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Govind Rao hopes to quickly produce complex drugs with a small, portable production system.

MEDICINES ON DEMAND

The next big revolution in pharmaceuticals could be miniature production systems — small enough to fit in a briefcase. **By Carrie Arnold**

Govind Rao greets visitors to his lab just outside Baltimore with two things: a warm handshake and a chart. Almost before introductions are complete, Rao ushers guests into his windowless office at the University of Maryland, Baltimore County (UMBC), and pulls up a graph on his battered laptop. On it, a steeply sloping line charts health spending in the United States over the past 40 years.

"It just goes up and up. How many lives is this costing?" he asks.

Rao's solution sits in a sleek, stainless-steel briefcase on a table across from his desk. He pops the latch and flips open the lid to reveal a series of interconnected, fist-sized black boxes. They are filled with vials the size of a paper clip, fed by syringes and joined by clear plastic tubes not much thicker than a human hair. Add a source of electricity, some freeze-dried cell parts and a pinch of DNA, and the portable devices allow anyone to start making sophisticated drugs for just a few dollars. The system is called Bio-MOD, or Biologic Medications on Demand, and Rao says that it has the potential to change the direction of the precipitous curve on his laptop.

Rao isn't alone. Teams at the Massachusetts Institute of Technology (MIT) in Cambridge, Virginia Commonwealth University (VCU) in Richmond, and hospitals in Latin America and Europe have all been experimenting with producing on-demand pharmaceuticals. Their prototype systems represent a complete reinvention of drug manufacturing.

Historically, the pharmaceutical industry has relied on economies of scale, mixing hundreds of litres of reagents in massive reaction chambers to make millions of doses of a single drug. Bio-MOD and related systems, however, cycle small amounts of chemicals through a series of thumb-sized chambers that can produce hundreds or thousands of doses of multiple drugs, all in less than 24 hours. Several teams have won support for this vision from the US military: the Defense Advanced Research Projects Agency (DARPA) has handed out more than US$15 million to support these do-it-yourself drug-makers.

"It's crazy but rational," says Geoff Ling, a former DARPA project manager, who helped to initiate some of the grants and sees these systems as crucial for physicians working in some of the world's most challenging environments. He likens the devices to 3D printers that will assemble drugs such as antibiotics, antibodies to treat autoimmune conditions or insulin for diabetes. Their portability should increase the ability to deliver much-needed drugs to people affected by war or disaster.

Sceptics say Bio-MOD is an interesting idea, but would require an overhaul of the drug regulatory bureaucracy. And both Rao's team and the one at MIT have struggled to purify their final products to match batch-produced medications. Plus, the machines themselves have cost millions of dollars to develop and include components costing tens of thousands of dollars, putting them out of reach — at least for now — for many who would need them. The question is whether engineers such as Rao can overcome these hurdles.

Claudia Vaca González, a pharmacologist at the National University of Colombia in Bogotá, hopes that they will. "The top ten most expensive drugs in our country are biotherapeutics for cancer," she says. "These drugs have always been unaffordable for developing countries, and now they're becoming unaffordable even for the richest countries."

