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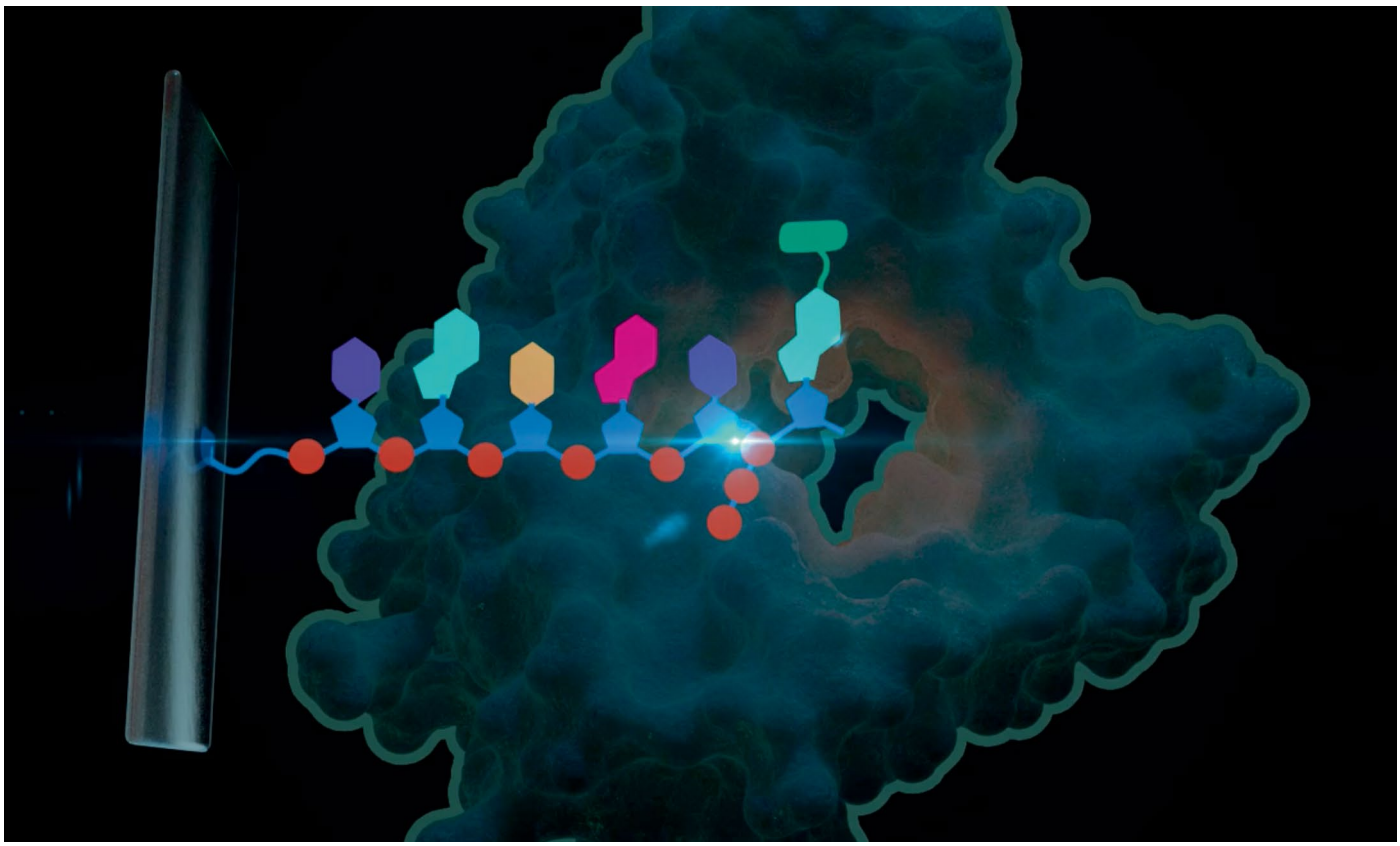

Artist's rendering of a polymerase–nucleotide conjugate adding its tethered nucleotide to the 3′ end of a DNA primer.

