translation systems to decipher the genetic code and establish the standard RNA-codons table[8] (Fig. 1a). In the past fifteen years, a new generation of cell-free expression systems, more versatile and high yielding, has emerged to understand, harness, and expand the capabilities of natural systems. In one example, the PURE technology[9] (protein synthesis using recombinant elements) has been advanced to produce proteins in test tube reactions. This *E. coli*-based reconstituted cell-free protein synthesis system, made of purified molecular components, allows the user to define all of the elements and set their concentrations. Writing in this issue of *Nature Chemistry*[10] Hiroaki Suga and co-workers elegantly re-design the standard genetic code and use the PURE technology to effectively expand the number of different unnatural amino acids that can be directly polymerized into peptides during translation. The redundancy found in the standard genetic code is decreased without removing any of the 20 canonical amino acids. Ultimately this approach could create a dozen 'free' codon boxes that can be reassigned to non-proteinogenic amino acids, although Suga and co-workers have only re-assigned three new codons so far.

To create a customized genetic code, Suga and co-workers first realized that all of the standard amino acids are coded when the third codon base is limited to either C or G (Fig. 1), reducing the number of boxes from 64 to 32. This reduction leaves one stop codon and eleven redundant codons that can be used for new amino acids. As a demonstration of their conceptual framework, three of the eleven free boxes are reallocated to unnatural residues, each replacing one of the redundant valine, arginine and glycine codons (Fig. 1b).

To achieve specific incorporation during translation, the number of required tRNAs, 45 out of 86 *in vivo*, is reduced to 29, enough to cover the twenty natural amino acids, while the three other tRNAs are synthesized with non-proteinogenic amino acids. Using a technique previously developed by the team, the 32 tRNAs are produced using *in vitro* transcription reactions, and then each one is loaded with its specific amino acid using a ribozyme called flexizyme. A messenger RNA that codes for the desired polypeptide sequence is then transcribed *in vitro* and added to cell-free translation machinery containing only the tRNAs necessary to incorporate twenty natural amino acids and three unnatural ones from a catalogue of eight different flavours. Translation of the mRNA then produces the peptide containing the unnatural amino acids at any desired position along the peptide chain (Fig. 1c). The number of unnatural amino acids incorporated into the polypeptide is potentially unlimited — although this requires very efficient rates of incorporation.

A step-by-step demonstration of this approach is provided, supported by biochemical characterizations and validated by mass spectrometry. Transcripts of increasing lengths, incorporating up to four codons for three different unnatural amino acids, are successfully translated *in vitro*, with negligible crosstalk and contamination. Synthetic peptides of up to 32 amino acids are polymerized. A natural anti-cancer macrocyclic peptide, containing five unnatural amino acids, is synthesized by using a modified start codon.

The platform presented by Suga and co-workers represents a tour de force in the construction of tailor-made genetic codes, holding promise to make small peptides with novel functionalities. Indeed, the possibility to produce synthetic peptides incorporating multiple, distinct unnatural amino acids at any position and in unlimited number may allow ribosome repurposing in fundamentally novel ways. This could have profound implications for production, screening, and selection of peptidomimetic, or non-standard peptides as novel drugs. While the system has not yet supported the synthesis of proteins, and the approach would not be easily feasible in cells because one would need to additionally evolve multiple mutually independent aminoacyl tRNA synthetase systems as well as radically recode genomes, the new technology will shed light on which sense codons might be most easily recoded. By testing sense suppression in ways not yet possible in cells, this work will contribute understanding to tRNA decoding, as well as open new coding channels for genetic code expansion. ❑

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OXIDE INTERFACES

Mismatched lattices patched up

Controlling interfaces between transition-metal oxides and dissimilar structures is crucial for practical applications, yet has remained a quandary. Now, a coherent interface that bridges a perovskite and a fluorite structure has been formed using judiciously chosen metal cations.

