IN THE corner of the lab, a machine the size of a coffee shop espresso maker quietly whirs and hums. It is dispensing not drinks, but complex chemicals. Everything is automated. Syringes tighten imperceptibly, sending solutions dribbling through a tangle of spaghetti-thin tubes into reaction vessels. Between loading the raw starting materials and collecting the final result, not a hand touches the set-up. Yet this nondescript machine could be the first step to banishing one of chemistry’s biggest demons.

The fact is, fabricating molecules takes a lot of time. Martin Burke at the University of Illinois, the machine’s inventor, encountered the problem while working as a doctor in the late 1990s. He talks of his hospital days when he saw the agony of incurable disease. It was then that Burke recognised the problem was partly down to the lack of drugs pouring out of research labs, so he decided to change tack and become a chemist. He quickly saw for himself how making molecules that could enter drug trials could be a painfully slow process. Done the traditional way, this involves trying out one reaction after another, building upwards from small molecules to larger, more complex ones. Every failed reaction was another day without concrete medical progress.

Burke and his machine are now part of a mission to change that by automating and rationalising chemical synthesis, and fashioning a science out of what was previously considered more of an art. If this crusade is successful, the time it takes to create a new drug could go from years to months or days. The age of chemistry as bottleneck in the drug discovery process could be entering its twilight.

Step into any lab working at the border between chemistry and biology and you’ll probably already see a fridge-sized unit in the corner chugging away. It could be stitching together amino acids into proteins or nucleotides into DNA. If you slot vials of the four different nucleotides that make up DNA, or the amino acids that constitute proteins, into place, the machine will take a careful slurp from each in succession and build the biomolecule you programmed in.

Crafty carbon

Proteins and DNA are special types of molecule, though. They are normally composed of a finite set of building blocks joined one after the other in a line. Automated – or even particularly logical – ways to make other types of molecule have remained much harder nuts to crack.

The problem comes in the shape of what chemists call “small molecules” or sometimes “natural products”, reflecting the fact that many of these compounds are made by living organisms. These molecules are the scents that flowers produce and the toxins on the backs of poisonous frogs – along with many of the drugs used in modern medicine.

But the term “small molecules” hides a devilish complexity. A team led by chemist...
Chemical warfare
Making new drugs involves battling with big problems

Get in the ring Persuading strings of atoms to loop back on themselves and form rings is tricky. There are ring-forming reactions, but if they aren’t appropriate for the chemical you want, you have to build upwards from natural materials that already contain these shapes.

Elemental issues Small molecules contain an array of chemical elements. Some are desperate to react with anything – including moisture in the air – while others need a kick to do much at all. Chemists must often come up with workarounds to protect sensitive elements while getting others to form new bonds.

Twin tangle Some chemicals have a property called chirality, meaning they come in mirror-image forms, much like a pair of gloves. When making these isomers, chemists have ways of controlling which version comes out at the end of a reaction. But finding out what is needed for a new molecule is often a process of trial and error.

Purity problem After a reaction, chemists need to extract their desired compound from a soup of chemicals. There could be unreacted starting materials, catalysts and solvent, and side products from unwanted reactions. Distilling, filtering or evaporating these away can be awkward and time-consuming.
Jean-Louis Reymond of the University of Bern in Switzerland recently put some figures on their variety. They looked at molecules with up to 17 atoms, containing any mixture of carbon, nitrogen, oxygen, sulphur and halogens such as iodine or chlorine. These elements, all common in medicinal chemicals, can combine to form a whopping $166.4$ billion realistic drug-like entities, the team calculated.

It is carbon that’s behind all this complexity. Its ability to form bonds with up to four other atoms at once rapidly leads to a dizzyingly large tree of diverse molecular structures. Things get even worse with chiral molecules. These come in two mirror-image forms that behave almost identically, except when it comes to interacting with biological machinery. One may be toxic, the other a wonder drug. For this and other reasons, labs attempting to make useful small molecules face an immense challenge (see “Chemical warfare”, page 35). Burke calls it the synthesis barrier.

Many chemists have come to relish a difficult “total synthesis” – making a molecule from scratch using basic starting materials – in the way mountaineers enjoy testing themselves on challenging peaks. The north face of the Eiger has been scaled many times, but is the synthesis barrier.