DNA WRITING TECHNOLOGIES MOVING TOWARD SYNTHETIC GENOMES

As new technologies hit the market, synthetic DNA is available faster and cheaper than ever before. Regulators are preparing to step in to limit opportunities for misuse. **By Caroline Seydel**

Made-to-order DNA is the cornerstone of synthetic biology. To access the vast potential of this emerging sector, DNA writing needs to be fast, cheap and accurate. As researchers move toward synthesizing chromosome-length DNA from scratch en route to creating entire synthetic genomes (Box 1), traditional chemical synthesis can't do the job. "It's affordable to buy a human genome in oligos, but you can't assemble it," says George Church of the Wyss Institute at Harvard University. "And the main reason you can't assemble it is because there's too many errors."

Yet the landscape may be poised for a major shift as companies make improvements in DNA synthesis, assembly and purification. Several companies now offer DNA synthesized enzymatically, a method that not only works in aqueous solution, thus avoiding the array of toxic compounds that are used in the more conventional synthesis, but also can produce complex sequences that can't be made by chemical synthesis. Other companies are improving the accuracy of the final product by optimizing the assembly and purification

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BOX 1

Fully synthetic genomes

Technological advances may accelerate the quest to create fully synthetic genomes, a once inconceivable undertaking that now sounds plausible.

In 2016, J. Craig Venter announced the creation of the first synthetic cell containing a genome designed completely de novo, rather than copied from an existing microbe. The novel cell contains the smallest genome of any independent organism (that is, organisms excluding viruses), at 531 kb — a mere 473 genes. The scientists chemically synthesized overlapping oligonucleotides, assembled them into larger fragments and assembled in yeast to generate the complete genome. The goal of Venter's project is to understand the minimum genetic requirement for an autonomous, self-replicating cell. At the other end of the synthetic biology spectrum, that same year, George Church helped launch the Genome Project-write (GP-write), which includes plans to create a complete synthetic human genome. One aim of the project is to recode the entire genome of cells to make them resistant to viral infection by changing how codons are translated to amino acids. As the ribosome is assembling proteins, it 'reads' the sequence of amino acids with the help of tRNA molecules that link each three-letter codon to a particular amino acid. Each amino acid corresponds to multiple codons. Deleting the tRNAs that correspond to certain codons and then replacing those codons in the cell's genome with synonymous codons makes the cell's translation machinery unable to read the viral genome. This genomic compression and recoding has already been demonstrated in bacterial cells[3,4].

Jason Chin of the Medical Research Council Laboratory of Molecular Biology in Cambridge works on recoding genomes for a variety of purposes, including virus resistance and enabling cells to build synthetic polymers the way they currently make native proteins. "How do you go from bits of DNA that you can make in a test tube, that might be on the order of hundreds of bases to a few kilobases, to booting up a genome in a living cell?" Chin asked. His lab published two new methods, called BASIS (bacterial artificial chromosome stepwise insertion synthesis) and CGS (continuous genome synthesis). Using these tools, they successfully assembled 1.1 Mb of human chromosome 21, featuring a variety of genomic elements, including exons, introns, and repetitive sequences[5]. These methods build on a technique they developed previously, called REXER (replicon excision-enhanced recombination), for integrating synthetic DNA segments of 100 kb or more into the *Escherichia coli* genome at designated sites. By performing this iteratively, they could replace up to half a megabase, or about one-eighth of the *E. coli* genome. "If you do that in parallel and get eight different strains corresponding to different segments of the 'pie'," Chin explains, "you can then put all those pieces of the pie together in one strain and have an entire synthetic genome." Using that method, Chin's lab created the recoded *E. coli* genome, replacing some 18,000 codons all at once.

"Our first genome synthesis probably took about a year, year and a half," says Chin. "Now we have a process where we think we can get this down to something on the order of weeks, and that we can massively parallelize this process."

steps. Finally, several companies are reviving the dream of benchtop DNA printers, with user-friendly design and fast turnaround times. As these and other innovations make gene synthesis faster, cheaper and more accessible than ever before, biosafety experts say it's time for legislation to protect against misuse (Box 2).

