purified c-subunits studied *in vitro*, whereas bedaquiline's affinity is a million times higher (in the nanomolar range) when tested in *M. tuberculosis* cells[4]. A previous structural study[12] of the c-ring, using X-ray crystallography, suggested that one bedaquiline molecule binds to each of the nine c-subunits, and identified key features of the binding interaction that the drug makes with the c-ring's proton-binding sites.

By contrast, Guo and colleagues revealed (Fig. 1) seven bedaquiline molecules bound to seven of the nine c-subunits; the other two potential c-subunit binding sites were obstructed by the adjacent a-subunit. Five of the bedaquiline molecules were bound to c-subunits (at 'c-only' sites) in the same type of binding as previously revealed by X-ray analysis[12], whereas the other two sites in c-subunits that bound to bedaquiline had further interactions with subunit a. Designated as leading and lagging sites, respectively, these two sites are located in c-subunits that, in the absence of a drug to hinder enzyme function, would have either just picked up a proton in the proton-entry channel of the c-ring (the leading site) or just deposited a proton in the proton-exit channel of the c-ring (the lagging site).

When the authors washed the complex to remove the drug, bedaquiline disappeared from the images of the five c-only sites but remained clearly visible in the leading site, with some also remaining in the lagging site. The reason for this became clear when the authors looked at where the drug interacted with the protein: the leading site was created by large movements of specific amino-acid residues in the c- and a-subunits that formed a deeper and more extensive binding pocket for the drug compared with that of the c-only binding site. This difference provides a probable explanation for the striking difference between the drug's potency *in vitro* and *in vivo*. By binding particularly tightly to the leading and lagging sites that are created as the c-ring rotates, bedaquiline jams the rotation of the ring, thereby blocking proton transport and halting ATP synthesis.

It is unsurprising that a binding site's location with regard to the peripheral stalk should affect the possible conformations at that site, but it is nonetheless beautiful to actually observe the difference it makes to drug binding. The structural details of the leading-site pocket offer information for researchers wanting to develop an improved version of bedaquiline. But most of us will be riveted by the movies made possible by cryo-electron microscopy, showing ATP synthase at work. It highlights exactly how complex this machine — the basis of almost all life — actually is, while simultaneously revealing a vulnerability that bedaquiline exploits. The 2017 Nobel committee recognized how crucial it is to be able to visualize biochemical processes in three dimensions; we hope they are proudly watching the movies in this paper.

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Computational materials science

# The complexity of dense amorphous silicon

**Paul F. McMillan**

Transitions between amorphous forms of solids and liquids are difficult to study. Machine learning has now provided fresh insight into pressure-induced transformations of amorphous silicon, opening the way to studies of other systems. **See p.59**

Machine-learning approaches are being developed to produce accurate simulations of the structure and chemical bonding of disordered solids and liquids, modelling a sufficient number of atoms to enable direct comparison with experimental data. On page 59, Deringer *et al.*[1] report their use of this approach to probe the structure of amorphous silicon under compression, as the element transforms from semiconducting to metallic states. Their work demonstrates that the structural transformations of amorphous forms of materials can take place much more gradually than those between crystalline phases, and can involve the formation of nanostructured domains and localized atomic arrangements that are not found in any of the crystalline states.

Silicon is one of a small class of elements whose density increases on melting[2]. This unusual behaviour is shared with crystalline ice, which floats on top of liquid water. Such unexpected reversal of solid and liquid densities has been linked to a phenomenon called polyamorphism — the ability of a substance to exist as different amorphous phases that have distinct structures and properties.

Liquid silicon is a metallic electrical conductor, whereas solid silicon is a semiconductor in ambient conditions, a fact that underpins its use in technologies ranging from computer chips to solar panels. The solid can adopt either a crystalline or a structurally disordered amorphous form at room temperature and pressure; in both cases, each atom bonds to four others in a tetrahedral arrangement. However, both the crystalline and amorphous solids transform into denser structures under compression, a process that is accompanied by a transition to metallic conducting behaviour.

In the 1970s, calorimetric experiments were carried out to study the energy changes that accompany the transformations between amorphous and crystalline forms of silicon during heating and cooling[3]. Analysis of the results suggested that two amorphous forms of silicon exist, with a phase transition between them. Simulations have since suggested that silicon transforms from a low-density amorphous (LDA) phase, in which the coordination number — the number of neighbouring atoms around each silicon atom — is four, to a high-density amorphous (HDA) phase whose structure is similar to that of metallic liquid silicon[3,4]. The LDA–HDA transition has been observed both during rapid heating of the amorphous solid and on compression of amorphous silicon at ambient temperature[5–7].

Structural transformations between crystalline phases of silicon are readily observed using diffraction methods[8], but those involving the amorphous state are more difficult to study because they occur less abruptly as

