ordinary liquid in thermal equilibrium.

By measuring both the free and forced oscillations of a rigid pendulum immersed in an ordinary liquid, the temperature and viscosity of the liquid can be determined[1]. This is due, in part, to a relation from equilibrium statistical mechanics known as the fluctuation–dissipation theorem[2], which, in a precursor to its modern form, was devised by Einstein[3] to explain the diffusive Brownian motion of small particles suspended in liquids[4]. Driven granular materials, such as shaken sand, are systems far from equilibrium — they have strong spatial and temporal variations in quantities such as density and local particle velocity, and would consequently not be expected to obey the fluctuation–dissipation theorem.

Yet, in many instances, the macroscopic behaviour of granular materials seems, at least superficially, liquid-like[5]. One might then wonder whether an experiment using a rigid pendulum would reveal a similar fluctuation–dissipation relation in driven granular materials, despite their dissipative nature. On page 909 of this issue[6], D'Anna and colleagues take up this question and find, surprisingly, that the answer seems to be yes. In particular, their experiments show that the free and forced motions of the probe are related by a fluctuation–dissipation-like relation, and that an effective viscosity and temperature can be defined.

Granular materials — such as peas, coal,

pills, breakfast cereal and, not least of all, sand — are usually defined to be discrete solid bits that interact with each other through energy-dissipating contact forces (although the definition is sometimes stretched to include wetted grains and powders for which attractive surface forces are also important). Many industrial practices require the efficient handling and mixing of granular materials: food and agricultural processing, sorting and assembly of parts, cement manufacturing, mining, radiation shielding and, of ever increasing scope, pharmaceutical production. Despite their somewhat humble nature, granular materials behave unusually because they combine properties of both liquids and solids[7,8]. Examples of such behaviour include the ability to de-mix when poured[9], to form waves or ripples when shaken[10] or blown[11], and to expand when squeezed[12] (as anyone can attest who has walked on wet sand and observed a dry halo around their foot).

Many of the unique properties of granular materials arise because, unlike an ordinary fluid, the kinetic energy associated with the relative motion of macroscopic particles (called 'granular temperature' by physicists) is not constant. Instead, it is continually and irrevocably transferred by collisions to internal (thermal or non-kinetic) degrees of freedom. Although individual grains possess a well-defined thermodynamic temperature,

derived from the complex susceptibility and the noise power spectral density, and so relates collective response to individual grain motion. This ratio turns out to be nearly constant for varying frequency, which enables D'Anna et al. to define an effective temperature for the grains. For a classical liquid, this ratio is equal to kT and is strictly independent of frequency. Using the average value of the ratio as their measure of thermal energy, the authors show that the temperature increases as the square of the driving-force amplitude — a result that would be naively expected if the bead velocities were linearly related to the container velocity, which in turn increases in direct proportion to the drive amplitude. These findings are intriguing, and they support results from other analyses of model systems that have indicated that the fluctuation–dissipation theorem, or a slightly modified version of it, applies to granular materials[13–15]. There are also signs that the temperatures obtained through application of the fluctuation–dissipation theorem[13] are compatible with the temperature obtained from a new form of statistical mechanics that is applicable to granular systems and possibly to other non-energy-conserving systems[16].

D'Anna and colleagues' findings that granular ensembles with strong dissipation have a definable viscosity and approximately obey the fluctuation–dissipation theorem are exciting, but they do not yet definitively answer the question of how deep the similarities run between moving grains and ordinary liquids. Some puzzles remain. Why does the effective temperature vary by approximately a factor of 10 for differently shaped probes? What influence does the probe have on the measurements? Why is the fluctuation–dissipation ratio an increasing function of frequency (albeit slowly)? The answers themselves may be mundane, but they might lead to deeper insights into the properties of granular materials and other related non-equilibrium subjects such as traffic flow, flocking, evolving networks and turbulence[14]. ∎

Paul Umbanhowar is in the Department of Physics and Astronomy, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60208-3112, USA.
e-mail: umbanhowar@nwu.edu

1. Uhlenbeck, G. E. & Goudsmit, S. *Phys. Rev.* **34,** 145–151 (1929).
2. Reichl, L. E. *A Modern Course in Statistical Physics* 545–560 (Univ. Texas Press, Austin, 1991).
3. Einstein, A. *Ann. Physik* **17,** 549–560 (1905).
4. Brown, R. *Phil. Mag.* **4,** 161–173 (1828).
5. Jaeger, H. M., Nagel, S. R. & Behringer, R. P. *Rev. Mod. Phys.* **68,** 1259–1273 (1996).
6. D'Anna, G., Mayor, P., Barrat, A., Loreto, V. & Nori, F. *Nature* **424,** 909–912 (2003).
7. Kadanoff, L. P. *Rev. Mod. Phys.* **71,** 435–444 (1999).
8. de Gennes, P. G. *Rev. Mod. Phys.* **71,** S374–S382 (1999).
9. Makse, H. A., Havlin, S., King, P. R. & Stanley, H. E. *Nature* **386,** 379–382 (1997).
10. Melo, F., Umbanhowar, P. B. & Swinney, H. L. *Phys. Rev. Lett.* **75,** 3838–3841 (1995).
11. Bagnold, R. A. *The Physics of Blown Sand and Desert Dunes* (Methuen, London, 1941).
12. Reynolds, O. *Phil. Mag.* **20,** 469 (1885).
13. Makse, H. A. & Kurchan, J. *Nature* **415,** 614–617 (2002).
14. Aumaitre, S., Fauve, S., McNamara, S. & Poggi, P. *Eur. Phys. J. B* **19,** 449–460 (2001).
15. Colizza, V., Barrat, A. & Loreto, V. *Phys. Rev. E* **65,** 050301(R) (2002).
16. Edwards, S. F. in *Granular Matter: An Interdisciplinary Approach* (ed. Mehta, A.) 121–140 (Springer, New York, 1994).