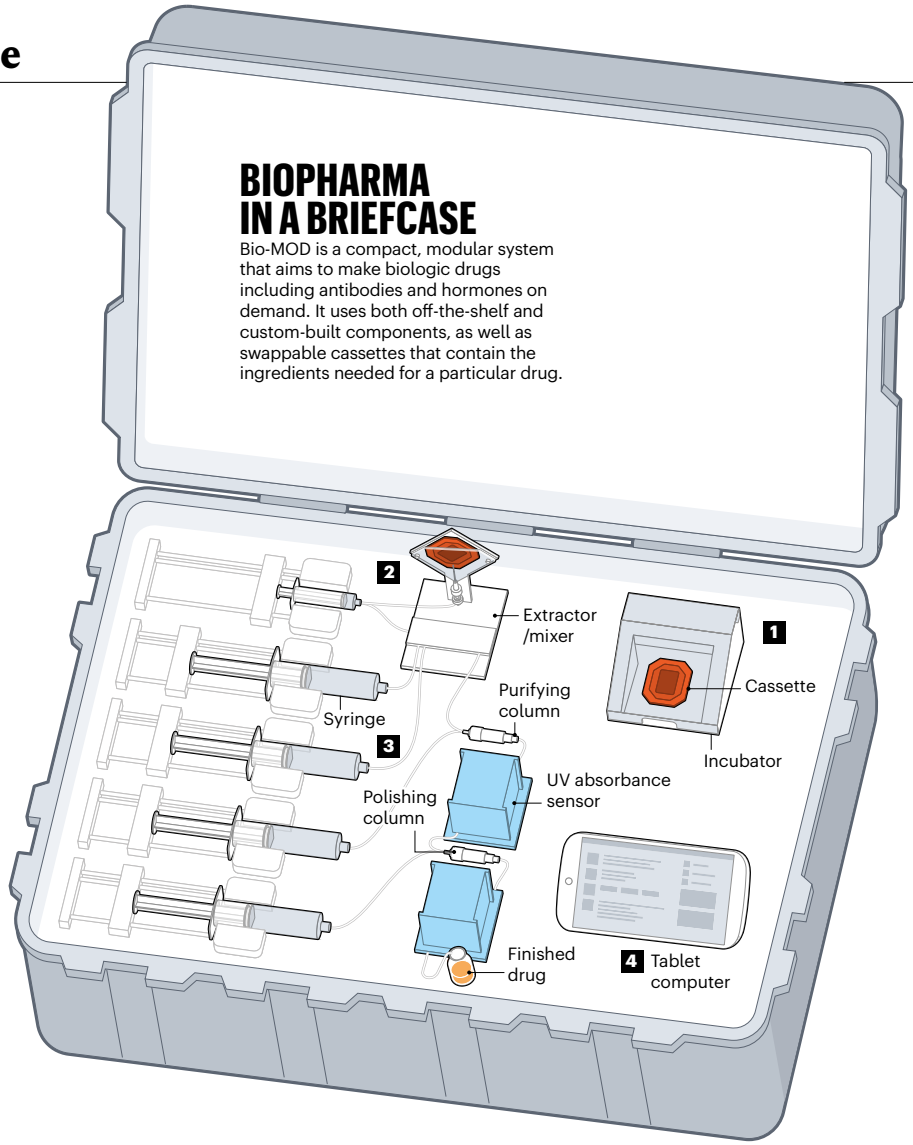
Ingenuity and thrift

Rao describes himself as an engineer and inventor, but he likes to use a third word, too. "I'm cheap," he says, laughing with the sheepish pride of someone who has kept his ageing Toyota minivan on the road for some 300,000 kilometres.

Ingenuity and thrift seem to run in the family. Rao's grandfather scrimped and saved for years to make the long journey from what was then Madras, India, to London to take the British civil service exam in 1927. Although he passed, the United Kingdom had filled its quota of Indian employees and turned him away. Instead, Rao's grandfather enrolled at University College London to study engineering. Money was tight, and he recorded his income and expenses in a small diary that Rao still keeps in his top desk drawer. Carefully opening the book, now missing its black leather cover, Rao reveals yellowed pages bearing an elegant script. The entries cover everything from the cost of books (£5) to a hot bath (2 shillings).

His grandfather eventually returned to India, passing on his cost consciousness and love of engineering. When Rao was a teenager in the late 1970s, he built his first radio by scavenging parts from electronics stores; it proved to be both cheaper and more reliable than commercial models. By the time he enrolled at the Indian Institute of Technology (IIT) in Madras (now Chennai), it seemed a forgone conclusion that he would become an engineer.

Both at the IIT and while pursuing his PhD in chemical engineering at Drexel University in Philadelphia, Pennsylvania, Rao thrived in an environment in which he had the resources to design sensors for chemical reactions. But what was missing from the work was any attempt to address the cost of these devices. Thinking back to the desperate poverty he saw in India, he knew technology wasn't any good if no one could afford it. After completing his PhD in 1987, Rao was hired by the Center for



1
A cassette containing DNA, cell extract and other necessary biomolecules is incubated in a temperature-controlled shaker to produce therapeutic proteins.

2
The cassette is then moved to another location, where its contents are extracted and mixed with solutions that will help separate the drug.

3
Syringes inject buffering solutions to stabilize and wash the drug as it passes through purifying and polishing columns.

4
A tablet computer controls the system's pumps and sensors to monitor the purity of the finished drug.

Advanced Sensor Technology (CAST) at the UMBC, where he's been ever since. Over the past three decades, he has devoted himself to creating low-cost chemical sensors and using them and other homespun creations, to solve real-world problems. His inventions include a disposable cardboard incubator for premature babies, which he's currently testing in a clinical trial in India, and a wearable fluorescent blood-glucose sensor for people with diabetes in the Philippines.

"He has all of these crazy ideas," says Leah Tolosa, Rao's colleague and assistant director at CAST. "Working with him is very unpredictable but also very comfortable."

