# How chemists are building molecular assembly lines

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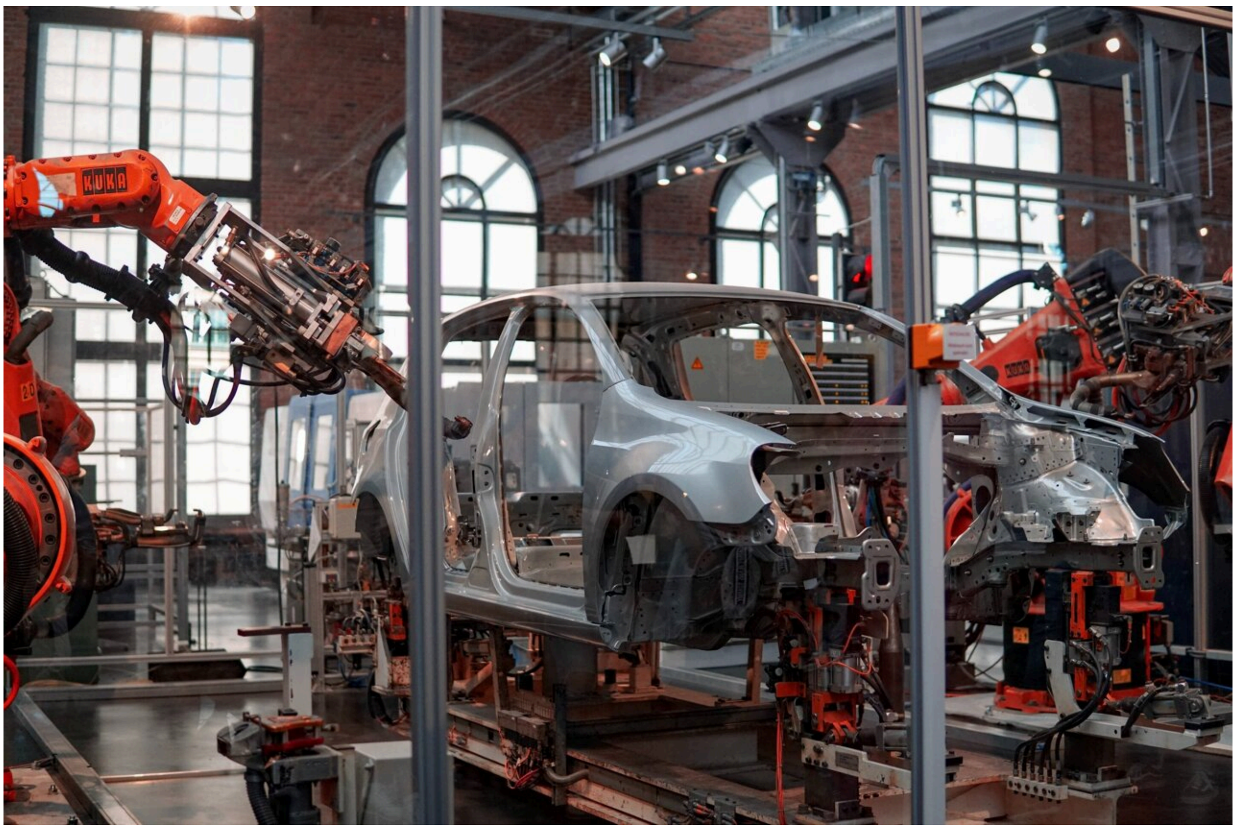


Building a molecular machine is a job for elite chemists but the basic tricks of the trade are easy enough to grasp. Credit: Lenny Kuhne / Unsplash

Four huge robot arms surround the gleaming metal shell of what will soon be a top-of-the-range automobile. They jerk into life, attaching the bonnet, the wing mirrors, and other panels. It's the kind of precision operation you can find at car factories around the world these days. But here's a question worth considering: could we pull off a feat like this only about a billion times smaller?

In 2016, three pioneers of molecular machines were recognised with a Nobel prize. The first tranche of molecular machines that they were rewarded for creating were mostly simple affairs such as rotors, switches and the like. Now, chemists like Professor David Leigh at the University of Manchester, U.K., are trying to build sophisticated molecular machines with several components and that can do useful jobs.

Building a molecular machine is a job for elite chemists but the basic tricks of the trade are easy enough to grasp. Some of them involve building molecules that are mechanically linked to one another. For instance, they might build a rotaxane, a ring-like molecule threaded onto a shaft. Placing different groups of atoms along the shaft and then manipulating their properties—for instance, giving and taking away an electrostatic charge—can impel the ring to move along the shaft. This is the kind of simple component that could be used in a more elaborate molecular machine.

