example of such a problem is the Hubbard model[6], which is a model of the dynamics of electrons arranged on a periodic lattice. Despite its simplicity and potential for use in a variety of technological applications, the Hubbard model remains a difficult problem in general. Electrons are fermions — particles whose key property is that only one of them can occupy a particular quantum state at any given time. Such behaviour is most efficiently simulated using an analog device, rather than a digital one. It is an exciting prospect for future applications that fermions could be incorporated into Kokail and colleagues' versatile set-up, with the help of a quantum processor containing ultracold fermionic atoms.

In general, large-scale analog quantum simulators could be much more versatile than anticipated on the basis of their behaviour with only a few qubits. This is because quantum many-body systems can behave very differently from few-body ones. For instance, in high-energy physics, the 'empty' vacuum is already a complex quantum system that requires a huge number of qubits to simulate it. However, only a small subset of the microscopic details of the underlying theory is relevant for the computation of measurable physical properties, using a concept known as the renormalization program of quantum field theory[7]. As a result, for an analog quantum simulation of such an underlying theory, many of the detailed properties of the device have no effect on the outcome of the simulation.

An extreme case is when the dynamics of a quantum many-body system becomes fully 'universal'. Here, universality means that certain measurable properties have no dependence on microscopic details. Then, a single analog quantum device could be used to simulate all physical systems that belong to the same universality class, subject only to general requirements such as physical symmetries. This concept is well established for some ground-state or static properties. But universality has now been extended to run analog quantum simulations of dynamical aspects far from the ground state, such as the dynamics of the early Universe, with the help of ultracold atoms[8,9].

As Kokail and colleagues point out, future developments might bridge or even close some of the gaps between the concepts of analog and digital quantum simulation. The authors' work is a key step in that direction. ■

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MOLECULAR ENGINEERING

Protein assembles into Archimedean geometry

A natural protein has been engineered to self-associate into an architecture previously unknown among biological molecules: a cage structure based on one of the classic polyhedra identified by Archimedes. SEE LETTER P.439

TODD O. YEATES

A combination of ideas from geometry, computer science and molecular biology is ushering in a golden age for the design of nanometre-scale materials made from protein building blocks[1]. Naturally occurring cellular and viral structures highlight the diverse architectures that can be formed from protein molecules, and also hint at possible technological applications for designer proteins with predetermined shapes[2]. On page 439, Malay *et al.*[3] report the production of a surprising and extraordinary protein structure: a cage-like architecture composed of 264 protein subunits held together at their edges by gold ions.

Efforts to make geometric protein architectures have generally focused on symmetrical 3D shapes. In particular, the Platonic solids[4] — which include the tetrahedron, cube and icosahedron — have provided strategic design targets owing to their geometric simplicity[5]. These architectures can be realized by arrangements in which multiple protein subunits occupy identical spatial environments in the protein assembly.

Cubes, for example, have been constructed[6–8] from protein trimers (complexes of three identical protein subunits). Each trimer occupies a corner of a cube, so that eight of them are needed to form the complete shape (Fig. 1a). Each subunit in a trimer can contact a subunit from another trimer along one of the edges of the cube. Those contacts are all identical, and hold the assembly together.

All three types of symmetry embodied by the Platonic solids — tetrahedral, octahedral and icosahedral — have been assembled using protein building blocks[6–9]. But the family of Platonic solids consists of just five shapes, which limits the architectures that can be made, and also constrains the geometries of the protein building blocks that can be used to construct them. This raises the question of what other shapes could be constructed using building blocks whose geometries make them unsuitable for making Platonic solids. A membrane-protein assembly described in 2014 showed evidence of unusual possibilities[10].

Enter Malay *et al.*, who started with a naturally occurring protein that forms a ring-shaped assembly containing 11 identical copies of the protein molecule (an undecamer). They engineered the protein's sequence to incorporate a cysteine amino-acid residue, which has a thiol group (SH) in its side chain. The resulting undecamer ring therefore presents 11 thiol groups around its perimeter. Thiol groups can bind to metal atoms, so the perimeter thiol groups allow multiple undecamers to assemble into larger structures through thiol–metal interactions.