### Synthetic landmarks

**Building chemicals from scratch is not easy, but there have been notable successes over the years**

**Urea** *(1828)*

When Friedrich Wöhler combined lead cyanate and ammonia to synthesise urea, a new era began. The molecule is a constituent of urine, so the breakthrough was seen as disproving the theory of vitalism. Vitalists held that substances produced by living things are fundamentally different to other chemicals.

**Quinine** *(1944)*

It’s the bitter taste in tonic water and an anti-malaria drug. When Robert Woodward proposed a way to synthesise it near the end of the second world war, he made waves because most of the *Cinchona* trees it naturally comes from weren’t in allied territory. The trees, however, remain the only economically viable source of it.

**Morphine** *(1952)*

Marshall Gates was the first to demonstrate synthesis of morphine, but several other methods have been proposed. At Gates’s time there was uncertainty about the exact chemical structure of morphine. By making it in a lab and comparing the compounds, we have been able to pin down the details.

**Taxol** *(1994)*

Before its synthesis by Kyriacos Nicolaou, this chemotherapy drug also known as paclitaxel was harvested from the sap of rare Pacific yew trees, making it scarce and costly. There are stories from the 1990s of relatives of people with cancer going into forests at night looking for the drug. Synthesis lessened pressure on the trees.
synthesis machine capable of making any molecule. Swift progress is, he says, “held back by culture, including the culture of funding people rather than equipment”.

Another thing that’s lacking is good data on how well any given reaction works. This is particularly true of failed reactions. Researchers know crossing off dead-end chemical reactions is a valuable exercise, but they’re loath to publicise their misfires – and few journals want to publish them, regardless. Dial-a-Molecule is encouraging as many labs as possible to switch from paper to electronic notebooks to record their reactions. This would help provide data way beyond the limited scope of published research.

In the meantime, the first synthesis machine is bubbling away back in the Illinois lab. Burke is using it to make better versions of a complex polyene called amphotericin. It is the only treatment for certain types of fungal infection, such as fungal meningitis, that kill 1.5 million people every year. The problem is that while amphotericin kills the fungus, it is also toxic to humans. Burke has been working on making variants that are fungicidal, but do not harm people. Promising candidates are already in preclinical trials – an advance that, done the traditional way, would have taken years, but which has taken just months.

### Making bonds

The old ways are not ready to die yet though. Kyriacos Nicolaou is a specialist in total synthesis at Rice University in Texas. He agrees that automation is long overdue, but he still sees value in the conventional approach. His team has recently been working on one of the most complex natural compounds known, a neurotoxin found in marine animals called maitotoxin. Even if this molecule were accessible to a machine like Burke’s – which it isn’t – pursuing problems like this the old-fashioned way is useful, he says, because it yields new ways of reacting carbon and helps train each generation of chemists.

Burke’s machine has arrived at a good time. Chemists are getting better at predicting what shape and type of molecule they need for many applications, be it a new drug or as a component in solar panels. Many will welcome the chance to build those hypothetical molecules for real more quickly.

But perhaps the real promise of automatic chemistry lies in democratising the power to make and break chemical bonds. Synthesis machines will eventually mean anyone, scientist or layperson, can make a new molecule.

When it comes to automation and its power to unleash collaboration, “our field lags others”, says Nicolaou. Engineers, for instance, might help chemists build better machines to begin with. But before long they might also ask what sort of molecules they would like to make themselves.

History shows us that putting technology into the hands of non-experts can have tremendous impacts, says Burke. “These are exciting times.”

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**Medicine machine:**

*the first set-up to rapidly churn out potential new drugs*

This would help provide data way beyond the limited scope of published research.

**Tamiflu (2006)**

The UK government created a £500 million stockpile of oseltamivir (Tamiflu) during the 2009 swine flu outbreak. It is manufactured using a long process starting with a compound found in star anise. One better route proposed in 2006 by Elias Corey begins from much more common chemicals.

**Maitotoxin (not yet achieved)**

In January, a team led by Nicolaou was one step away from completing the synthesis of this marine toxin – a cause of certain types of food poisoning – when their funding was pulled. Some consider it the hardest target out there. Nicolaou had a team of up to 20 chemists working on it for eight years.

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