Kenneth R. Poeppelmeier and James M. Rondinelli

Semiconductor and oxide heterostructures are omnipresent in modern society, as components of a wide variety of devices. A growing challenge for manufacturing layered devices, such as nanocapacitors, light emitting diodes and batteries, is ensuring that heterointerfaces are stable and do not hinder performances — interfacial phenomena are especially important as devices are increasingly being scaled down.

Well-behaved interfaces are achieved by interleaving isostructural components — that is, sharing structurally identical cation and anion sublattices. This maintains lattice coherency without large stresses that may otherwise produce misfit dislocations or form unintended secondary phases. Nonetheless, successful technological materials exhibit a wide range of structure types, inevitably leading to interfaces

between non-isostructural layers within devices. Moreover, a resurgence of interest in non-isostructural complex (multi-cation) oxide interfaces is arising from the substantial recent progress in isostructural perovskite/perovskite interfaces, found to display emergent electronic, ferroic and superconducting behaviour[1,2]. Non-isostructural heterointerfaces may also host exquisite phenomena that remain to be fully exploited[3–5].

The complication that arises at heterointerfaces is that of a 'crystal-structure mismatch'. Now, writing in *Nature Chemistry*[6], Matthew Rosseinsky and colleagues have disclosed how they achieved coherent heteroepitaxy between non-isostructural complex oxides. The researchers formed a transition phase comprising cations of various ionic sizes and coordination capabilities that was able to bridge the two structure types — an ABO_3 perovskite substrate ($LaAlO_3$) and an oxygen-deficient $(AA')O_{2-x}$ fluorite film (A = Nd or La; A' = Zr; x = 0.25) — through pulsed-laser deposition of ceramic zirconate $A_2Zr_2O_7$ pyrochlore targets (Fig. 1a).

Fluorite- and perovskite-derived structures tend to display synergistic properties that make them desirable as adjacent layers in devices. For example, the fluorite yttrium-stabilized zirconia is an excellent ion conductor and is used in conjunction with the perovskite lanthanum strontium manganite cathode material in solid oxide fuel cells. The union of these two structure types, among others (Table 1) such as magnetic spinel/perovskite interfaces[7,8], is of great interest for device optimization, but controlled interfaces have been produced only recently[9].

One approach to minimize the lattice mismatch is to rotate the fluorite's cubic lattice by 45° on the perovskite (001) surface, but this results in three-dimensional (island growth) rather than the desired layer-by-layer growth that would lead to homogenous, smooth and fully strained thin films without degraded properties.

This 2D film growth challenge has now been overcome by the researchers through a careful study of how the ion sublattices are arranged in each structure and the cation chemistries amenable to both. It has proved possible to utilize what solid-state chemist Michael O'Keeffe refers to as a eutactic[10] relationship — an arrangement of nearly close-packed ions that can approximate maximal atomic packing efficiency — by formation of a bridging structure. The interfacial layer, $La_2Zr_2O_7$, was deposited from a pyrochlore composition, which is itself an anion-deficient fluorite derivative with a cation-to-anion ratio of 1:1.75 that
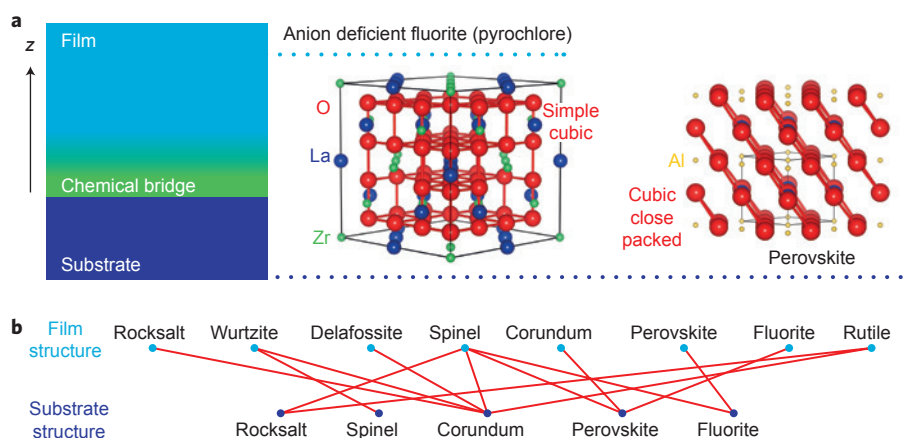