Malay and colleagues observed that the undecamers assembled into cage-like structures when mixed with a source of either gold or mercury ions. The authors knew that the 11-fold symmetry of the undecamers was incompatible with the construction of a Platonic solid, but the flexibility and reversibility of metal-mediated interactions could allow a diverse range of other architectures to form[11]. Characterizing the structure was challenging, but the researchers ultimately succeeded in visualizing it in atomic detail using cryo-electron microscopy.

The structure is of a type not seen before in molecular systems: 24 copies of the 11-membered ring are held together by specific interactions between the rings. Malay *et al.* identified the arrangement as a snub cube, which belongs to a group of polyhedra known as Archimedean solids[4]. The vertices in Archimedean solids are all equivalent, but the faces and edges can be of distinct types.

Each vertex in the snub cube is connected by the edges to five other vertices, but — in contrast to the case for Platonic solids — the angles between the connections at a given vertex are not all the same. Instead, one of the angles is larger than the other four (Fig. 1b). Fortuitously for Malay *et al.*, the edges of the snub cube very nearly match up with the alternating 'spokes' that radiate from the centre of an undecagon to its edges. This means that one of the authors' undecamers can be placed at each of the 24 vertices of a snub cube to make

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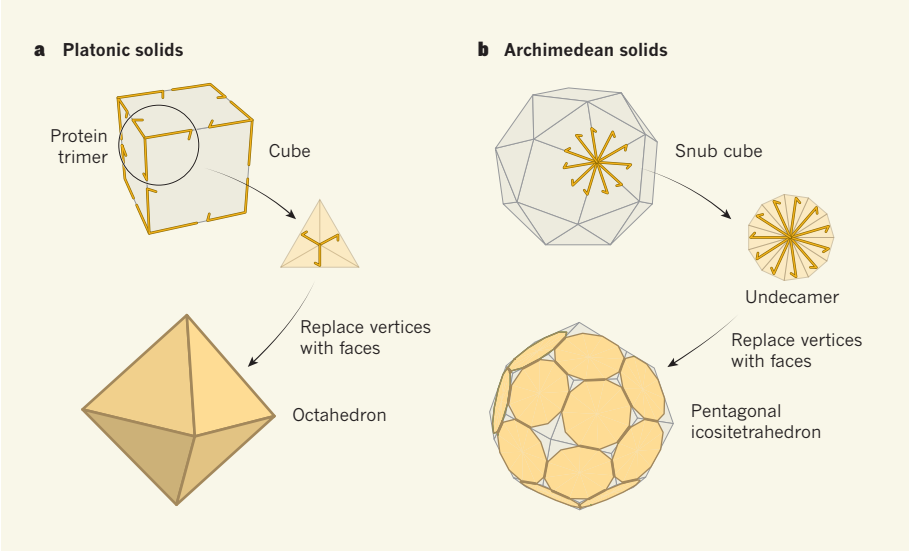

Figure 1 | The assembly of proteins into Platonic and Archimedean geometries. **a**, Platonic solids are a family of symmetrical 3D shapes that includes the cube. To assemble proteins into these shapes, protein multimers (such as trimers, for a cube) can be placed at the vertices. Interactions between multimers along a shape's edges hold the assembly together. Dual shapes form if the vertices are replaced by faces, and vice versa; the dual of a cube is an octahedron. **b**, A snub cube is an Archimedean solid — a polyhedron that has identical vertices but different types of edge and face. Malay *et al.*[3] found that an undecameric protein complex (an assembly formed of 11 identical protein subunits) can be engineered to assemble at the 24 vertices of a snub cube. The connections between subunits are mediated by metal ions along the edges. The resulting protein assembly has the shape of a pentagonal icositetrahedron, which is the dual of the snub cube.

contacts with the other undecamers, thus forming 60 edges.

Only 10 of the 11 thiol groups in any given undecamer participate in metal-mediated connections. This feature arises as a result of using metal ions for assembly: the strategy tolerates the presence of potential sites of attachment that do not actually form interactions through metal ions. This contrasts with design approaches that are based only on direct interactions between protein subunits[6] — the 'sticky' hydrophobic surfaces on proteins that mediate such interactions can lead to random aggregation if they do not interact successfully with other protein subunits.

