

The authors overcame these experimental challenges and uncovered crucial evidence that confirms the high-temperature superconductivity in lanthanum hydride compounds. To verify that a material is superconducting, researchers typically look for three features: zero electrical resistance; a reduction in the critical temperature under an applied magnetic field; and an expulsion of magnetic fields from the interior of the material on cooling (a phenomenon known as the Meissner effect). Drozdov *et al.* detected the first two of these signatures of superconductivity. The final criterion — observation of the Meissner effect — is currently unattainable because the samples are too small.

The search for high-temperature superconductivity in hydrogen-rich compounds can be linked to predictions¹¹ made in 2004. The reasoning behind these predictions hinges on a theory that forecasts that, under certain circumstances, elements that have low atomic masses can contribute to high critical temperatures. Hydrogen, being the lightest element, is optimal for high critical temperatures. And, by this logic, replacing hydrogen with the heavier isotope deuterium should lower the critical temperature. Drozdov *et al.* observed this isotope effect and found that, compared with the lanthanum hydride samples, the critical temperature in lanthanum deuteride samples is lower by almost exactly the amount predicted by the theory.

From a scientific standpoint, these results suggest that we might be entering a transition from discovering superconductors by empirical rules, intuition or luck to being guided by concrete theoretical predictions. The superconducting critical temperature has long been considered to be one of the most difficult properties to compute accurately. But the hydrogen sulfide and lanthanum hydride experiments were motivated by computational results that anticipated both the necessary pressures and the resulting critical temperatures^{9,12}. These remarkable successes for theory seem to be driven by innovative computational methods that were enabled by advances in computing power.

What is the practical importance of superconductivity in materials synthesized in minuscule quantities at more than one million times atmospheric pressure? The answer depends on whether the superconducting states can be recovered at ambient pressure. Diamond itself is an example of a material that forms at high pressure but is metastable at ambient pressure. The effort to manufacture synthetic diamond provided substantial motivation for the development of high-pressure methods. Today, however, synthetic diamonds are grown using a low-pressure technique called chemical-vapour deposition. Optimistically, it might eventually be possible to use similar low-pressure methods to produce metastable superconducting compounds that are initially discovered at high pressure.

In the next few years, experiments will probably focus on searching for superconductivity in other pressurized hydrogen-rich materials. Given that only a small fraction of possible hydrogen-rich systems have been subjected to experiments at these tremendous pressures, it seems more likely than ever that the dream of room-temperature superconductivity might be realized in the near future. At that point, the grand challenge will shift from pushing the necessary temperatures higher to pushing the required pressures lower. ■

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SYNTHETIC BIOLOGY

Genome construction amends building codes

The biggest synthetic genome so far has been made, with a smaller set of amino-acid-encoding codons than usual — raising the prospect of encoding proteins that contain unnatural amino-acid residues. SEE ARTICLE P.514

BENJAMIN A. BLOUNT & TOM ELLIS

Over the past decade, decreases in the costs of chemically synthesizing DNA and improved methods for assembling DNA fragments have enabled researchers to scale up synthetic biology to the level of generating entire chromosomes and genomes. So far, synthetic DNA has been constructed with up to one million base pairs, notably a set of chromosomes from the yeast *Saccharomyces cerevisiae* and several versions of the genome of the bacterium *Mycoplasma mycoides*^{1,2}. Now, on page 514, Fredens *et al.*³ report the completion of a 4-million-base-pair synthetic version of the *Escherichia coli* genome. This is a landmark in the emerging field of synthetic genomics, and finally applies the technology to the laboratory's workhorse bacterium.

Synthetic genomics offers a new way of understanding the rules of life, while at the same time moving synthetic biology towards a future in which genomes can be written to design. The pioneers in the field — the researchers at the J. Craig Venter Institute in Rockville, Maryland — have used this method to better define the minimal set of genes required for a free-living cell. By adopting an approach that involves redesigning genome segments by computer, chemically synthesizing the fragments and then assembling them, these pioneers succeeded² in reducing the size of the *M. mycoides* genome by around 50%. Doing the

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same with just genome-editing tools would be much more laborious, as past work with *E. coli* demonstrates: here, gene-deletion methods have removed, at best, only 15% of the genome⁴.