Enzymatic synthesis takes the stage

Since the 1980s, the only practical approach to commercial-scale oligonucleotide synthesis has been the phosphoramidite method, a chemical process that performs well for sequences up to 200 nucleotides in length[1]. Advanced assembly methods allow providers to offer longer DNA while techniques such as array synthesis have sped up production and reduced the cost. "We brought down the price of synthesis maybe 10,000-fold, just by converting to chips," says Church.

Still, chemical methods have drawbacks, including reliance on organic solvents, inability to synthesized highly repetitive sequences, and side reactions that can incorrectly remove purine bases, reducing purity and yield of the final molecule. The idea of using enzymes to synthesize DNA — the way living cells do it — has long tantalized researchers as a way to get around these limitations. "Chemical oligo synthesis is an incredible technology, but it has reached a performance plateau in terms of the quality of DNA it can make," says Dan Lin-Arlow, CEO of Ansa Biotechnologies. "It slowly damages the DNA as it's being made." This chemical damage caps the length of the DNA molecule that can be efficiently made by the chemical method.

Cells usually make DNA by copying an existing template, whereas synthetic biologists want to build DNA de novo. Fortunately, an enzyme exists with this very function: terminal deoxynucleotidyl transferase, or TdT. The challenge is how to direct TdT to add bases according to a programmed sequence.

In 2018, Lin-Arlow and Sebastian Palluk published a proof-of-concept paper for a technique for modifying TdT that allowed them to synthesize custom sequences[2]. "We take this enzyme, TdT, which indiscriminately adds bases to DNA, and we tether one nucleotide to the enzyme using a linker," explains Lin-Arlow (Fig. 1). "Then we have a DNA primer attached to a solid support, and we expose it to the conjugate of the base you want to add." The TdT–nucleotide conjugate adds the nucleotide to the end of the primer, with the TdT enzyme still attached. This blocks the other conjugates that are floating around from doing a second extension. The next step is to wash everything away and remove the enzyme with a cleavage enzyme, exposing the end of the DNA molecule for the next cycle of extension.

To commercialize their method, Palluk and Lin-Arlow formed Ansa Biotechnologies, and in March 2023, Ansa announced the synthesis of a 1,005-base-long oligonucleotide — the longest ever produced in one

BOX 2

Biosecurity

As artificial intelligence tools such as large language models (LLMs) grow more sophisticated, they increase the opportunity for non-experts to design biological agents. Recently, instructors at MIT conducted an exercise challenging students to use LLM chatbots to start a pandemic. "In one hour, the chatbots suggested four potential pandemic pathogens, explained how they can be generated from synthetic DNA using reverse genetics, supplied the names of DNA synthesis companies unlikely to screen orders, identified detailed protocols and how to troubleshoot them, and recommended that anyone lacking the skills to perform reverse genetics engage a core facility or contract research organization," the authors wrote in a preprint. Industry leaders, advocacy groups and legislators agree that the time is right to tighten security measures around synthetic DNA.

In July 2023, a bill was introduced to the United States Congress that would require DNA synthesis providers to screen their products for potentially hazardous sequences. The new regulation would also require any researcher receiving federal funding to purchase synthetic DNA only from suppliers compliant with screening regulations.

If passed, this legislation, called the Securing Gene Synthesis Act, would be the first law worldwide requiring gene synthesis companies to implement screening protocols, even though commercial DNA synthesis has been around for decades. Establishing appropriate oversight has been a work in progress as the industry has developed. "When these discussions first started, there was real concern within the US government about avoiding harm to the industry, letting it grow fast, being internationally competitive, not wanting to put a damper on things when they didn't really understand the direction of the technology evolution yet," explains James Diggans, who is chair of the International Gene Synthesis Consortium (IGSC) and the director of biosecurity at Twist Bioscience. "I think some of those concerns no longer apply."