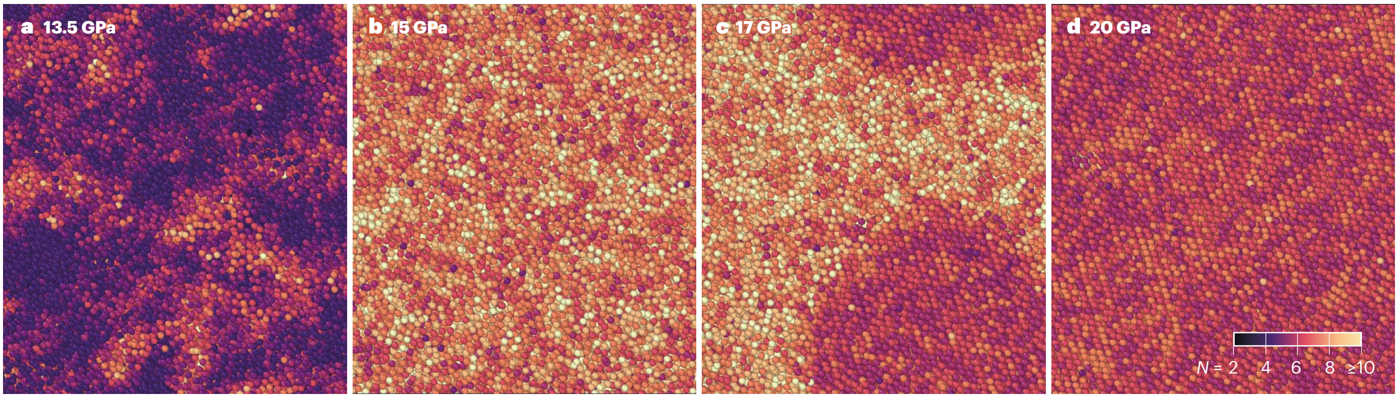

**Figure 1 | Large-scale simulations of amorphous silicon.** Deringer *et al.*[1] used machine learning to simulate a system of 100,000 silicon atoms at increasing pressures and at 500 kelvin, to predict the resulting changes in structure and properties of the element. The colour of each atom indicates the number of other atoms bonded to it (the coordination number, *N*). The coordination number is four at ambient pressure. **a**, At 13.5 gigapascals, most atoms still have a coordination number of four, corresponding to a low-density semiconducting phase of silicon, but high-density regions of atoms with higher coordination numbers and metal-like conductivity have appeared. **b**, At 15 GPa, these regions predominate, and have coalesced to form a high-density metallic phase. **c**, At 17 GPa, domains of a new, very-high-density amorphous phase have started to form within the material. **d**, At 20 GPa, the amorphous structure has rapidly equilibrated to produce a crystalline metallic phase that has a simple hexagonal structure. (Images from Extended Data Fig. 4 of ref. 1.)

density increases. This is where computational simulations come into play: they can visualize the arrangements of atoms in different phases, and predict and explain the resulting properties. The main challenge is always to model enough atoms to enable the comparison of simulation results with macroscopic data for real samples, while maintaining sufficient accuracy to describe the arrangements and bonding of the atoms.

Computational simulations are also limited by their characteristic timescales when studying phase transitions. Currently available computational resources often restrict simulations based on accurate quantum-mechanical calculations to systems that incorporate a few tens to hundreds of atoms, which are typically examined over timescales of up to several femtoseconds (1 femtosecond is $10^{-15}$ s). Simulations that use less computationally demanding modelling strategies can be extended to several hundreds or a few thousands of atoms. However, the accuracy of the predictions of the structural and physical properties of the material being investigated is sacrificed as the system size increases, or as the simulation time is extended.

Deringer *et al.* now describe a machine-learning approach that gives unprecedented levels of information about the structure and bonding energetics for a system of 100,000 silicon atoms as it is cooled from the liquid state and compressed to pressures up to 200,000 atmospheres (20 gigapascals). This represents a great increase in the number of atoms that can be modelled (see Extended Data Fig. 1 of the paper[1]). The accuracy of the method approaches those of the best simulations carried out from first principles using quantum-mechanical calculations.

Crucially, the modelled system was large enough to reveal the metastable aggregation of amorphous clusters of atoms. The simulations also uncovered crystallization phenomena that could not be observed using simulations with smaller numbers of atoms, or by using less-accurate models to describe the atomic interactions. The findings closely reproduce the temperatures and pressures observed experimentally for the macroscopic melting of silicon, for the other phase transitions, and for the onset of metallic behaviour.

The simulations show that the structural changes that occur on compression are more complex than was previously realized (Fig. 1). The atoms do not transform simultaneously between an arrangement with a coordination number of four to a phase that has a higher coordination number, as occurs in transitions between crystalline phases of silicon[8]. Instead, the amorphous structure evolves more gradually to produce high-density nanoscale domains of high coordination number, which develop within the original tetrahedral LDA structure. Linkages form between the HDA domains as the density increases, producing a material that exhibits bulk metallic conduction. It might be possible to modify this metallic conductivity in the real world by applying directionally oriented stresses to compressed silicon.

> **“The structural changes that occur on compression are more complex than was previously realized.”**

The authors' simulations also show that, as the system is compressed further, it quickly collapses by about 25% of its volume, thus producing a very-high-density metallic state. This crystallizes rapidly on the nanosecond timescale of the simulations, to form nanodomains of a metallic phase of silicon.

The results have implications for our understanding of how polyamorphic transitions might emerge between different liquid phases and glassy structures more generally[9]. Deringer and colleagues' machine-learning approach has allowed them to accurately simulate amorphous silicon structures on a picosecond timescale (1 picosecond is $10^{-12}$ s), and over temperature and pressure ranges that are relevant to transitions between liquids and crystal phases, between liquids and glasses, and between two amorphous phases. Their findings therefore offer the chance to study transitions of a wide array of amorphous materials that have previously been difficult to probe.

The authors' approach could also now be used to explore the possibilities of transforming amorphous silicon, or 'doped' materials in which silicon contains small amounts of other elements, to produce nanostructures that contain metallic and semiconducting domains. Such nanostructures could open up many opportunities for developing new technology, such as in electronic communication, data processing and energy harvesting.

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