



Alix DNA Writing

Market Deep Dive
August 2020

Summary

Synthetic Biology Market	DNA Writing Technology
<ul style="list-style-type: none">● Large, rapidly growing market (CAGR: 28.8%)● Majority of capital invested in medical and healthcare sectors● Advancements in DNA sequencing and editing have led to an increased demand for synthetic DNA● Growth limited by high costs of oligo manufacturing● Large, entrenched companies dominate the market using biomanufacturing-as-a-service plays	<ul style="list-style-type: none">● Phosphoramidite chemistry has been the dominant synthesis methods since its advent ~35 years ago● Methods relying on microchips are rising in popularity (i.e. Twist)● Existing methods have long turnaround times, high costs, and low accuracy for longer sequences● Emerging methods include microfluidics and enzymatic synthesis which may increase accuracy and speed of synthesis● Companies building these technologies are shifting towards all-in-one desktop synthesizers

Market Overview

Synthetic Biology Market

- Valued at \$5.2 billion in 2019 and is projected to grow to \$18.9 billion by 2025
- CAGR: 28.8%

Oligonucleotides Market Size

- \$214M in 2014

Genes Market Size

- \$137M in 2014

Key Features:

- Large market with applications in drug discovery, pharmaceuticals, gene therapy, protein engineering, agriculture, chemicals, energy...
- Driven by increased R&D funding and growing demand for synthetic DNA
- Limited by the high cost of biomanufacturing
- Researchers rely on biomanufacturing-as-a-service companies as sources of synthetic DNA
- There are few do-it-yourself gene synthesis technologies on the market, however due to high cost of equipment and comparable turnaround time, the lab-as-a-service model is more popular

Major Players

	Twist	IDT	GenScript	GENEWIZ	Agilent	Eurofins
Method	Silicon microchip	Chemical	Chemical	Chemical	Microarray	Chemical
Price per base	\$0.07	\$0.17	\$0.23	\$0.21	-	-
Max Gene Length	1800 bp	3,000 bp	8,000 bp	10,000 bp	-	10,000 bp
Time	7-10 days	10-15 days	4 - 25 days	8 - 40 days	-	6 - 12 days