Even their laboratory space reflects the centre's cost-conscious ethos. Situated in a residential neighbourhood of squat, brick post-war houses, CAST occupies the basement of a small building that was a juvenile detention centre in the early twentieth century. Rao's lab sits in its former kitchen and is cluttered with ageing equipment and half-built designs. It was in this space that Rao cooked up the gadget he's proudest of, an invention which was born out of conversations with Ling, whom he first met in 2012.

In 2003, as a US Army physician in Bagram, Afghanistan, Ling often had trouble procuring medication for the soldiers and civilians he was treating. He remembers in particular one US soldier with a head injury, whose blood pressure and pulse were unstable. It was a condition easily treated with a generic drug called bromocriptine. But the hospital didn't have any. To save his patient, Ling asked the US Air Force to fly in the drug from Landstuhl in Germany.

"The medication was cheap, but it cost a fortune in jet fuel," he says.

Ling, who has a PhD in pharmacology, was convinced that there had to be a better way to deliver drugs to the front lines. He realized that, with the right recipe and ingredients, he could probably cook up his own bromocriptine. The idea stuck with him when he moved to DARPA in 2004. And in 2012, when he was asked to head DARPA's new biotechnology division, he decided to try to make it a reality. Ling started reaching out to labs with a tall order: to create a portable pharmacy that can produce 1,000 doses of high-quality pharmaceuticals within 24 hours.

Ling divided the challenge into two categories: one for small-molecule drugs created through classical organic chemistry, and one for biologic drugs which are typically made by living cells. A team of engineers at MIT immediately took the lead on a small-molecule system, one that was later handed off to the lab of synthetic organic chemist Thomas Roper at VCU. To Roper, who moved there after 22 years at drug maker GlaxoSmithKline, the DARPA contract was an opportunity to force radical change in a typically conservative industry.

"It was a huge challenge," Roper says. "We had to figure out whether the system was suitable for making drugs for humans."

For Rao, the quest had a personal edge. He had recently watched a colleague face bankruptcy trying to pay for a cancer medication for his wife, a biologic agent known as granulocyte colony-stimulating factor (GCSF), which helps to replenish the body's supply of white blood cells.

As a chemical engineer, Rao thought he could find a better, cheaper way to make prescription drugs. After reading about DARPA's interest in on-demand biologics, he called Ling to learn more. But Rao was also hesitant. The number of moving parts that have to function flawlessly, in tandem, every time, for such a system to work was staggering. Sensing Rao's

trepidation, Ling shared his secondary dream for the project: to provide an alternative, lower-priced source of life-saving medication.

Rao sat up straighter. The project satisfied both his idealist streak and his inner cheapskate. He remembers pausing, thinking of his colleague's struggle with the prices set by drug companies, then replying, "Let's put them out of business."

Assembly line

Pharmaceuticals on demand is an idea that requires rethinking drug manufacturing from the ground up. Ever since mass production of medicines began, manufacturers have relied on batch chemistry. For common drugs that are stable at room temperature and have a long shelf life, it was — and still is — the most economical way to produce drugs.

But the strategy has drawbacks. It tends to be both time consuming and centralized, because corporations synthesize or purchase chemical precursors, ship them to a large plant, perform more reactions in massive vats, then process, purify and analyse the final product. Only then can a drug meet the standards of quality and purity set by agencies such as the US Food and Drug Administration (FDA). Managing the vagaries of intercontinental supply chains and regulations means it can take more than 12 months for a medication to reach store shelves. Ramping up production to help in crisis situations isn't always possible, and the system is prone to disruption if a single piece of the chain fails. But over the past decade, pharmaceutical chemists have been investing in an alternative.

Known as continuous-flow synthesis, this strategy involves pumping two or more reagents through a series of microchambers connected by thin, flexible tubes. This creates an uninterrupted succession of reactions as the chemicals move through the system. Various sensors monitor the progress and purity of the reactions, altering the flow and amounts of reagents to optimize conditions. MIT synthetic biologist and engineer Timothy Lu compares it to the assembly line that revolutionized industrial manufacturing a century ago.

"It's trying to push the envelope on how quickly we can do things," Lu says. "Continuous flow also has the advantage of being able to monitor quality over time."

The only way to meet DARPA's desire for portability and 24-hour turnaround was to use continuous-flow processing.

By 2016, the small-molecule team at MIT had created a refrigerator-sized unit with two modules. The first contains components that can be snapped in and out, like a coffee pod, to synthesize one of four different medications: diphenhydramine, an antihistamine; the anaesthetic lidocaine; diazepam, a sedative, and the antidepressant fluoxetine. The second module purifies the compound and processes it into a solution that can be given to people. In 2018, Roper came aboard, and the process moved to VCU for further improvements. Once in Virginia, the group shifted its focus to producing tablets of the antibiotic ciprofloxacin.