In the reported snub cube, the 11 subunits in a given undecamer ring occupy different spatial environments and connect differently to neighbouring rings, breaking the symmetry of the system. Symmetry-breaking is also a feature of the architectures of many viral capsids (protein shells). A diverse array of viral capsids can be understood as systems in which a simple icosahedron is elaborated into something more complex, for example by subdividing its triangular faces into smaller triangles[12]. In such systems, large numbers of protein subunits can be tiled onto capsid faces so that there are only modest differences in the angles between them and in the environments they occupy. This 'quasi-equivalence'[12] allows unbroken interactions between subunits to be maintained throughout the capsid, so that an essentially solid shell can be formed.

Malay and colleagues' structure shows that molecular Archimedean architectures break symmetry differently: by not using a subset of potential lateral interactions. The resulting architectures therefore contain sizeable holes (Fig. 1b), which renders them more cage-like than shell-like. Interestingly, holes have previously been observed in other large, artificial protein shells that deviate from quasi-equivalence[13].

The authors' findings suggest an explanation for why (as far as we know) Archimedean protein architectures haven't evolved in nature, for use in cells, for example. The apparently unavoidable openings in such structures might have made them less suitable as enclosures, compared with their quasi-equivalent icosahedral (Platonic) counterparts, which evolved many times in viruses.

The current result was a serendipitous finding, but further studies should address whether similar outcomes can be obtained predictably using other protein building blocks. With this in mind, Malay *et al.* have produced computer models of architectures based on other Archimedean solids (such as the cuboctahedron), which might be constructed using other ring sizes, including 7-, 10- and 16-sided polygons. Success in building those architectures would be another exciting development in the field of designed protein assemblies. ■

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50 Years Ago

As pollution of crops and foodstuffs with pesticides increases, the continued use of persistent chemicals such as the chlorinated hydrocarbons, DDT and dieldrin, is being challenged. In the United States, Michigan and Arizona have already banned the use of DDT … while an organization known as the Environmental Defense Fund is fighting the continued use of the pesticides in a test case against the State of Wisconsin. From the beginning of 1970, DDT will also be banned in Sweden for domestic purposes … In Britain, the use of dieldrin and aldrin on spring sown seed has been banned since 1967, and a working party of the Advisory Committee on Pesticides and Other Toxic Chemicals is now reviewing the use of these pesticides in a wider context.
From *Nature* 17 May 1969

100 Years Ago

A memoir on Mars from the pen of Mr Harold Thomson, president of the British Astronomical Association, appears in *Scientia* for May. Mr Thomson narrates … the facts known about the planet from observation, and takes the very proper view that it is not specially the function of the astronomer to indulge in speculations as to the possibility of inhabitants of other worlds based on such facts, but only to collect them. Nevertheless, he makes the point that the changes in the form of the dark markings and in their positions may represent changes on the surface of the planet which have analogies on our Earth in the destruction of large forest areas, the ploughing up of vast tracts of land, or the changes caused by the operations of husbandry, and this may supply arguments to those who assert the existence of intelligent beings on Mars of as great weight as those furnished by the canals.
From *Nature* 15 May 1919

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DIABETES

A map of β-cell differentiation

The use of stem-cell-derived β-cells to replace those destroyed in pancreatic islets has the potential to cure diabetes. A new analysis provides a deep mechanistic understanding of islet-cell differentiation from stem cells. SEE ARTICLE P.368

FABIAN J. THEIS & HEIKO LICKERT

The islets of Langerhans in the pancreas contain insulin-secreting β-cells and glucagon-secreting α-cells. Insulin and glucagon are hormones that cooperate to regulate the levels of glucose in blood. Destruction or dysfunction of β-cells leads to diabetes. Currently, no treatment can stop diabetes progression and its devastating vascular complications. Islet transplantation can often normalize blood glucose levels for several years and prevent the secondary complications of diabetes. However, organ donors are scarce, and alternative sources of islet cells are urgently needed. Stem-cell-derived cells are promising in this respect. On page 368, Veres *et al.*[1] map the molecular steps in the differentiation of stem cells into islet-like cells. The work will inform future efforts to produce islet cells for transplantation.

Human pluripotent stem cells can indefinitely self-renew and generate every cell type in the body. Therefore, immense efforts are ongoing to develop *in vitro* protocols to produce differentiating islet cells from stem cells[2–5]. An ideal protocol would promote the differentiation of stem cells into fully mature α-cells and β-cells, which would then be isolated, purified and reassembled into islet-like structures for transplantation into patients. To achieve such an ambitious goal, the differentiation programs of all islet cells, and the way in which islets are built, need to be fully understood.