## Biochemical factory

What kind of things might we do with a more advanced molecular machine—or 'nanobots," as some call them? Prof. Leigh is particularly interested in building nanobots that act like a chemical assembly line, synthesising new chemicals with interesting properties. He's inspired by the ribosome, a biochemical factory in cells that builds proteins. It takes simple building blocks called amino acids, which come in just 20 different natural varieties, and stitches them together into long chains or polymers. Depending on the sequence of amino acids, those chains fold themselves up into an array of biomaterials, from the keratin that makes up skin and hair to the fibres of muscles.

Chemists have made many artificial polymers, but it is extremely difficult to control the order in which the building blocks are joined. "Sequence-specific polymers are an unsolved challenge in chemistry," said Prof. Leigh. But he thinks molecular machines could be a solution. If we had molecular machines that could assemble polymers, they wouldn't be limited to just the 20 natural amino acid building blocks, so the result could be a much broader array of materials.

Achieving machines that can make sequence-specific polymers is far from trivial, says chemistry Professor Nathalie Katsonis at the University of Groningen in the Netherlands. "But I am convinced that this research will play a big part in (the) future of chemistry, and possibly of materials science too."

Prof. Leigh has been chasing this goal through his MOLFACTORY project, which began in 2014. In a key paper in 2017, Prof. Leigh and his team showed they could build a molecular robot arm, a simplified and much smaller version of the ones that put cars together. This arm grabs hold of one reactive chemical and moves it to one of two sites. Depending on which site it is positioned at, the chemical reacts in different ways to produce different chemical products. Developed further, machines like this could produce sequence-specific polymers akin to the proteins produced by ribosomes. And just as different proteins can generate force (muscle) or be five times stronger than steel (spider silk), that might enable similar things with artificial polymers such as a sequence-specific polystyrene.

"David and his group are doing phenomenally creative work," said Professor Raymond Astumian at the University of Maine in Orono, U.S. "Not only are the molecular machines they make of potential practical use, but they are also directed toward answering fundamental questions."

Another project, called ProgNanoRobot, led by Dr. Germán Zango working in Prof. Leigh's laboratory, tried to take this production robot further. The project had a number of objectives, including producing robotic arms that could run on a chemical fuel and a nano-device capable of transporting molecular cargo over long atomic-scale distances.

The project ran between 2019 and March 2021 and as yet, no results are published. But Dr. Zango had some key successes. He said he produced a device in which a molecular cargo could be produced from one robotic arm to another, meeting the goal of transport over long distances.

"Working on research that could lead us toward the dawn of useful molecular nanotechnology was at the same time an enormous challenge and a thrilling experience," said Dr. Zango.

## Triggers

In the near future, there are several big challenges that nanobot research needs to overcome. At the moment, it is often the case that molecular machines need to be fed a number of chemical triggers in a particular series to get them to work. If the systems were to be used to produce polymers at scale, it would produce a lot of waste. Part of Dr. Zango's work investigated reducing the number of chemical triggers needed or using light as a trigger instead. "One of the most challenging things we were trying to achieve was to use a single chemical input to fuel a whole operating cycle of the machine or to use only photoswitches," said Dr. Zango.

Another huge challenge, says Prof. Leigh, is error correction. Machines at the nanoscale are distinctly unlike human-scale robots in that they are always subject to stochasticity; you can set up a molecular machine to do a particular job, but you can never ensure it will work correctly all the time. Biology has to grapple with this problem, too. In the human body there is one set of molecular machines that build biomolecules and another whole set with the specific job of finding and correcting the errors made by the first set. Prof. Leigh says that at some point, artificial molecular machines will have to include error-correction mechanisms. That kind of work is still in its infancy.

Still, in October 2020, Prof. Leigh and his team took a significant step toward a sequence-specific polymer synthesiser. They built a rotaxane-based robot in which a ring 'walks' down a track, picking up molecules along the way and joining them together. The results only joined four molecules together—a far cry from the hundreds or thousands in a protein—but it was a big step nonetheless.

Prof. Leigh said that there can sometimes appear to be hype about what molecular machines can do. But he reckons it will be justified in the long term. "I really do think that eventually molecular machines will revolutionise things in the way the industrial revolution or the internet did," he said. But it's definitely going to take time, he added.

He admits there's nothing he can yet do with a molecular machine that can't be done more simply by other means. But when you're inventing something new, that is somewhat to be expected. "It's very much like Stone Age man making a wheel to grind corn," said Prof. Leigh. "He doesn't know that one day it will be used to make a car."

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