science-based approaches, uninterrupted funding and abundant political will. That the tiger is renowned as India's national animal surely aided such endeavours.

Second, megafauna declines can disrupt entire ecosystems. Large animals such as tigers and elephants have key roles in ecosystems, for example, as dominant predators, seed dispersers, ecosystem 'engineers' and movers of soil nutrients[7]. A decline in such ecosystem functions seems probable given the severity of megafauna declines. Terrestrial wild mammals, for instance, now comprise just 2% of all mammalian biomass on Earth, with humans and livestock accounting for the remaining 98% (ref. 8).

Third, before planning reintroduction efforts, one must consider the wider effects of megafauna on ecosystems and people. For instance, restoring tiger populations in certain landscapes might exclude other rare predators such as Indian wolves (*Canis lupus pallipes*) and sloth bears (*Melursus ursinus*), and might therefore be inadvisable. Tiger introductions in other sites might increase human–tiger conflicts, requiring problematic animals to be removed to protect local inhabitants. In India, a large body of knowledge about tiger behaviour, movements and population genetics[9] has helped wildlife managers to develop workable and scientifically based strategies for tiger recovery.

Finally, Jhala and colleagues' findings underscore the importance of correctly applying land-sparing and land-sharing strategies for nature conservation[10]. Land-sparing involves prioritizing certain lands, such as national parks and tiger reserves (Fig. 1), to conserve ecosystems, whereas land-sharing involves efforts to make agricultural and production landscapes less hostile to native species. These approaches are often considered mutually exclusive, but Jhala *et al.* show that both have real validity for tigers — and that neither approach would be as effective if used on its own. Tigers rely crucially on nature reserves and the abundant prey populations they sustain, but they also need expanses of nearby land to roam and disperse more widely.

Given these findings, what is the future for Indian tigers? As Jhala *et al.* note, tiger recovery in India has mostly been concentrated in a few key landscapes. Large parts of eastern India, for example, remain poorly occupied by the animals. Concerted efforts across Indian states and conservation bodies will be needed to advance habitat protection, population recovery and movements of tigers to expand their geographical range. Beyond this, socio-political interventions will be needed to help alleviate poverty and limit negative human–tiger interactions in lands shared by rural people and tigers.

Tiger recovery is gaining ground in India despite the country's large human population, intense land-use pressures[11] and the growing effects of wildlife hunting[12]. Dealing with such diverse threats typically requires work by various branches of the government, by civic groups and by academics from the natural and social sciences. These efforts should not only aid tiger recovery, but also advance landscape-scale planning to limit human land-use pressures and other threats to ecosystems generally. Real-world conservation is a daunting challenge, but India has shown that it is taking the future of its endangered tigers extremely seriously indeed.

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1. Pires, M. M. *Ann. Rev. Earth Planet. Sci.* **52**, 133–158 (2024).
2. Jhala, Y. V., Mungi, N. A., Gopal, R. & Qureshi, Q. *Science* **387**, 505–510 (2025).
3. Sanderson, E. W. *et al. Front. Conserv. Sci.* **4**, 1191280 (2023).
4. Karanth, K. U., Nichols, J. D., Samba Kumar, N., Link, W. A. & Hines, J. E. *Proc. Natl Acad. Sci. USA* **101**, 4854–4858 (2004).
5. Gray, T. N. E. *et al. Front. Conserv. Sci.* **4**, 1124340 (2023).
6. Walston, J. *et al. PLoS Biol.* **8**, e1000485 (2010).
7. Malhi, Y. *et al. Proc. Natl Acad. Sci. USA* **113**, 838–846 (2016).
8. Greenspoon, L. *et al. Proc. Natl Acad. Sci. USA* **120**, e2204892120 (2023).
9. Khan, A. *et al. Proc. Natl Acad. Sci. USA* **118**, e2023018118 (2023).
10. Phalan, B., Onial, M., Balmford, A. & Green, R. E. *Science* **333**, 1289–1291 (2011).
11. Srivathsa, A. *et al. Nature Sustain.* **6**, 568–577 (2023).
12. Velho, N., Karanth, K. K. & Laurance, W. F. *Biol. Conserv.* **148**, 210–215 (2012).

U.R. declares competing interests; see go.nature.com/4cjt3er for details.

