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MATERIALS CHEMISTRY

Machines learn chemical intuition

Failed chemical reactions are often not reported, which means that vast amounts of potentially useful data are going to waste. Experiments show that machine learning can use such data to optimize the preparation of porous materials.

SETH COHEN

Intuition often guides our choices throughout life. In science, it can also play a part in the design of experiments to answer or probe a question of interest. For example, it guides chemists to select a specific set of reagents, reactions or conditions when devising the synthesis of a target compound. Writing in *Nature Communications*, Moosavi *et al.*[1] report their use of machine learning to capture this sort of intuition to optimize the synthesis of an emerging class of material known as metal–organic frameworks (MOFs), which have applications as diverse as fuel storage, catalysis and the capture of water from the atmosphere.

To make a MOF, inorganic 'nodes' are connected by organic 'linker' molecules[2]. One can imagine these materials as molecular climbing frames, in which the linkers are the frames' metal rods and the nodes are the connections where the rods are riveted together. MOFs have large, extended molecular structures and consist mostly of empty space. The open voids in these structures make them among the most porous materials ever synthesized, and this underpins their many potential applications.

The wide variety of available linkers and nodes makes the number of MOFs that could be created nearly limitless — thousands have been synthesized in the past 20 years or so[3]. However, for every reported synthesis of a MOF, dozens (and possibly even hundreds or thousands) of failed reactions will almost certainly have been attempted that did not produce the desired material. If this unreported wealth of knowledge of failed reactions could be captured, it could be used to predict and optimize the syntheses of new MOFs in the future.

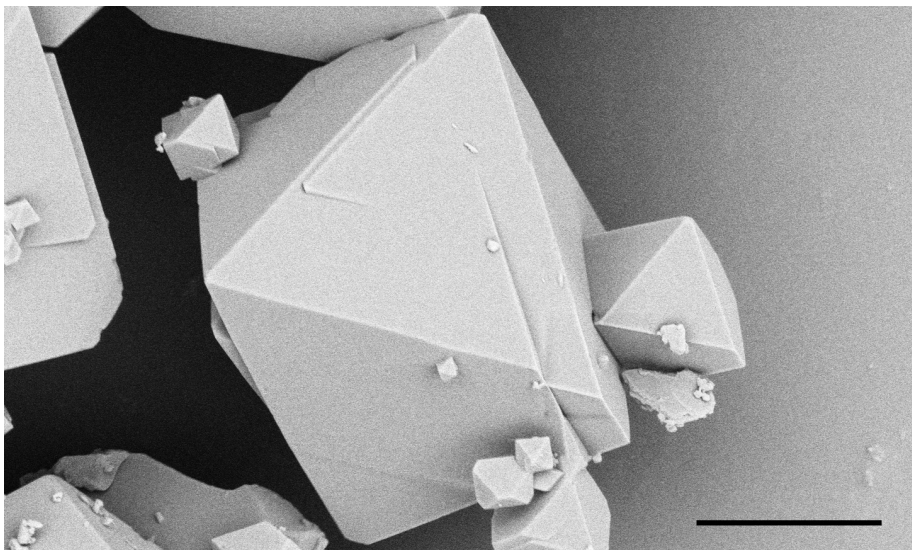

Figure 1 | Optimized synthesis of a metal–organic framework produces highly crystalline material. Moosavi *et al.*[1] used machine learning to optimize the synthesis of HKUST-1, a porous material known as a metal–organic framework. This micrograph shows that the resulting material is highly crystalline, as required for potential applications. Scale bar, 5 micrometres. (Image from Supplementary Figure 11e of ref. 1.)

To try to reproduce, and thereby capture, this type of unpublished information, Moosavi *et al.* used a robotic system to run a series of experiments that explores the effects of different reaction conditions — changing the solvent, temperature, reactant concentration and so on — in the synthesis of a widely used, copper-based MOF known as HKUST-1 (ref. 4). The robot could run 30 reactions per day, and thereby obtained a data set of conditions that led to successful and failed reactions. The data were then processed by an algorithm that mimics genetic and evolutionary processes: each iteration of the algorithm applies a selection pressure to the data that causes evolved conditions to emerge as a result of 'survival of the fittest'.

Moosavi and colleagues performed 3 rounds of 30 experiments, using the algorithm and the quality of the MOF samples produced in each round to guide the conditions for the subsequent rounds. The authors thereby identified an optimized procedure for making HKUST-1, yielding material that had superb crystallinity (Fig. 1) and phase purity (which measures the proportions of different crystal forms present in the material), and a high surface area — all of which are desirable properties for applications of MOFs. Ordinarily, only the optimized conditions would be published in the literature, with all the other reactions being lost within the confines of a dusty notebook (or perhaps, these days, buried in the digital archives of an e-notebook).

