will evaluate the biodistribution of labelled nanoparticles in compartments outside of the joint space. This may better illustrate the routes of clearance from the joint, be they lymphatic or vascular, as well as indicate the functional residence times of the drugs in the tissue. In addition, erosion and proteolysis of the cartilage matrix in diseased joints can be expected to affect the transport of the nanoparticles, the efficiency of collagen targeting and clearance by lymphatic or synovial routes. These manifestations of pathology may help or hinder this approach to drug delivery, and only further investigations will reveal the answer.

In this study, the need for particles of small dimensions to deliver drugs to cartilage is confirmed, and the important ability to circumvent cellular or lymphatic microparticle clearance by using collagen-targeting peptides is revealed. With the development of this technology, we can be hopeful about our prospects to overcome the difficulties of targeted drug delivery for the treatment of osteoarthritis.


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GRANULAR MATTER

# Sticky sand

The mechanical properties of granular matter are affected by the addition of liquid — however, over a wide range, the actual amount of liquid is unimportant. Now, imaging techniques look inside the wet granular pile, or 'sandcastle', to help solve this puzzle.


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Adding a small amount of liquid to granular matter transforms its properties in practical ways. Wet sand can be easily sculpted[1], grain segregation can be prevented[2,3], and particle agglomeration can be manipulated[4], making it an important phenomenon in industrial processes. On the other hand, landslides can occur when the ground becomes saturated with rain.

Liquid in the interstitial space initially collects near points of contact between grains, because it is drawn there by surface tension. The curvature of the liquid interface leads to low pressure in the liquid phase causing a force of attraction between grains. Remarkably, the static mechanical properties resulting from this cohesion is insensitive to the actual liquid content over a wide range[1,5]. On page 189 of this issue, Stephan Herminghaus and colleagues take a major step in explaining this observation, using X-ray microtomography to uncover the morphology of the liquid inside the pile[6].

When a liquid is added to granular matter, a three-phase system is formed, composed of liquid, solid and interstitial fluid. Interfaces exist between liquid and solid, and liquid and displaced interstitial fluid (Fig. 1a). The cohesive strength between grains initially increases sharply for very small volumes of liquid because of the roughness of the grains[7,8]. After this increase, however, the cohesivity is effectively constant until the liquid saturates the space between the grains and cohesion decreases to zero, just as when the grains are completely dry.

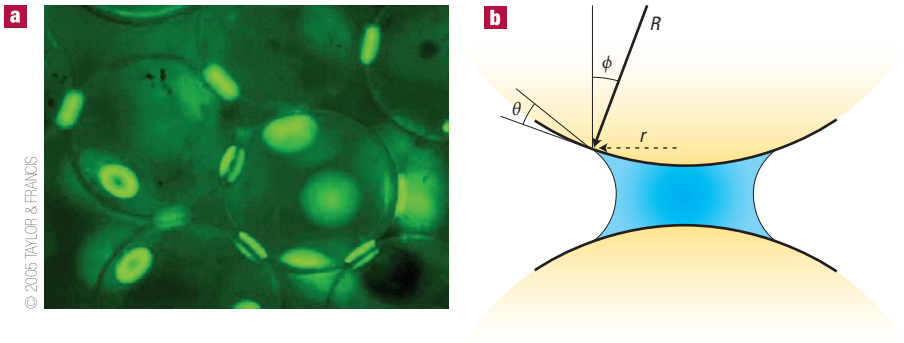




**Figure 1** Liquid bridges form at the point of contact between grains, as a result of surface tension. **a**, Fluorescence microscopy image of liquid bridges between 375-μm-diameter glass beads[5]. **b**, Schematic of a liquid bridge (blue) between spherical surfaces (yellow). $\theta$ is the liquid–solid contact angle, $\phi$ is the half-filling angle, defined as $\phi = \tan^{-1}(r/R)$, where $r$ is the radius of the liquid bridge, and $R$ is the radius of the grain.

It is well known[1,7] that for a perfectly wetting liquid bridge between spherical grains in contact with each other, the strength of the cohesive force is independent of the volume of liquid and approaches $2\pi\gamma R$, where $\gamma$ is the surface tension of the liquid and $R$ is the radius of the grain (Fig. 1b). This occurs because the increase in liquid bridge size is balanced by the decrease in its curvature. As the liquid volume fraction is increased further and neighbouring

liquid bridges coalesce, multiple grains can be in contact with a volume of liquid. A hierarchy of such contacts has been shown to cause agglomeration of drying colloidal particles into geometric clusters[4].

The opacity of the wet granular pile makes the actual organization of the wetting liquid an unknown, and results in a lack of understanding of its effect on the observed constant cohesivity. Herminghaus and colleagues use X-ray microtomography to measure the distribution of wetting liquid inside a pile of glass beads, a simplified model of wet sand. To optimize the contrast between the solid and liquid phases, they used aqueous zinc oxide as the liquid. From the measured liquid structure, they identified the volume that was in contact with more than two beads. As the liquid content increased, it was found that simple liquid bridges between particles merged to give rise to a hierarchy of polyhedral structures, starting with trimers, tetrahedra and pentamers (Fig. 2). For the highest liquid contents measured, they found that more than 90% of the liquid was contained in one contiguous cluster. Using the identified shapes, they then calculated the number of bridges on a sphere, and the volume and surface area of the clusters. By creating this well-defined method of measuring cluster properties, it was possible to quantify the frequency of the clusters inside the entire sample as a function of liquid content.