Analytical chemistry

X-ray structures of 'oily' molecules determined

Hongyi Xu

Porous crystals have been engineered to trap 'oily' molecules — enabling X-ray structures to be determined for these compounds that defy standard crystallographic analysis. **See p.676**

On page 676, Wu *et al.*[1] report a groundbreaking method for determining previously elusive molecular structures. The researchers developed a crystalline porous material containing molecular 'docking stations' that securely capture flexible molecules that have long alkyl chains (hydrocarbon groups that contain chains of carbon atoms). By fixing the conformation of these otherwise highly flexible molecules in the host material's rigid crystal lattice, the X-ray structures of the molecules can be determined at atomic resolution. This advance addresses a long-standing challenge that has hindered drug developers, materials scientists and chemists who study compounds isolated from natural sources, all of whom need precise insight into the structures of alkyl-bearing compounds that resist analysis by conventional crystallography.

Conventional X-ray crystallography requires target molecules to form high-quality single crystals, typically a few tens of micrometres in size in all dimensions. However, many molecules do not crystallize easily because they interact only weakly with each other, and therefore don't tend to pack into ordered arrangements. Emerging techniques such as 3D electron diffraction[2] (3DED), also known as MicroED, have enabled structure determination from nanometre-scale crystals[3], but still struggle with molecules that bear flexible alkyl chains. That's because the intrinsic conformational disorder and dynamic nature of such molecules make it challenging to achieve the necessary crystalline order.

This challenge has driven the development of innovative solutions. In 2013, the 'crystalline sponge' method was reported, in which a preformed porous crystalline compound known as a metal–organic framework (MOF) absorbed guest molecules[4]. The molecules were guided into an ordered arrangement by the weak interactions they form with the MOF, enabling structure determination without the need for the guest to be crystallized independently.

In 2016, a different approach was reported[5] in which molecules were locked into an

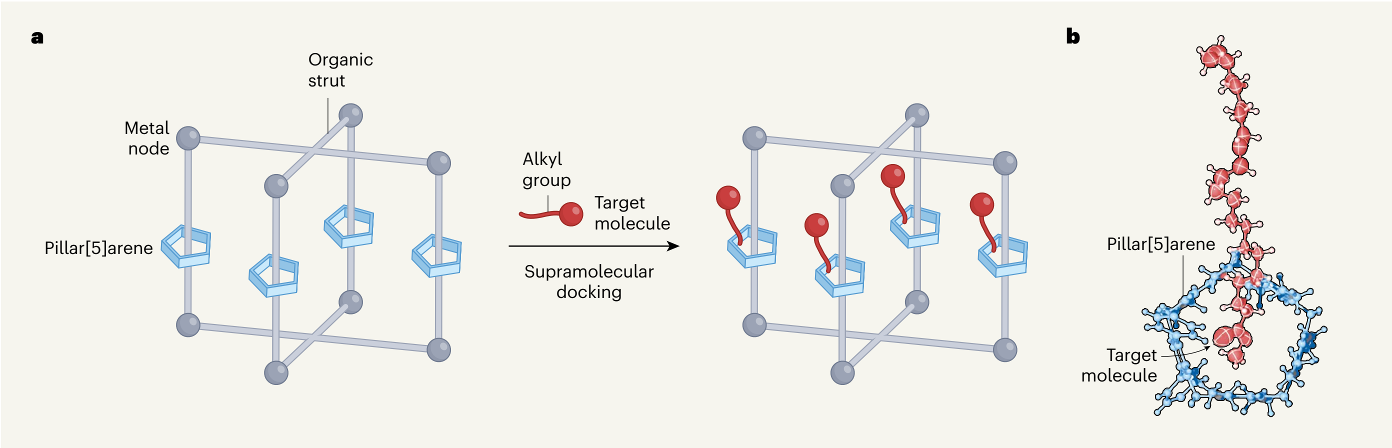

Figure 1 | Molecules with flexible alkyl groups docked for X-ray analysis. Molecules that bear long, flexible hydrocarbon chains (alkyl groups) are often hard to crystallize, which prevents their structures from being determined by conventional X-ray crystallography techniques. **a**, Wu *et al.*[1] prepared a porous crystalline material, known as a metal–organic framework (MOF), that consists of metal 'nodes' linked by organic 'struts'. The MOF also incorporates structures called pillar[5]arenes that can trap alkyl groups. When crystals of the MOF are soaked in solutions of alkyl-bearing molecules, the molecules are trapped by the pillar[5]arenes and locked into a single conformation. **b**, X-ray crystallography can then be used to determine the structures of the trapped molecules. In this structure, only the pillar[5]arene unit of the MOF and the 'docked' molecule are shown, for clarity. (Adapted from Fig. 1b of ref. 1.)

ordered arrangement by connecting them through covalent bonds to the metal atoms of a rigid MOF. This strategy enabled the structures of previously uncrystallizable compounds to be solved. Moreover, because the MOF was chiral — the pores provided an environment that has a 'handedness' — this method could be used to determine the specific geometric arrangement of groups (the absolute stereochemistry) around carbon atoms in chiral guest molecules.