Malaria

To kill a parasite

Robert G. Ridley

Artemisinins have been used since ancient times to treat malaria. A new theory could explain how this age-old medicine is able to cause the death of the malaria parasite.

The Chinese herb qinghao *(Artemisia annua)* has long been used to treat malaria — Taoist manuscripts dating back to the third century describe the use of qinghao extracts to treat malaria-related fevers[1]. Over the past two decades, derivatives of the herb's active ingredient, artemisinin, have made an increasing contribution to malaria treatment. But the precise mechanism by which artemisinin derivatives kill the parasite has remained obscure. Writing on page 957 of this issue, Krishna and colleagues[2] propose a radical new theory to explain the molecular basis of the antimalarial activity of artemisinin.

Malaria remains a scourge of the developing world, killing over a million people each year and infecting around 500 million[3]. Most of the victims are children under the age of five living in sub-Saharan Africa, but the disease also afflicts Southeast Asia, South America and the Indian subcontinent. The situation has worsened over recent years as resistance has developed against chloroquine and sulphadoxine-pyrimethamine, the two drugs most commonly used to treat malaria[4]. Hope for the containment of the disease now rests largely on a remarkable set of artemisinin drugs developed by Chinese scientists in the 1970s and early 1980s, which rapidly kill the malaria parasites.

The parasites are small 'protozoan' cells (the most prevalent species infecting humans are *Plasmodium falciparum* and *P. vivax*), which enter their human host through a mosquito bite. They first invade the liver and replicate there for two weeks, before beginning a cycle of red-blood-cell invasion, then growth, replication and red-cell destruction that leads to the disease symptoms. The artemisinin drugs are known to act specifically during this blood stage.

Artemisinin contains a structural feature called a peroxide bridge (Fig. 1), and this is believed to be the key to the drug's mode of action. Ferrous iron (Fe^{2+}) catalyses the cleavage of this bridge, forming highly reactive free radicals[5]. The theory has been that these artemisinin-derived free radicals chemically modify and inhibit a variety of parasite molecules, resulting in parasite death[5,6].

A rich source of intracellular Fe^{2+} is haem — an essential component of haemoglobin — and it has long been suspected that Fe^{2+}-haem is responsible for activating artemisinins inside the parasite. In support of this, Fe^{2+}-haem activates artemisinins in the test tube and haem–artemisinin complexes can be formed. This theory appealed to malariologists because it seemed to explain the specificity of the drug within the context of a unique aspect of parasite metabolism. During its growth and replication inside the red blood cell, the parasite ingests and degrades up to 80% of host-cell haemoglobin in a compartment called a food vacuole. This releases Fe^{2+}-haem, which is oxidized to Fe^{3+}-haematin and then aggregates within the food vacuole into an ordered crystalline pigment called haemozoin. A theory developed that the specific antimalarial effect of artemisinin was due to its entry into the parasite food vacuole and its interaction with Fe^{2+}-haem. Here, it would set off a 'cluster bomb' of free radicals, inhibiting several key parasite components and eventually resulting in parasite death.
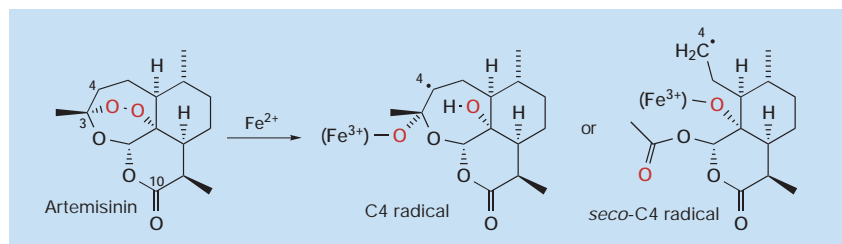
This theory has been challenged[7], however,

Figure 1 Structure of artemisinin. The molecule contains a peroxide bridge (red), which becomes cleaved when artemisinin interacts with ferrous iron (Fe^{2+}). Cleavage creates 'C4' and '*seco*-C4' free radicals, each capable of chemically modifying biological molecules.