The IGSC was formed in 2009 to coordinate the industry and government approach to biosecurity issues. The IGSC produced a Harmonized Screening Protocol establishing the standards and practices that IGSC member companies are expected to apply to their DNA synthesis products. These include screening gene sequences against a regulated pathogen database, screening customers against international sanctions lists and other criteria, and complying with all federal regulations, such as export licensing.

According to the Nuclear Threat Initiative (NTI), a nonprofit organization based in the United States that evaluates nuclear and biological threats, about 80% of DNA synthesis orders are currently screened, which leaves plenty of opportunities for malicious or negligent users to obtain dangerous sequences. Sarah Carter of Science Policy Consulting, who works with NTI on biosecurity, points out that, overall, industry leaders favor government regulation, if only to standardize the screening protocol. After years of setting up and paying for screening mechanisms on their own, she says, "they're feeling a lot of the responsibility, but none of the support."

"[Screening] is not a low-cost process," says Diggans. He points out that Twist shipped 558,000 genes last fiscal year. "That's 558,000 screening activities that were carried out," he says. Regulation could open avenues for centralized funding to develop new screening tools. The cost of keeping screening tools up to date can place a significant burden on a startup, for instance. "It's expensive to maintain, and that makes it hard for smaller companies," says Jaime Yassif, vice president of Global Biological Policy and Programs at NTI. NTI is developing a software tool for screening, called the Common Mechanism, with the goal of making it available at low cost. "We're trying to create a tool that could make it easy for a wide range of companies or nonprofit providers to screen their orders," Yassif says.

"This is all kind of a moving target because there are lots of new methods in artificial intelligence-assisted biological design that are churning out constructs that may not necessarily have homology to existing known proteins," Diggans says. "How do we develop new and improved screening tools that can then continue our history of risk assessment on these newer designs with the same level of rigor that we carry out right now?" Rather than expecting individual companies to foot the bill for developing new screening tools, he says, "it's something that governments would be really well placed to help with in terms of R&D spending."

Benchtop synthesizers could pose a particular risk because they can give the end user complete control over the sequence. In May 2023, NTI issued a report recommending that benchtop synthesis device manufacturers "conduct rigorous customer screening" and "ensure that each DNA fragment produced by the device undergoes rigorous sequence screening." If passed, the Securing Gene Synthesis Act applies to "gene synthesis providers or manufacturers of gene synthesis equipment."

DNA Script is working with Aclid, a screening company co-founded by Harris Wang and Kevin Flyangolts, to optimize biosecurity screening on the devices, both online and offline. "The workflow for online devices ends up being somewhat similar to manufacturers with centralized facilities," says Flyangolts. "An order is placed on the device, the device is connected to the internet, and that sequence is then submitted to us. We provide real-time information on pathogenicity or toxicity. If there's any potential concerns, that kicks off a separate flow on the device, either having the device need to be unlocked or need to be approved for further action by somebody within DNA Script."

Offline devices pose more of a challenge, he says. "We're still figuring out how that would work from a process standpoint," he says. "Our software is relatively easy to load onto the device, but [if a sequence is flagged] do you lock the device? Do you need someone to come in person and unlock it? That's still a work in progress."

(continued from previous page)

Ybert says that the company carefully screens their customers and provides safeguards against the devices falling into unauthorized hands through resale. "We are working with the different authorities both in the US and Europe to make sure that we have a clear vision of who we can sell to and who we cannot sell to," he says. If a verified customer sells the device to someone on a government's restricted list, Ybert says, DNA Script would not supply that buyer with the specialty reagent kits needed to run the machine. "This person will end up with a very fancy, expensive, one-trick-pony liquid handler," Ybert says.

Ultimately, careful attention to biosecurity not only protects society, but is critical for the future of synthetic biology. "If we want to see a future where there are more things that are biologically engineered," Flyangolts says, "we need to make sure that we do that safely and responsibly."