Fredens and colleagues used this reduced genome from *E. coli* as the template for a synthetic genome with another kind of minimization in mind — codon reduction. The genetic code has inherent redundancy: there are 64 codons (triplets of 'letters', or bases) to encode just 20 amino acids plus the 'start' and 'stop' points that mark the beginning and end of a stretch of protein-coding sequence. This redundancy means, for example, that there are six codons that encode the amino acid serine, and three possible stop codons. Through design, synthesis and assembly, Fredens *et al.*³ have been able to construct an *E. coli* genome that uses only 61 of the 64 available codons in its protein-coding sequences, replacing two serine codons and one stop codon with synonyms (codons that are 'spelt' differently but give the same instruction). Past work using genome-editing tools has already produced a synthetic *E. coli* that uses just 63 of the 64 codons, but this required only the stop codons with the sequence TAG (of which there were just 321 around the genome) to be changed to an alternative stop codon⁵. Reduction to 61 codons demanded that a whopping 18,214 codons be changed, necessitating a genome-synthesis approach.

Fredens and colleagues built their synthetic

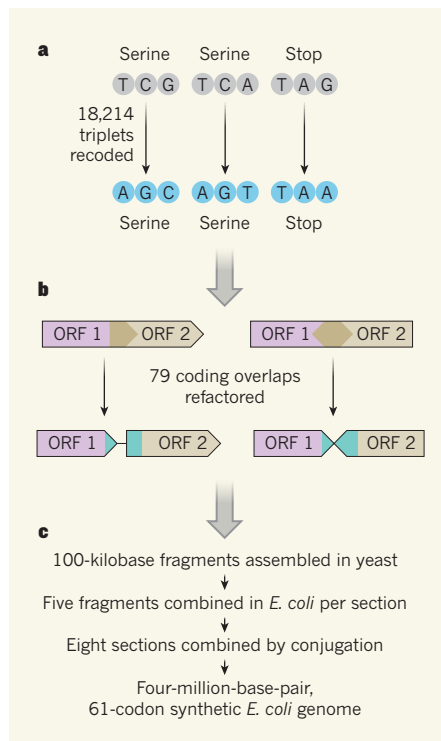


Figure 1 | Design and construction of a recoded genome. **a**, Fredens *et al.*³ recoded three base triplets (codons) — TCG and TCA, which encode the amino acid serine, and TAG, a stop codon that marks the end of a protein-coding sequence — to alternatives that have the same functions (AGC, AGT and TAA respectively) in the genome of the bacterium *Escherichia coli*. **b**, In some genomic locations, open reading frames (ORFs; protein-coding regions) overlap, and a change in the codons of one ORF might produce an unwanted change in the overlapping region. Fredens *et al.* ‘refactored’ these ORFs to separate them, as illustrated for ORF1 and ORF2 (the two ORFs on the left are ‘read’ in the same direction; the two on the right are read in opposite directions). **c**, Redesigned DNA was synthesized and assembled into 100-kilobase fragments in the yeast *Saccharomyces cerevisiae*; fragments were then combined into sections and integrated into the *E. coli* genome. The sections were brought together to generate the complete functional synthetic genome.

E. coli genome by using large-scale DNA-assembly and genome-integration methods that they had developed previously⁶ to probe the limits of codon changes in *E. coli*. In their approach (Fig. 1), DNA is computationally designed, chemically synthesized and assembled in 100-kilobase fragments in vectors in *S. cerevisiae*; these vectors are then taken up by *E. coli* and integrated into the genome in the direct place of the equivalent natural region. Iterating this process five times resulted in 500-kilobase sections of DNA being replaced by synthetic versions. Eight strains of *E. coli* were produced in this way, each harbouring synthetic DNA sections that covered a different region of the genome. These sections were then combined using conjugation methods to

make the complete synthetic genome.

The large-scale construction was impressively successful, with very low off-target mutation rates, but was not without its challenges. Many genes in the *E. coli* genome partially overlap with others, and in 91 cases the overlapping regions contained codons that needed to be changed. This is complex because synonymous alterations in one protein-coding sequence might alter the amino acids encoded by the overlapping one. To tackle this, the team ‘refactored’ 79 locations in the genome, duplicating the sequence to separate out overlapped coding sequences into individual recoded ones (Fig. 1). Although this approach was generally successful, it did require careful debugging in a few cases in which refactoring also altered gene regulation.