Instead, Moosavi *et al.* returned to the suboptimal reactions, and used machine learning to analyse them. In this way, the authors identified the reaction parameters that have the largest effect on the quality of the resulting MOFs. For example, they found that changes in reaction temperature have a much greater effect on the crystallinity and surface area of the products than have the stoichiometry of the linkers and nodes used in the reaction. By ranking and analysing the relative importance of nine reaction metrics, the authors generated information akin to a chemist's intuition.

Moosavi *et al.* used this chemical intuition to develop a synthesis of Zn-HKUST-1, which is a MOF that has the same structure as HKUST-1, but with zinc nodes instead of copper ones. This might sound like a trivial challenge, especially considering the chemical similarities between copper and zinc. However, the authors found that the top ten most widely used reaction conditions for synthesizing HKUST-1 all failed to produce Zn-HKUST-1. This sort of situation is tremendously frustrating for chemists, who typically must then work out how to obtain the desired material from scratch, by trying out many different sets of reaction conditions.

By contrast, Moosavi *et al.* focused on the dominant reaction parameters identified by machine learning, and discovered two sets of conditions that produce Zn-HKUST-1 after just 20 trial reactions. The authors suggest that taking a completely unguided approach would have required thousands of reactions to achieve the same result.

Moosavi and colleagues acknowledge that the data produced in their experiments are ideal for machine-learning analysis — their robotic set-up precisely controls the reaction parameters, reducing variables in the reaction outcomes, and only one synthetic reaction was considered. Data produced from a more disparate set of synthetic reactions would have been more difficult to handle. Moreover, the authors focused on the quality of the MOF materials, but did not report other key outcomes, such as reaction yields. Low-yielding MOF syntheses would be impractical, even if they produce the most pristine materials known.

Nevertheless, Moosavi and colleagues' work has the potential to greatly improve and accelerate the synthesis of MOFs. The authors have made their software available online (see go.nature.com/2dtppxn), so that chemists can contribute to collective chemical intuition by reporting successful and failed reaction conditions. This kind of group engagement should be applauded, and could greatly benefit the MOF community. Now, if only they could improve my intuition at the roulette table … ■

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MEDICAL RESEARCH

Multiple sclerosis enters a grey area

Studies of multiple sclerosis have long focused on the white matter of the brain. Insights into how immune cells target the brain's grey matter now illuminate the stage of the disease at which neurodegeneration occurs. SEE ARTICLE P.503

JENNA L. PAPPALARDO & DAVID A. HAFLER

Multiple sclerosis is an autoimmune disease with a genetic origin. The condition is characterized by an attack on the brain mediated by the immune system, leading to diverse symptoms caused by damage to neurons[1]. Animal models are available for the early stage of the disease, which is called relapsing–remitting multiple sclerosis. However, the progressive forms of multiple sclerosis associated with neurodegeneration and disability are comparatively understudied, and what shapes the course of disease progression is largely unknown. Insights into the later stage of the condition could help the development of clinical approaches that tackle the underlying causes. On page 503, Lodygin *et al.*[2] shed light on the progressive stage of the disease. Using a rat model and blood samples from people who had multiple sclerosis, the authors identify the protein target of an immune cell that attacks the brain region called grey matter.

Multiple sclerosis is usually diagnosed at the relapsing–remitting stage, in which people have periods of symptoms and then remission when the symptoms subside. There is growing evidence that relapsing–remitting multiple sclerosis originates from inflammation that is driven by immune cells[3]. A hallmark of this disease stage is a targeted attack by immune cells, including T cells and macrophages, on the brain region called white matter, which contains parts of neurons known as axons or nerve fibres (Fig. 1). Myelin, a mixture of lipids and proteins that covers and protects nerve cells in the white matter, is thought to be the T-cell target in this destructive process[4]. Much progress has been made in understanding how this process occurs[5–7], particularly from studies of a mouse model called experimental autoimmune encephalomyelitis.

Relapsing–remitting multiple sclerosis often leads to the progressive stage of the disease. If this progression occurs, people stop experiencing remission periods and have a gradual loss of nerve-cell function that might be linked to destruction in the brain's grey-matter region[8,9]; grey matter harbours the parts of nerve cells called cell bodies, which contain the nucleus. Immunosuppressive treatment for relapsing–remitting multiple sclerosis can help to decrease the chance of progressive disease developing[10], but what causes this switch is not understood.

The destruction of material in white and grey matter in people with multiple sclerosis might arise from distinct inflammatory processes[8]. What drives immune-system cells to infiltrate