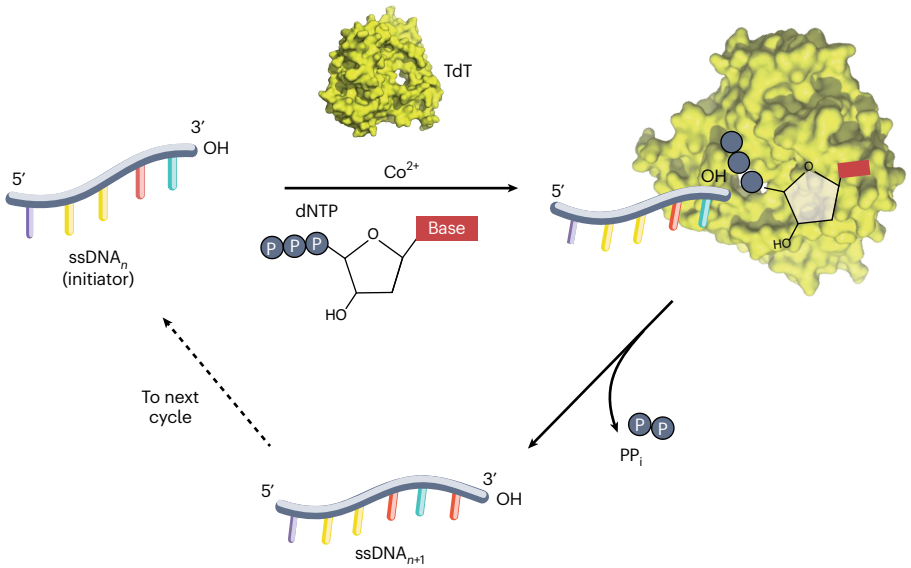

Fig. 1 | Enzymatic synthesis and modification of high molecular weight DNA using terminal deoxynucleotide transferase. Adapted from Yoo, E., Choe, D., Shin, J., Cho, S. & Cho, B.-Y. *Comput. Struct. Biotechnol. J.* **19**, 2468–2476 (2021), CC BY 4.0.

synthesis. But the benefit of enzymatic synthesis goes beyond length, Lin-Arlow points out. "We can make certain kinds of sequences that are extremely difficult for other people to stitch together from the shorter oligos that chemical synthesis produces," Lin-Arlow says. The company recently shipped its first product, complex DNA promoter sequences, to early-access customer Enoda Cellworks, a small cell therapy startup.

"One of the hardest things to get is the non-coding elements that allow the ORFs [open reading frames] to be expressed," says Michael Chavez, CEO of Enoda. One element he needed was the CMV promoter, which is 600 base pairs long, highly repetitive and GC-rich. When he tried to obtain it from existing DNA synthesis companies, they declined to fill the order, he says, which led him to try Ansa. "I thought, 'I'm just going to have to stitch it together.' I'm still not sure how much time it would have taken us," he says. "Ansa just synthesized it and sent it to us, and they were 100% accurate the first time."

Another enzymatic DNA synthesis company, Molecular Assemblies, partnered with enzyme engineering company Codexis in 2020 to develop their own version of TdT, which they patented. "We modified the enzyme by about 25%," says CEO Michael Kamdar. The enzyme can withstand high temperatures, the better to synthesize sequences prone to folding. "The enzyme can operate up to 70° Celsius," says Phil Paik, chief technology officer of Molecular Assemblies. "Linear DNA wants to fold over to itself when it finds a complement. It will bind to itself and interrupt the process of being able to add nucleotides. By raising the temperature, we're able to melt away that secondary structure and synthesize without issues."

Molecular Assemblies launched their key customer program last year and shipped to their first customer, NovoHelix, in February 2023. NovoHelix founder and CSO Steve Bischoff says he approached Molecular Assemblies to make some difficult CRISPR knock-in sequences, incorporating lox sites and Cas9-targeting sequences for site-specific recombination. "Those sites have inverted repeats with a spacer, and based on the topology of the oligo, it's challenging to synthesize because of the three-dimensional folding structure," Bischoff says. The oligos he received from Molecular Assemblies were sequence-perfect, he says, whereas with chemical synthesis, complex G+C-rich sequences like these may come back "riddled with indels." That's a problem worth spending a little more to avoid. "For me, the end result is putting [the construct] in an animal model or cell-based model," he says. "There's a high cost to making sure that is correct the first time."