The final strain proved viable and was able to grow in a range of typical laboratory conditions, albeit a little less vigorously than its natural counterpart. It no longer uses the stop codon TAG or the two serine codons TCG and TCA, so the cellular machinery that recognizes these can now be either deleted or reassigned to recruit ‘non-canonical’ amino acids beyond the usual 20 used by most living cells. Such recruitment has already been shown to be useful in the 63-codon *E. coli*, both for biotechnology projects, in which non-canonical amino acids are encoded into desired sequence positions to provide residues that can take part in chemical reactions that natural proteins can’t; and for biosafety reasons, in that the natural transfer of readable DNA-encoded information in and out of the synthetic *E. coli* is limited because the cell operates with a slightly different genetic code from the rest of the natural world⁵. Expect all of these applications to be expanded in the new 61-codon *E. coli*, which has the potential to encode the use of more than one non-canonical amino acid, and to generate a more stringent genetic firewall (because 3 of the 64 codons are no longer recognized).

Synthesis of a 4-million-base-pair genome and reduction of the genetic code to 61 codons are new records for synthetic genomics, but might not be for much longer. The international Sc2.0 consortium is closing in on synthesizing all 16 chromosomes of the 12-million-base-pair *S. cerevisiae* genome — the first synthetic genome of a eukaryotic organism, the group that includes plants, animals and fungi — and the synthesis of a 57-codon *E. coli* genome is also under way^{1,7}. A genome of the bacterium *Salmonella* Typhimurium that has two fewer codons than the natural organism is also being constructed⁸. This could one day enable bacteria with synthetic genomes to be used as cell-based technologies in the human gut.

From a technological standpoint, the most interesting aspect of all these different projects is that the workflows for synthetic-genome construction are remarkably similar, with kilobase sections of synthesized DNA being assembled (by the process of homologous



50 Years Ago

More than a hundred hearts have been transplanted in the 18 months since Dr C. N. Barnard first undertook the operation. The largest single group — fifteen operations — has been performed at the Texas Heart Institute by Dr Denton A. Cooley and his colleagues. The summary of their experience is that ... a heart transplant improves the quality of, but does not greatly prolong, the life of the average recipient. But length and quality of survival are directly related to closeness of histocompatibility between donor and recipient, a factor on which future operations should be made to depend. Cooley and colleagues report that the mean survival time of their fifteen transplant patients is 111 days compared with the 74 days lived by patients marked as potential recipients but for whom no donor became available.

From *Nature* 24 May 1969

100 Years Ago

A correspondent forwards us a newspaper cutting from South Africa directing attention to the possibilities of the prickly pear (*Opuntia* spp.) as a source of industrial alcohol ... The plant in question covers thousands of acres of good soil in South Africa, and is a pest to farmers ... It may be remarked that the question of producing alcohol from the prickly pear has been carefully studied in Australia; the conclusion drawn, however, was unfavourable ... Distillation experiments yielded alcohol equivalent to only 0.5 per cent of the weight of the plant used, so that the manufacture was considered unprofitable, and, indeed, scarcely practicable. But the South African prickly pear is said to be much richer in sugar ... and this, of course, may make all the difference between success and failure in utilising the plant.

From *Nature* 23 May 1919

recombination) into 50- to 100-kilobase pieces in yeast cells, and these pieces then being used to replace natural sequences inside the target organism (by selectable recombination methods). Standardization of methods will enable steps to be automated and more research groups to enter the field. Genome minimization and codon reduction are just the first uses of this new technology, which could one day give us functionally reorganized genomes and

genomes that are custom designed to direct cells to perform specialized tasks. ■

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ATOMIC PHYSICS

Quantum gases show flashes of a supersolid

Supersolids are highly sought-after structures whose atoms can simultaneously support frictionless flow and form a crystal. Hallmarks of a supersolid have now been observed in three experiments that involve quantum gases of dipolar atoms.

LODE POLLET

Sixty years ago, the theoretical physicist Eugene Gross suggested that a substance could have properties of both a solid and a liquid at the same time, provided that the liquid is a superfluid¹. A superfluid is a state of matter that can flow without friction and is known to exist^{2,3} in helium-4 at temperatures below 2 kelvin. Gross's putative substance was called a supersolid. But despite this theoretical simplicity, supersolids in the purest sense of the term have evaded experimental detection⁴. Now, Tanzi *et al.*⁵, writing in *Physical Review Letters*, and Böttcher *et al.*⁶ and Chomaz *et al.*⁷, writing in *Physical Review X*, report transient signatures of supersolidity in quantum gases of atoms that have strong magnetic dipole moments.