The previous two MOF-assisted methods were revolutionary, but they have limitations. Both require complex, time-consuming procedures to exchange solvent molecules trapped in the pores of freshly prepared MOFs with solvents that are more conducive to analysing the structures of target molecules, and the guest molecules need suitable chemical features to interact with the framework. More importantly, highly flexible molecules and hydrocarbons — particularly molecules with long alkyl chains — remain a challenge. Even if these molecules diffuse into the MOF's pores, the lack of interactions with the host material results in conformational disorder that prevents structural determination.

Wu *et al.* have tackled this problem head-on by designing a class of MOFs that incorporate structures called pillar[5]arene rings into a MOF framework (Fig. 1). Pillar[5]arenes are molecular rings that bind to hydrophobic alkyl chains inside their hollow cavity through a series of weakly attractive non-covalent interactions[6], rather than by forming strong chemical bonds.

The authors successfully tested their method on 63 molecules, including 48 that contained alkyl chains, many of which had previously defied crystallographic analysis. Among these were six natural products, two drugs that have been approved for use by the US Food and Drug Administration and numerous synthetic compounds collected from 16 research groups. One highlight was the structure determination of triheptanoin, a therapeutic oil that contains three long alkyl groups and is liquid at room temperature. By simply soaking one of their MOF crystals in triheptanoin, the authors obtained the first clear 3D structure of this oily drug — something that neither conventional X-ray crystallography nor previously reported MOF-based methods could achieve.

Perhaps most strikingly, Wu and colleagues' method is much faster and more user-friendly than the other MOF-based approaches, both of which require soaking steps that take days and careful solvent-exchange procedures to incorporate guest molecules into the host lattice. By contrast, Wu *et al.* demonstrated that their pillar[5]arene MOF can capture guest molecules in minutes, simply by immersing the MOF crystal in a solution of the target compound. The selective host–guest interactions between pillar[5]arenes and alkyl chains enable rapid inclusion of guests without the need for tedious crystal handling. This efficiency could make the technique much more attractive for routine use than the other MOF-based methods. When combined with emerging crystallographic techniques such as 3DED and serial crystallography[7], Wu and co-workers' approach has the potential to unlock the structures of compounds that are even more challenging to obtain than those currently reported.

"The authors' method is much faster and more user-friendly than earlier related approaches."

It should be noted that the method requires guests to have hydrophobic regions that can interact with the pillar[5]arene host. Fortunately, many biologically and industrially relevant molecules — such as lipids, natural products and numerous drug scaffolds — contain alkyl chains that make them excellent candidates for this approach. Another consideration is the difficulty of synthesizing stable pillar[5]arene MOFs. Wu and colleagues' integration of large, flexible pillar[5]arene rings into a crystalline MOF without disrupting the structural order of the material is a considerable achievement in materials chemistry.

Increased research interest in MOF-assisted structure determination and further refinements to the technique could soon lead to the development of suites of target-specific MOFs — or even 'universal' MOFs that work well for all molecules — that become standard tools in crystallography. Wu and colleagues' innovation not only expands the frontiers of structure determination, but also paves the way for advances in drug discovery, natural-product chemistry and materials science.

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1. Wu, Y. *et al. Nature* **640**, 676–682 (2025).
2. Gemmi, M. *et al. ACS Cent. Sci.* **5**, 1315–1329 (2019).
3. Jones, C. G. *et al. ACS Cent. Sci.* **4**, 1587–1592 (2018).
4. Inokuma, Y. *et al. Nature* **495**, 461–466 (2013).
5. Lee, S., Kapustin, E. A. & Yaghi, O. M. *Science* **353**, 808–811 (2016).
6. Ogoshi, T. *et al. Angew. Chem. Int. Ed.* **54**, 9849–9852 (2015).
7. Schriber, E. A. *et al. Nature* **601**, 360–365 (2022).

The author declares no competing interests.