Not everyone is banking on TdT for enzymatic synthesis. Camena Bioscience, in Cambridge, UK, developed a synthesis platform involving "a proprietary mix of enzymes that utilizes a ligation-based method," says Steve Harvey, CEO and co-founder of Camena. They start with a highly pure class of nucleotide reagents they call Addamers, which are produced by fermentation rather than inorganic chemistry methods, making it more environmentally friendly as well as ensuring the accuracy of the synthesized molecule. One problem with optimizing TdT synthesis, Harvey says, is that nucleotide manufacturers will typically guarantee their product to something like 95% purity. "That 5% error is a range of things that are derivatives of the process of making the nucleotides you want," he says. "That then becomes a great source of error in your synthesis approach." Increasing that purity eliminates time-consuming downstream purification steps, and Harvey says Camena can deliver gene-length DNA in around 10 days.

Founded in 2016, Camena closed a $10 million series A financing round in July 2023. "We've hit multi-million revenue stream already," Harvey says. "People are turning to

us because they can't get hold of the gene sequences they want."

Still, large-scale synthetic DNA providers such as Twist Bioscience have spent years developing highly efficient industrial-scale manufacturing processes, which include assembly and error-correction methods to generate longer DNA molecules than can be built in a single phosphoramidite synthesis step. "It remains to be seen whether enzymatic synthesizers can scale to serve the market," says Twist CEO Emily Leproust. "At this moment, chemical synthesis is cheaper, more accurate and can produce longer strands of DNA." She adds that Twist is developing an enzymatic synthesis approach for DNA data storage, a scenario where synthesis would need to occur on-site. "They're not set up to have the chemicals required for phosphoramidite synthesis on-site, so we are pursuing enzymatic for this application," she says.

DNA, PDQ

Enzymatic synthesis may be the key to putting DNA synthesis back on the lab bench. For users who place a premium on speed, enzymatic benchtop synthesizers may provide the right balance of turnaround time, autonomy and ease of use.

During the COVID-19 pandemic, Paul Freemont of Imperial College London recalls the frustration of waiting for DNA supply to catch up with demand. "There was a massive amount of interest in making spike protein variants for all sorts of studies," he says. "At Imperial College, we have a very strong virology group that's contributed a lot to our national COVID response, and they couldn't get DNA."

That experience drove home for him the appeal of benchtop synthesizers. In the 1990s, benchtop synthesizers using chemical synthesis gradually fell out of fashion as researchers turned to core facilities or large-scale production companies for their DNA. Now, several companies are revisiting the market for personal DNA printers. DNA Script, headquartered in Paris, offers a desktop printing platform called Syntax, which uses enzymatic synthesis and generates oligos up to 120 bases overnight.

As the director of the London Biofoundry, Freemont began working with DNA Script early on as a pilot tester. "At the moment, we can make 120-mers in a 96-well format, and what we want to do is extend that out so we can make 120-mers in a 384-well format," he says. "And if you make 120-mers, that's good enough to make a 2 kb gene using modular assembly technologies."

Systems biologist Harris Wang at Columbia University similarly turned to DNA Script after trying to do fast-paced virology work during the pandemic. "We were particularly interested in the use of these [benchtop] oligo synthesis platforms for rapid pandemic response," Wang says. "Oligos from centralized facilities may take a while to get, and that was our rate-limiting step."

The Syntax DNA printer requires less specialized training than its chemical predecessors, and all the reagents are aqueous, avoiding the problem of handling and disposing of toxic chemicals. "It's an exciting new technology that's very turnkey," Wang says. "You had to be a chemist to know how to run the old-school phosphoramidite synthesizers. This is a lot more streamlined."