In Gross's proposal, a supersolid is pictured as the superposition of a liquid and a periodic density variation. In other words, a supersolid comprises liquid droplets that consist of many atoms and that form a periodic structure (Fig. 1). Each droplet can be described by its number of atoms and a property known as a quantum-mechanical phase. In a supersolid, unlike in an ordinary solid, each droplet retains the same phase. Such phase rigidity requires the exchange of atoms between the droplets and is possible only if the droplets are sufficiently close to each other.

Historically, supersolidity was sought in solid helium-4 using an apparently different, but formally equivalent, concept⁸. In this picture, a supersolid is a mostly crystalline substance in which certain defects enable a flow of adjacent atoms, which in turn sets the neighbours of these atoms in motion. This process continues until the whole crystal develops a fluid component. Despite some

initial excitement^{9,10}, pure supersolidity is not observed in solid helium-4. However, in this substance, related phenomena such as giant quantum plasticity¹¹ are measurable and there is mounting evidence of frictionless flow along line-type defects¹² called dislocations, as was first proposed by theorists¹³.

Over the past decade, cold-atom systems have shifted the focus back to Gross's picture, because of the controllability and lack of defects and impurities in these systems. When atoms are cooled to temperatures near 0 K, they can form a state of matter called a Bose–Einstein condensate, which gives rise to frictionless flow. The difficulty in producing a supersolid then lies in imposing a periodic

density variation that is set by the intrinsic interactions of atoms in these extremely dilute systems. This imposition takes place through a mechanism known as roton softening.

A roton is a minimum in the energy–momentum spectrum of a superfluid's excitations. This minimum is located at a value of the momentum that is equal to the inverse of the average spacing between atoms. When the energy of the roton hits zero, the superfluid becomes unstable and forms a structure that has a periodic density variation. This structure could be, for instance, a supersolid or an ordinary solid. By contrast, alternative approaches for observing signatures of supersolidity have depended on external perturbations from lasers^{14–16}, rather than intrinsic properties of the system.

In the current experiments, Tanzi *et al.* and Böttcher *et al.* used dysprosium-162 atoms, whereas Chomaz *et al.* used dysprosium-164 and erbium-166 atoms. All of these atoms have intrinsically strong magnetic dipole moments. The interactions of these atoms have the theoretically required ingredients for supersolidity: a repulsive, tunable short-range (contact) component and an attractive, long-range (dipolar) component. Previously, some of the authors of the Böttcher *et al.* paper and their colleagues succeeded in producing

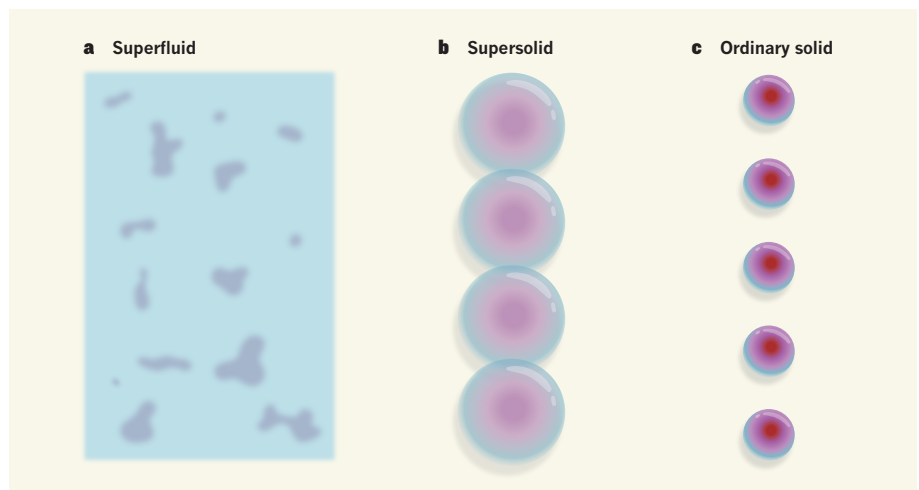


Figure 1 | Density distributions of three states of matter. a, A superfluid is a substance that can flow without friction. The density of a superfluid is uniform, apart from small fluctuations (as shown in this snapshot). b, Three papers^{5–7} report experimental evidence for a supersolid — a spatially ordered material that has superfluid properties. A supersolid comprises droplets that contain many atoms and that are coupled to each other. c, In these experiments, an ordinary solid consists of isolated droplets. The colours in a–c represent the atomic density from low (light blue) to high (dark red).