Veres *et al.* assayed more than 100,000 cells at different time points during the differentiation of stem cells into pancreatic progenitor cells and then hormone-producing (endocrine) cells. Single-cell RNA sequencing (scRNA-seq) of cells sampled at every step of the differentiation process, followed by computational analyses, made it possible to identify cell types and to track their lineages through time. The authors therefore produced a fine-grained picture of how pancreatic progenitor cells develop into different lineages of differentiated cells (Fig. 1). Current approaches for producing specific differentiated cells from stem cells have variable efficiency, mostly because of cellular heterogeneity and a lack of knowledge about the molecular signalling factors required for the differentiation process. Therefore, the authors' road map of *in vitro* islet-cell differentiation will inform the development of future differentiation protocols.

Veres and colleagues found that pancreatic progenitor cells can be efficiently differentiated. However, progenitor cells treated with slightly different combinations of signalling factors generated different ratios of hormone-expressing and non-endocrine cell types. This suggests that progenitor specification is key to producing the desired terminally differentiated cell types. In the authors' study, the three most abundant hormone-expressing cell types were stem-cell-derived α-cells (SC-α), β-cells (SC-β) and cells resembling enterochromaffin cells (SC-EC). Enterochromaffin cells are normally present in the intestine and produce serotonin, which contributes to the regulation of intestinal movements and digestion.

Interestingly, SC-β that were differentiated and grown for five weeks in the absence of external signalling factors maintained their defining molecular and functional properties. In particular, these cells showed stable glucose-stimulated insulin secretion throughout that period. This observation indicates that glucose responsiveness is a stable trait of SC-β that requires no exogenous factors, which is relevant if SC-β are to be used for antidiabetic-drug screening in the future.

The authors also observed that cells expressing the two islet hormones — insulin and glucagon — are probably immature SC-α, given that their global gene-expression profile matches that of human islet α-cells. These polyhormonal cells became monohormonal, glucagon-expressing cells after five weeks

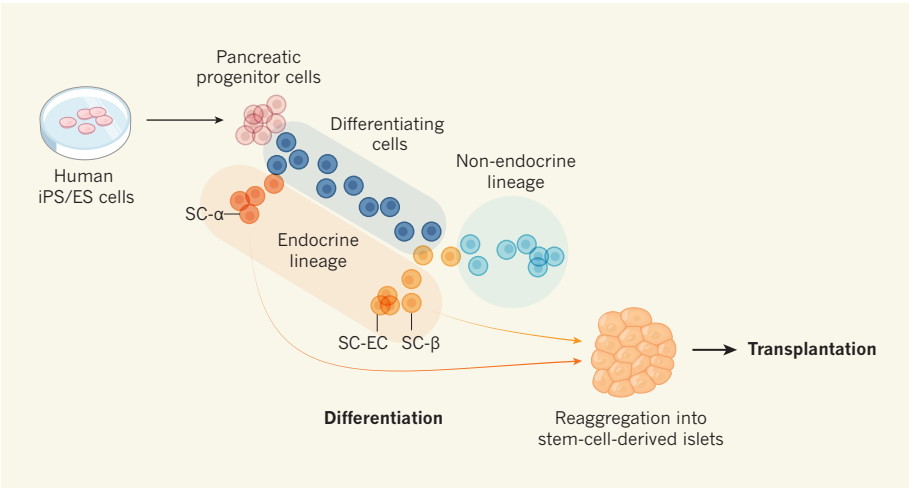

Figure 1 | Differentiation of human pancreatic islet cells *in vitro*. Veres *et al.*[1] studied the differentiation of induced pluripotent stem (iPS) or embryonic stem (ES) cells into: pancreatic progenitor cells; hormone-producing, stem-cell-derived α-cells (SC-α), β-cells (SC-β) and cells resembling enterochromaffin cells (SC-EC); and cells that do not produce hormones (non-endocrine cells). The authors performed detailed single-cell RNA sequencing and computational analysis to identify the cell types that emerged over time, to describe their lineage relationships and to characterize their maturation states. The authors used a concept called pseudotime to define how the gene-expression profiles of the various cell types changed over time. They also developed a purification protocol to increase the number of endocrine progenitor cells and β-cells that is a step forward from previously used protocols[2,3]. This study suggests that SC-α and SC-β can be purified and reaggregated to generate stem-cell-derived islets for cell-replacement therapy.

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