Although the glass beads are randomly packed, the pile can be approximated by a uniform arrangement of spheres because the capillary bridges start to merge soon after the half-filling angle ($\phi$; see Fig. 1) increases beyond $\pi/6$. Using the size of the capillary bridge as a pressure probe, it is found that the pressure inside the liquid levels off when the liquid occupies about 2.5 percent of the pile volume and $\phi = \pi/6$. Above this liquid content, the cohesive force between particles cannot grow, as the projected area over which the pressure acts on the particle is unchanged, giving rise to the observed constancy of the mechanical strength of the material. This constancy occurs at least up to the stage where the liquid occupies 15 percent of the volume fraction of the pile or about 35 percent of the available pore space.

To extend their results to non-spherical particles, which are more representative of natural granular materials, Herminghaus and colleagues also perform measurements with sand grains. They find the statistics of the liquid morphologies behave the same as the spheres — just as the randomness of the packing did not seem to alter the angle beyond which liquid bridges coalesce, it is possible that grain roughness is also unimportant. In this sense, it seems that a careful recipe to build a sandcastle from wet sand is not required.

Obtaining the liquid structure of this system provokes further questions that demand research. In the case of drying colloidal clusters, the sum of the square of the distance of the centre of the particles from the centre of mass of the cluster is minimized[5]. Are such simple geometric rules obeyed inside the wet granular pile as well? Furthermore, the insensitivity of cohesion to the actual liquid volume fraction relates to static properties, and dynamic properties can, in fact, change significantly over the same range. Although Herminghaus and colleagues argue that their results may hold for driven systems, counter examples may be noted. Lubrication can cause wet grains to flow more easily compared with dry grains, and as a result, offset the stability gained by grain cohesion[9]. X-ray microtomography may be applied to slow-flowing, wet granular matter to clarify how the grain–liquid–air interfaces interact and break as grains flow past each other, and while cohesion, lubrication and pore pressure compete. The investigation by Herminghaus and colleagues highlights the importance of geometry and surface tension, making sticky matter more tractable.

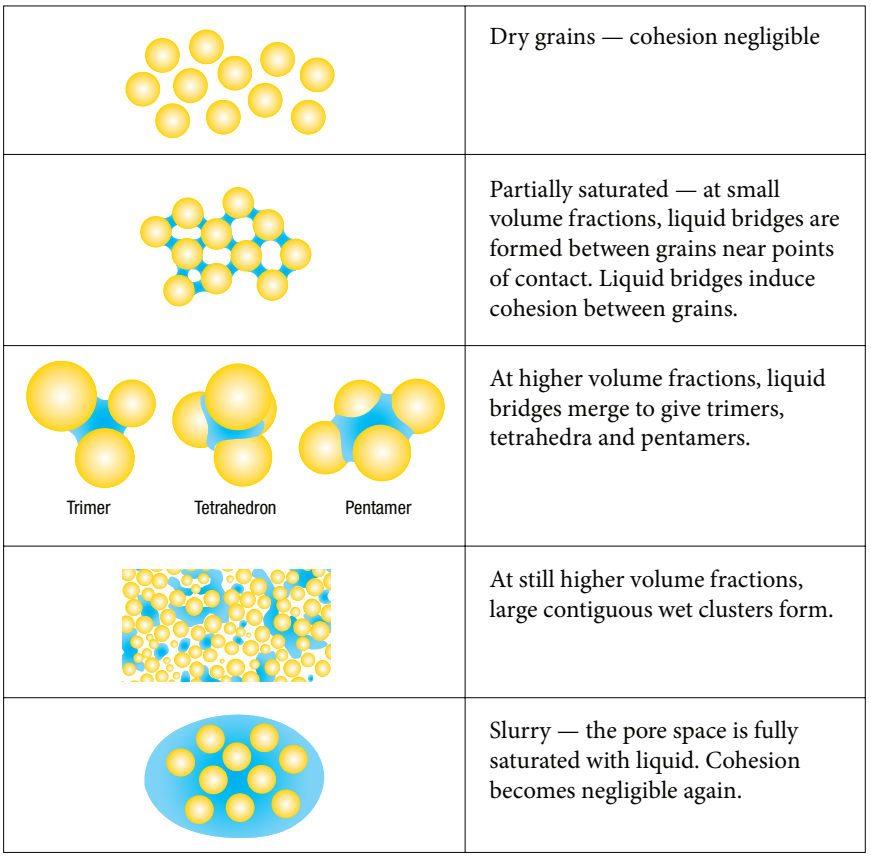


**Figure 2** Schematic diagrams showing the differing degrees of wetting in granular matter. Dry grains and a fully saturated system have no cohesion between particles. In between these states, cohesive forces are present between grains.

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