However, benchtop oligo synthesis may not replace large-scale suppliers for most users anytime soon. "I think it's going to be a mixed economy for a while," Freemont says. "I don't think one is necessarily going to take over the other." The London Biofoundry still orders most of its DNA from companies like Integrated DNA Technologies or Twist, but Freemont says the speed and control provided by in-house synthesis provide a real advantage over ordering when it comes to accelerating the design–build–test cycle that underpins synthetic biology. "[Ordering] can take weeks, and also, not all sequences can be synthesized," he says. "Some companies will just say, 'no, we can't do that.'"

Often, time is money. DNA Script CEO Thomas Ybert points out that in a clinical setting, faster DNA turnaround times both improve patient care and boost the bottom line. He cites the example of genetic testing in neonatal intensive care units. If sequencing reveals a rare mutation, that patient's sample must be resequenced, a process that requires custom-made oligos targeting the region of the mutation. In-house oligo production can reduce that turnaround from 15 days to 5 days, allowing the patient to get proper treatment sooner. While DNA Script oligos may cost more per base than oligos from a centralized supplier, if they increase the number of tests the clinic can run in a year, that may offset the extra cost.

Designer genes

Although enzymatic synthesis can generate longer oligonucleotides in a single reaction, even small rates of error will eventually limit the size that can be efficiently produced. For instance, with an approximately 99.9% average stepwise yield, Ansa's process to synthesize a 1,005-base oligo generated 28% sequence-perfect molecules. Manufacturing longer DNA molecules will always require an assembly step and a purification step to eliminate errors, so some companies are innovating ways to improve the efficiency of the overall workflow, not just the synthesis step.

UK-based Evonetix has partnered with Analog Devices to design advanced semiconductor chips that direct the synthesis, assembly and purification steps. Their goal is a benchtop synthesizer that can produce constructs up to 1,500 bases long. "We're trying to make a machine that synthesizes lots of different oligos as a pool, then assembles them together to make a gene-length double-stranded piece of DNA," says Matthew Hayes, cofounder and chief technology officer of Evonetix.

Evonetix adapted the phosphoramidite synthesis method to be temperature sensitive, which allows the chip to precisely manage the synthesis reaction by adjusting the temperature. "We have a thermal chip capable of creating these islands of independently controlled temperature within a flowing liquid," Hayes says. "That thermal control allows us to control the synthesis very accurately and also assemble the DNA in situ."

After the synthesis step, the chip contains 384 different oligos. Each oligo overlaps the preceding and following sequence by 50%, ensuring that every base in the sequence is represented on two complementary oligos. Electric fields direct the assembly of these oligos into longer, double-stranded fragments. "We can cause a group of oligos to be released from the surface, move directly to the next sequence they should attach to, and hybridize," explains Hayes. Once the oligos are assembled, the chip applies "thermal error removal," raising the temperature to a point slightly too low to melt correctly hybridized DNA, but high enough to melt fragments containing errors, leaving only perfect double-stranded sequences. "We get all the benefits of both pooled and liquid-handling assembly but with the addition of this error removal step," Hayes says. "And it's all done right on the surface of this chip with the tiny, tiny quantities that you synthesize in an oligo pool."

Roman Trogan, R&D head of bioelectronic platforms at Analog Devices, points out that biotech tools have conventionally involved complex instruments that use simple consumables. "We think that if we start moving the 'smarts' from the instrument into the consumable and make the consumables smarter,

we can really improve multiple parameters of whatever application we're going after," he says. "We're bringing biology as close to electronics in this case as possible."

California-based Elegen is making improvements across the entire synthesis–assembly–cloning workflow, reducing the turnaround time to produce next-generation sequencing-verified double-stranded DNA as long as 20 kb. "DNA production has challenges in length, accuracy, speed, scalability, throughput — all those things," says Elegen founder and CEO Matthew Hill. "You could innovate at any of those steps in the workflow. One of the most important problems that we addressed was the cell-based cloning and purification of DNA." They have developed an integrated system of instruments, technologies and methods, including a cell-free cloning method that produces DNA faster without compromising accuracy. "Elegen's DNA is long enough and accurate enough to meet the needs of therapeutic workflows," Hill says. "Scientists receive DNA that they can use immediately downstream without waiting weeks or longer for cell-based cloning."

