In addition to the enhanced three-photon cross-section, the Mn-doped quantum dots can be encapsulated in phospholipid shells, which allows them to be conjugated to targeting agents. The optical signal from the quantum dots identified the location of the targeting agent, and subsequently the cell receptors. Hyeon and co-workers demonstrate that a LyP-1 peptide coated onto the surface of the quantum dots could target the p32 receptors on MDA-MB-435 tumour cells in culture, and further show the targeting of $\alpha_v\beta_3$ receptors on tumour vascular cells in a xenograft mouse model by a surface-immobilized RGD peptide. These quantum dots are less toxic in culture in comparison with ZnS-capped CdSe, and CdSe quantum dots because a higher dose of Mn-doped quantum dots was required to kill the cells. Histopathology findings combined with liver and kidney biomarker analysis showed no *in vivo* toxicity after the injection of 100 μl of 40 nmol Mn-doped ZnS quantum dots. The results clearly show that these quantum dots are biocompatible, can be conjugated to targeting agents and are safer than Cd-based quantum dots.

Optical microscopy techniques are the dominant imaging modality for analysing cells and tissues *in vitro*. For *in vivo* clinical applications, however, optical imaging techniques are minimally used because of limited penetration depth and poor signal-to-noise ratio (Fig. 2). Many diseased tissues are typically deeper than 3 mm and therefore, there is a need to further improve the design of probes and instruments for this imaging modality to compete in clinical applications. One advantage of optical imaging over other imaging techniques is the ability to detect the molecular heterogeneity of diseases. Bioengineers are using various molecular biology techniques to identify homing molecules to target contrast agents and therapeutics to diseased tissues based on the unique receptor expression profiles[10]. By using multiple labels on different receptors, one could envisage the colour coding of diseases, which cannot be achieved by using magnetic or radio imaging. Apart from improving the optical imaging depth, there is also a need to enhance the delivery efficiency of nanoparticles to the diseased site and to engineer them to be eliminated from the body to mitigate the issues of long-term toxicity through repeated dosing[15]. Although optical imaging is an excellent technique for use in research, significant effort is required to advance this imaging modality for routine patient care and diagnostics. ❐

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GRANULAR MATERIALS

Highly evolved grains

By efficiently exploring the huge variety of possible grain shapes, computer algorithms that mimic evolution make possible the design of grains that pack into configurations with the desired mechanical or structural properties.

Corey S. O'Hern and Mark D. Shattuck

Biological systems are highly optimized through genetic mutation, reproduction and evolution. For example, the interactions between amino acid side-chains have been exquisitely fine tuned so that proteins can reliably fold and bind within cells to orchestrate all of the necessary cellular functions. Can such an optimization process be applied to designing robust, more energy-efficient and less-costly materials? The task is daunting. For each material, there are a vast number of possible combinations of microstructural variables, and the complex relationship between microstructure and bulk properties is in most cases not known. Therefore, traditional approaches to materials design are often trial-and-error combinatorial searches through high-dimensional parameter spaces.

Algorithms based on evolution — such as genetic algorithms — show great promise in solving such problems[1], where the complex relationships between the myriad microscale variables and the properties to be optimized are not known *a priori*. Reporting in *Nature Materials*, Marc Miskin and Heinrich Jaeger employed a genetic algorithm to optimize the mechanical properties of granular materials[2]. Granular media are ubiquitous in nature and industrial contexts; examples include the Earth's crust, pharmaceutical powders and agricultural products. Granular media are also used in composite materials to enhance strength, as in concrete, or acoustic properties, as in phononic metamaterials[3,4]. They are far-from-equilibrium systems, as they are too large to experience thermal fluctuations and thus must be externally driven to induce particle motion. Also, because traditional approaches based on statistical mechanics often fail to describe them, the design of granular materials poses particular difficulties.

Miskin and Jaeger sought to maximize the strength (elastic modulus) of static granular packings as a function of the possible shapes of the constituent grains. The researchers considered composite grains formed from two to five equal-sized spherical particles that can be rigidly connected into all possible non-branched shapes. Their genetic algorithm is able to efficiently identify the particle shapes that give rise to the stiffest (a compact shape) and softest (rod-like shape) packings (Fig. 1). Moreover, the authors used their algorithm to search for particle shapes

whose packings stiffen under strain by finding the maximum in the second derivative of the stress with respect to strain. They found that packings of grains with wishbone shapes indeed stiffen following a concave-up stress–strain curve, and possess failure stresses that are more than a factor of three larger than those for spherical grains. They also verified the predictions using triaxial tests on assemblies of three-dimensional-printed plastic particles.

Although the researchers maximized a single property (strength) as a function of one set of variables (describing particle shape), there are many other relevant properties of granular assemblies — such as the density and shear modulus — that can be optimized as a function of numerous additional parameters, including interparticle forces (friction and adhesion) and the packing-generation protocol (compression, shear and vibration).