Figure 1 | Heteroepitaxy of non-isostructural oxides from eutaxy and flexible cation coordination chemistry. **a**, Schematic heterostructure consisting of an anion deficient fluorite film on a perovskite substrate interfaced by a chemical bridge formed by a cation with variable coordination preferences. The ideal atomic structures for pyrochlore (simple cubic anion lattice) and perovskite (cubic close-packed) are shown to the right. The oxide ions are in red and ionic radii are used to highlight the packing of the oxide sublattice (linked atoms), which is simple cubic for the pyrochlore ($(AA')O_{2-x}$) and cubic close-packed (when the A cation is included) for the perovskite (ABO_3). **b**, Some possible combinations of the non-isostructural oxides in Table 1 that could be interfaced together, indicated by solid connecting lines, by applying a similar eutaxy and coordination chemistry approach to that utilized by Rosseinsky and colleagues. Note that isostructural combinations are not indicated.

is intermediate between that of perovskite (1:1.5) and fluorite (1:2). This allowed the researchers to achieve epitaxy or eutaxy[9] (meaning well-arranged), through an atomic reconstruction at the surface of each layer. Moving away from the interface, a gradual transitional change in stoichiometric ratio leads to the coherent scaffolding of the perovskite and fluorite lattices. This chemical principle — bridging heterointerfaces through deposition of an intermediate composition[11] to grow a

targeted structure — may enable improved epitaxy of other non-isostructural oxide interfaces formed by anions with dissimilar packing arrangements (Table 1).

Beyond the eutactic relationship, and the intermediate cation-to-anion ratio between the structures, the choice of bridging cations at the interfacial layer was also crucial to ensure successful coherency. This aspect relies on coordination-based principles. Indeed, Zr^{4+} deposited from the rare-earth pyrochlores is necessary to

Table 1 | Common oxide structure types in order of decreasing cation-to-anion ratio and differentiated by anion packing.

Structure type	Stoichiometry	Cation-to-anion ratio	Anion packing	Prototype
Rocksalt	AO	1:1	ccp	MgO
Wurtzite	AO	1:1	hcp	ZnO
Delafossite	ABO_2	1:1	–	$CuAlO_2$
Spinel	AB_2O_4	1:1.33	ccp	$MgAl_2O_4$
Bixbyite	A_2O_3	1:1.5	–	In_2O_3
Corundum	A_2O_3	1:1.5	hcp	Al_2O_3
Ilmenite	ABO_3	1:1.5	hcp	$FeTiO_3$
Perovskite	ABO_3	1:1.5	ccp	$CaTiO_3$
Ruddlesden–Popper	$A_2(A_{n-1}B_nO_{3n+1})$	1:1.33–1.5	ccp	$Sr_3Ti_2O_7$
Pyrochlore	$A_2B_2O_7$	1:1.75	sc	$Y_2Ti_2O_7$
Fluorite	AO_2	1:2	sc	CeO_2
Rutile	AO_2	1:2	hcp	TiO_2

Bridging structures are anticipated when the two components in the heterostructure exhibit different packing of the anion sublattice; in such cases, coherent film epitaxy may be achieved by growing a bridging structure from a phase with an intermediate composition ratio for a gradual change in anion eutaxy. ccp, cubic close-packed; hcp, hexagonal close-packed; sc, simple cubic; –, no simple packing classification.

achieve the defect-free interface as its cation size enforces a constraint on the interlayer spacing and composition of the layers in the bridging structure, which were resolved from detailed high-angle annular dark field scanning transmission electron microscopy studies. Together with calculations based on density functional theory and electron energy loss spectroscopy, the researchers showed that the first cation monolayer between the perovskite substrate and fluorite is formed by Zr^{4+}, which adopts distorted six- and seven-coordinate environments as La atoms fill vacant sites in the terminal cation-deficient perovskite layer.