In March 2023, Elegen shipped their first orders of Enfinia DNA, double-stranded DNA up to 7,000 bp long with a 7-day turnaround time. Then in May they announced an early access program offering delivery of plasmids up to 20,000 base pairs and highly complex sequences, including sequences with repeat regions of up to 200 base pairs and hairpins of up to 60 base pairs.

By optimizing production of these complex sequences, Hill hopes to mitigate one of the most frustrating aspects of the design–build–test cycle in synthetic biology: the failure of the 'build' step. "[Scientists] design a sequence in silico that they think is going to achieve the results inside a cell and they order it, only to find out the supplier can't make that sequence," he says. "Even before you try to build, you find out you can't make the parts."

Hill says he believes that further improvements at the systems level will bring about a new era of synthetic biology and begin to realize the potential of cells as a production platform. "Today, we are still in the mode of not even the punch card programming of the 50s and 60s, but the plugboard programming of the 40s," he says. "That is fundamentally blocking what I think is going to be the greatest revolution in humanity."

How soon is now?

As always, the revolution won't happen overnight. "The bottom line is that DNA synthesis is still really slow, expensive and inaccurate," says John Cumbers, CEO of SynBioBeta. "It still has so far to go in terms of what we know biology can do."

People's excitement level about the new offerings varies depending on the applications they are most interested in. "The biopharma industry is looking for fast turnaround," Cumbers says. "The research market in universities is looking for as long and as cheap as possible, less worried about the turnaround. The DNA data storage market, I think they're looking for high accuracy." The overall hope in the industry, he says, is that pharma will provide early customers who can pay the big bucks while DNA data storage customers will drive innovations that bring the price down, and together those markets will carry the technology forward to a point that enables a sustainable biomanufacturing revolution.

"Cost is incredibly important," says Barry Canton, chief technology officer at the synthetic biology company Ginkgo Bioworks. "You've got to design DNA, you've got to write it, you've got to put it into cells, you've got to measure how those cells perform, and you have to learn from that. The single most expensive step of that workflow is the synthesis of the DNA."

Ginkgo is one of the best-known synthetic biology companies, founded in 2008 with the goal of developing a platform for harnessing the power of living cells for manufacturing a variety of products. Because Ginkgo's workflow depends on making and testing tens of thousands of designs, Canton says, they have a longstanding supply agreement with Twist Bioscience. "They have been building a centralized DNA factory. They get a lot of economies of scale from that, and they can pass on to us this very aggressive, competitive pricing. What that means for us is more experiments."

Different applications benefit from different technologies, however, and Canton says Ginkgo is open to trying out the products produced by these new methods. "If you as a synthesis company let me make a longer piece of DNA, or a more complex piece of DNA, then I'm freed up to be more creative or more ambitious in the designs I take on," Canton says. Indeed, Ginkgo acquired DNA synthesis company Gen9 in 2017, gaining exclusive access to Gen9's BioFab gene manufacturing platform, as well as Gen9's proprietary synthesis and assembly technology, allowing them to produce DNA up to 10 kb in size in-house. Founded by George Church, Drew Endy and Joseph Jacobson, Gen9 was the first to synthesize DNA using silicon chips, producing millions of oligos in parallel. Engineered proteins that detect and remove errors enabled the synthesis of longer, more accurate sequences than had been previously possible.

Church, who has co-founded and advised several gene synthesis companies in addition to Gen9, points out that, to succeed, DNA synthesis companies not only need to provide superior technology, but also create a new market for their product or service. "What inevitably happens to them is they have a good idea, but then they get down in the tar pits, where they get sucked into this highly commoditized market where everybody is competing on exactly the same thing," he says. "The more radically you reduce the price, the faster you're going to go out of business."

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