To further emphasize the utility of evolutionary techniques for computational granular-materials design, we applied genetic algorithms to the long-standing open problem of identifying the most dilute jammed packings of spherical particles. Although dilute packings can be created by a method that involves removing particles from periodic assemblies, this technique cannot generate amorphous dilute packings[5]. Indeed, a dilution of the triangular lattice in two dimensions (Fig. 2a, left) yields the mechanically stable snub-hexagonal lattice (Fig. 2a, middle). Packing-generation methods that integrate Newton's equations of motion during compression of the system, such as the Lubachevsky–Stillinger algorithm[6], typically generate random close-packed configurations[7] (Fig. 2a, right), not dilute packings. In contrast, the genetic algorithms of Miskin and Jaeger applied to systems composed of bidisperse disks preferentially generate amorphous packings (Fig. 2b, left) that are significantly more dilute than those produced by the Lubachevsky–Stillinger algorithm (Fig. 2b, middle). Indeed, for the genetic algorithm the peak in the probability $P(\phi)$ of finding mechanically stable packings at packing fraction ϕ is shifted to significantly more dilute values (Fig. 2b, right).

The examples of granular-materials design provided by Miskin and Jaeger and those presented here illustrate that genetic and other adaptive search algorithms are powerful computational tools for developing novel materials with particular structural and mechanical properties. We advocate expanding the use of such algorithms to a broad range of materials-design problems, including the optimization of the glass-forming ability in bulk metallic glasses, the discovery of new crystalline structures in multicomponent alloys, and the design of cellular materials with tunable optical and transport properties. ❐

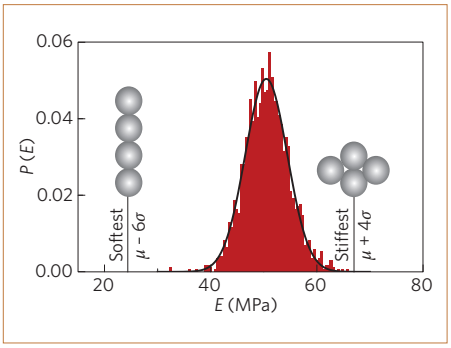

Figure 1 | Histogram of the elastic moduli of static granular packings composed of grain shapes each made of four identical spheres[2]. The softest and stiffest packings are made from rod-like and compact shapes, respectively. Whereas a random search to discover these two shapes would take roughly 500,000,000 (for the softest) and 15,000 (for the stiffest) guesses, the evolutionary approach of Miskin and Jaeger[2] needed only approximately 600. The line is a fit to a Gaussian curve with mean $\mu = 50$ MPa and standard deviation $\sigma = 4$ MPa.

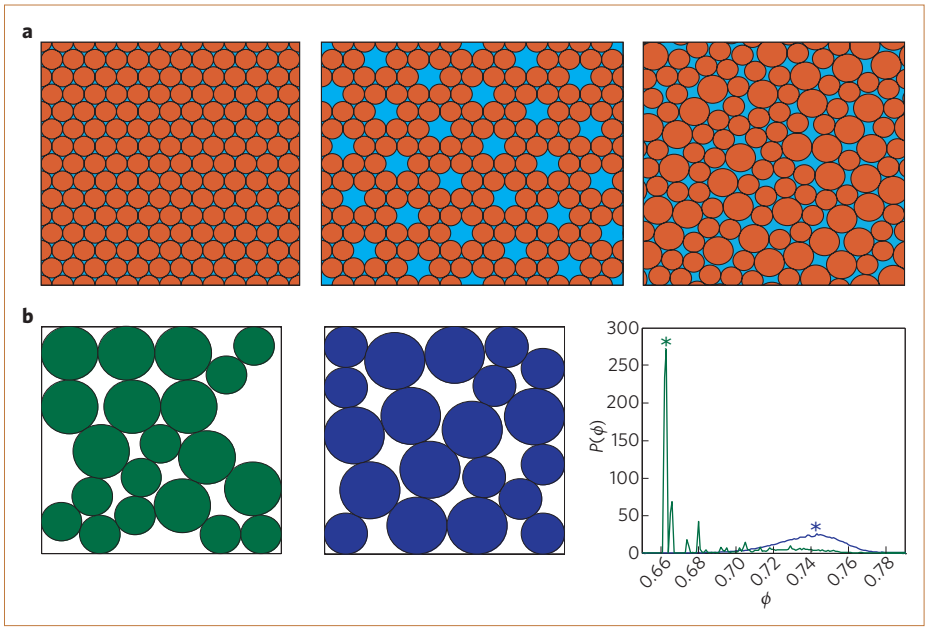

Figure 2 | Examples of mechanically stable packings of hard disks. **a**, 168 equal-sized disks on a hexagonal lattice at a packing fraction of $\phi \approx 0.907$ (left), and on a snub-hexagonal lattice with $\phi \approx 0.777$ (middle). The right panel shows 120 bidisperse disks (50:50 mixture with a diameter ratio of 1.4) at random close-packing with $\phi \approx 0.840$. **b**, Left: a dilute, amorphous configuration of 20 bidisperse disks at $\phi \approx 0.663$ generated using the genetic algorithm of Miskin and Jaeger[2]. Middle: most probable configuration of 20 bidisperse disks with $\phi \approx 0.742$ generated using the Lubachevsky–Stillinger compression algorithm. Right: comparison of the probability distribution, $P(\phi)$, normalized so that the areas under the curves are equal to 1, of finding mechanically stable particle assemblies at packing fraction ϕ using the genetic algorithm of Miskin and Jaeger[2] (green) and the Lubachevsky–Stillinger compression algorithm[6] (blue). The asterisks indicate the probabilities corresponding to the configurations in the left and middle panels. In the limit of a large system, the peak in $P(\phi)$ for the Lubachevsky–Stillinger algorithm (blue) shifts to $\phi \approx 0.840$ (ref. 8).

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