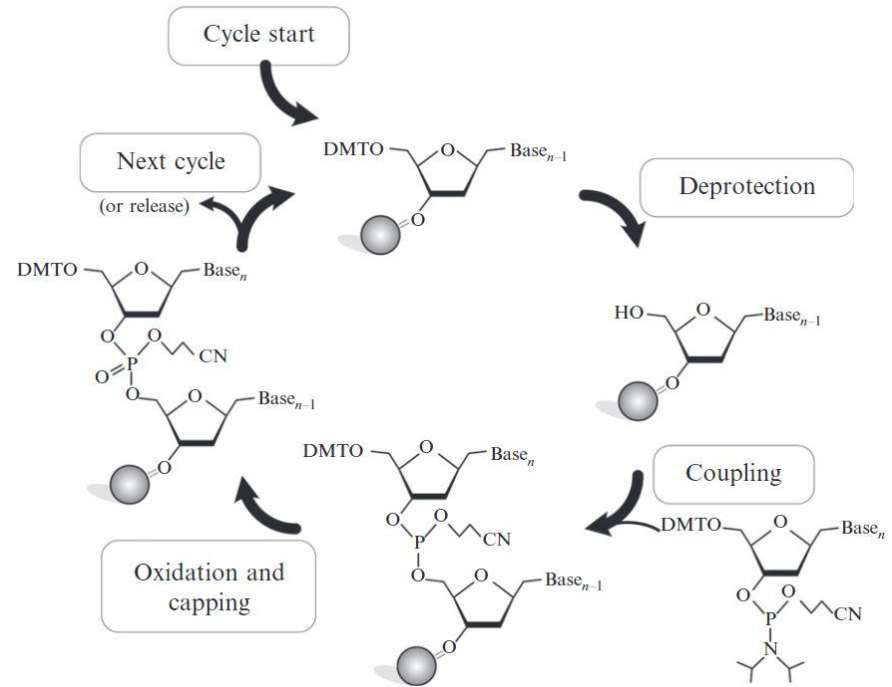
Technology Overview

Design Considerations for DNA Writing Platforms

- Decrease turnaround time
- Decrease cost
- Increase yield
- Increase accuracy
- Increase or retain accuracy for longer sequences
- Increase or retain accuracy for longer assemblies
- Allow for corrections to be made if necessary
- Reduce reagent consumption
- Improve robustness
- Increase throughput and ensure fidelity

Chemical Synthesis

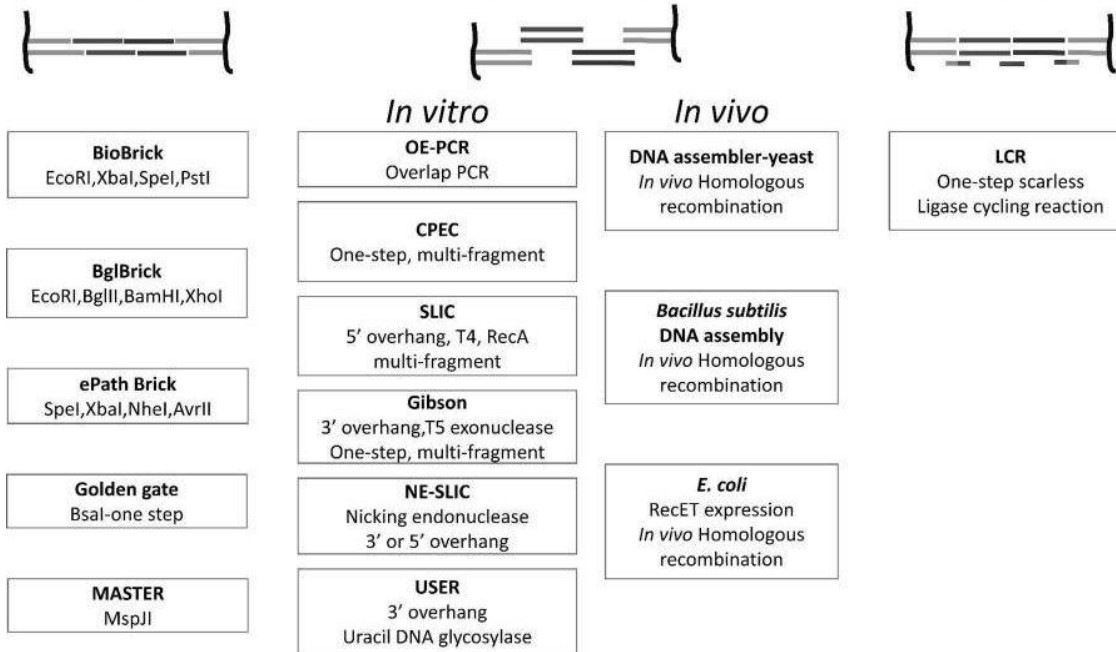
- Phosphoramidite synthesis (solid phase) invented in 1980s
- Each oligo formed in separate column or well
- Cycle adds oligo to chain in 3' → 5' direction
- High efficiency (99%) and high accuracy (99.5%) for only short sequences (<150 nt)
- Post synthesis purification necessary
- Production of toxic byproducts



Microchip Synthesis

- Similar to semiconductor lithography
 - Light-directed synthesis on microarrays selectively deprotect photolabile phosphoramidites
- Allows for parallel synthesis of thousands of unique oligos on a single chip
- Compared to solid phase synthesis:
 - Less expensive because less reagent is required
 - Yield for any one oligo is 2-4 orders of magnitude less (may be insufficient for gene assembly reaction)
 - Synthesis errors are more common
 - Comparable lengths of oligos can be synthesized
- Optimizing the parameters of the reaction (microchip design, reagent use, procedures) can be improved for synthesis of high-fidelity, longer oligos