DARPA's requirements, Roper says, made the task technically challenging. "We couldn't have any impurities greater than 0.1%, which is an extremely high barrier to meet," he says.

For the biologics-on-demand project, DARPA awarded contracts to both an MIT team (headed by chemical engineer Christopher Love and including Lu) and Rao's UMBC lab. Lu and Love decided to use *Pichia pastoris*, a yeast, in their system. *P. pastoris* can be engineered to secrete large amounts of drugs and, because it has much of the same complex cellular machinery as humans, it can create a human-like protein right out of the box. After several months of tinkering, the system was so successful that Lu began working to co-produce several biologics at once to simplify production of the kinds of drug cocktails used for treating HIV or cancer.

> "THE MEDICATION WAS CHEAP, BUT IT COST A FORTUNE IN JET FUEL."

Rao decided to forgo live cells in favour of freeze-dried cellular extracts: RNA, DNA, enzymes and fragments of endoplasmic reticulum, the ribosome-studded network of tubes in which proteins are made ("everything but the membrane and nucleus", Rao says). He compares his system to baking using a store-bought cake mix (see 'Biopharma in a briefcase'). The cell-free system is shelf stable for up to two years, which provides some advantages over even the fastest-growing cells, says Michael Jewett, a synthetic biologist at Northwestern University in Evanston, Illinois. The other main benefit is that the freeze-dried cell components produce a more consistent product, he says. "Cell-free systems are a little more like chemistry than biology."

The project wasn't all smooth sailing, however. The cell-free approach requires extra purification steps to remove debris, and the thin tubes in Rao's early prototypes were plagued by air bubbles that interfered with the reactions. Increasing the pressure in the system helped. His first success was with GCSF, the protein-based drug that nearly bankrupted his colleague; Rao's system made GCSF that was just as pure as commercially available products (R. Adiga *et al. Nature Biomed. Eng.* **2**, 675–686; 2018). Subsequent tests in animals, not yet published, showed that it worked just as well, too. Love's team has made GCSF and other compounds that are practically identical to existing drug products (L. E. Crowell *et al. Nature Biotechnol.* **36**, 988–995; 2018).

Such milestones are important for moving forward with federal regulators, according to Lu, Rao and Roper. All three groups have remained in a dialogue with officials at the FDA, which has expressed interest in and enthusiasm about continuous-flow and on-demand manufacturing. It is still unclear, however, what criteria the FDA will use to evaluate these devices, and how it will ensure consistent drug quality. Although one firm, Sutro Biopharma, based in South San Francisco, California, has begun the approval process for drugs made by cell-free manufacturing, no drugs made in this way are currently on the market.

One major drawback of Rao's cell-free platform is that it cannot add sugar molecules and other chemical groups to proteins and biomolecules in the same way that complex cells can, according to MIT bioengineer James Collins, who helped to create cell-free technologies for his synthetic-biology work more than a decade ago. Until such systems get better at these tasks, the palette of drugs they can create will be limited, Collins says.

Although DARPA funded these on-demand systems for battlefield medicine, Ling and Rao are most excited about their potential humanitarian uses. A system that creates drugs on demand could reduce the need for refrigerated delivery and storage chains in getting vaccines and drugs such as insulin to remote regions or areas affected by crises. If a briefcase system like Rao's were available, hospitals and pharmacists would be able to synthesize what they needed — no more, no less.

But a big question is whether such a system could ever synthesize a sufficient quantity of drugs to cope with a disaster. "Their promise in the lab is exciting, but it still needs more work," Collins says.

Rao freely admits that Bio-MOD and other such systems need improvement. He has already begun experimenting with the design of add-on modules that would, perform some of the chemical modifications that many biopharmaceuticals require. He is also trying to work out how to link several Bio-MOD units together to increase production, although it will take months of work before either alteration is ready for testing.

As he continues to tinker, his vision of more affordable medicines for all — any time, anywhere — hasn't wavered. He imagines such devices democratizing drug manufacturing and putting pharmaceuticals in the hands of the people. He wants, he says, to give them "power over the means of production". Rao pauses at the thought, then laughs. "I just sounded like Karl Marx there, didn't I?"

Carrie Arnold is a science journalist based outside of Richmond, Virginia.

Correction

This article (*Nature* **575**, 274–277; 2019) erroneously stated that an MIT project to produce biologic drugs was led by Timothy Lu. In fact, the project was led by Christopher Love with input from Lu. The article neglected to mention that this team was able to create drugs comparable to FDA-approved drugs and cite the appropriate reference. Finally, the cost estimate for medicine-on-demand systems was ambiguous.