Based on the present experiments, new structures with few atomic layers can serve as transitional phases to achieve coherent epitaxy of non-isostructural oxides. As Fig. 1b shows, there are many interfaces awaiting exploration. The composition of the interfacial structure should be derived from a structure type that is intermediate between the film and substrate, and the cations should have dual (or more) coordination capabilities, specifically variable ionic size and nearest neighbours. Some possible cations are those found in the $3d$ and $4d$ transition metal rows and group III elements. It is interesting to note that this new interface structure is unlikely to be a thermodynamic phase, as it exhibits broken inversion symmetry.

Thus, it may well exhibit unique properties of its own that merit further attention by researchers interested in finding hosts for metal–insulator transitions, topological phases or spin textures[12,13].

Back in 2012, a Commentary[14] in *Nature Materials* entitled 'Whither the oxide interface' challenged researchers not to remain complacent in layer-by-layer synthesis of popular perovskite materials in simple geometries, but rather to focus on a future of oxide interfaces in new topologies and different structure types. The work from Rosseinsky and colleagues demonstrates that a happy marriage between non-isostructural oxides, some of which share eutatic relationships with silicon, is possible. In fact, it may rely in a very real way on another sort of intersection: materials scientists and condensed-matter physicists, who have dominated the oxide interface field, could intermingle more with their colleagues in chemistry to find the necessary chemical bridges for epitaxy to occur.

Synthesis of new coherent interfaces continues to be frontier science; yet, these new heterostructures also pose opportunities to synthesize bulk single crystals with different structure types for substrates, to develop new quantitative symmetry and crystal chemistry based theories for interface structures and local bond coordination preferences, and invent tools to quantitatively determine interfacial structure. Such programs, concepts, and analytics are already emerging[15], and we are hopeful that the continued unification will lead to breakthroughs in interface science and a future of oxide electronics with beyond-complementary metal oxide semiconductor functionality. ◻

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METAL–ORGANIC FRAMEWORKS

A thin film opening

The properties of metal–organic frameworks — promising for a myriad of applications — can be commonly tuned by judicious choice of the building blocks used to prepare the material. Now, simply downsizing a rigid, non-porous MOF to a thin film has been shown to endow it with dynamic, gate-opening-type guest uptake behaviour.

Christopher J. Sumby

A glimpse of single crystals at the bottom of a reaction vessel is an alluring sight for chemists engaging in the discovery of metal–organic frameworks (MOFs). Yet the perfect single crystals or crystalline powders commonly produced in the laboratory may not be the most desirable form to extract novel properties from a material, or to enable downstream applications. Now, writing in *Nature Chemistry*, Hiroshi Kitagawa and co-workers[1] have demonstrated structural flexibility and 'gate-opening' porosity in a thin-film MOF that, in its bulk crystalline state, only exhibits a rigid, non-porous form. This dramatic alteration in properties arose by the preparation of the MOF as a highly orientated thin film of precisely controlled thickness.

MOFs, a group of porous materials formed from the systematic combination of organic linkers and metal-ion-based nodes, are characterized by their high surface areas and chemically mutable structures[2]. The molecular-level understanding that originates from their single crystal nature has enabled rapid, iterative discovery and development of these intriguing materials. The field now boasts some 20,000 MOF structures, a number rapidly growing year on year.

The properties of MOFs have thrust a spotlight on potential applications, many of those exploiting in some form their porosity. In some MOFs the guest-free form — its activated form — is structurally indistinguishable from its guest-loaded form: the backbone of the framework stays the same, and its pores can either be empty of or filled with guests (Fig. 1a, top). In other cases, in which MOFs are said to have flexible or dynamic structures, changes occur upon guest removal or loading (Fig. 1a, bottom)[3]. In certain instances, the structural transformations facilitate a gate-opening behaviour (also referred to as responsive-adsorption behaviour), in which guest uptake and release occur above specific threshold pressures. This is the behaviour