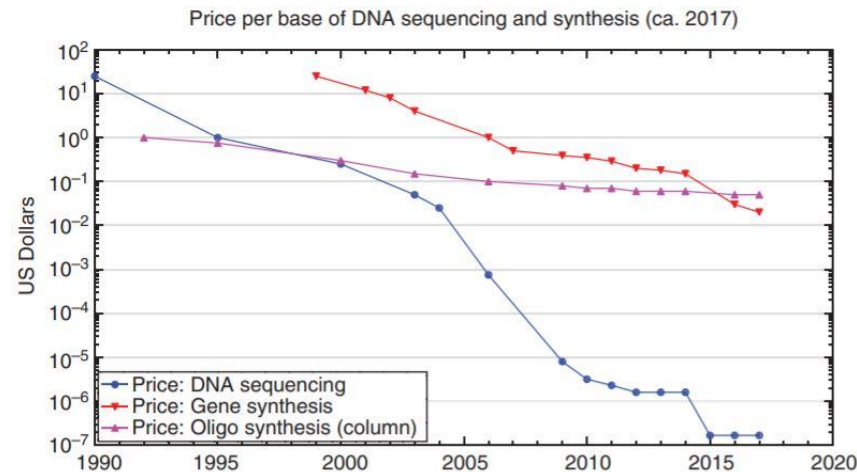
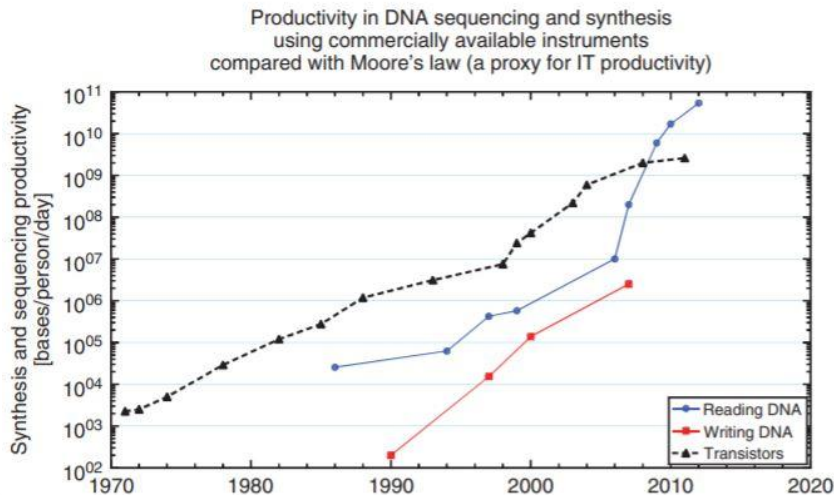
Oligo Assembly - Gene Synthesis



There are many methods of assembly which allow for formation of large constructs. Accuracy and speed of oligo synthesis is the core bottleneck.

History, Key Trends, Future Development

- Advances in DNA reading and editing have driven the synthetic biology and genomics markets
- Productivity in DNA sequencing has increased at a rate surpassing Moore's Law
- Competition has rapidly driven down price of DNA sequencing
- DNA synthesis has lagged behind in terms of cost and productivity
- Given significant technological advances in DNA writing, it is expected that competition will result in decreases in price and increases in productivity (and accessibility) following this trend



Emerging Technologies

Microfluidics Approach

- Makes use of phosphoramidite chemistry
- Advantageous in terms of cost, programmability, and robustness
- Reduction in the amount of reagents required
- Shorter turnaround times due to automation
- Limited in terms of accuracy and oligo length

ELEGEN

evonetix

Enzymatic Approach

- New synthesis method involving polymerase TdT (terminal deoxynucleotidyl transferase)
- Jay Keasling @UC Berkeley is a key pioneer of this method
- Not yet commercially available
- Cannot yet rival chemical synthesis in terms of length or efficiency

DNA SCRIPT

NextGen DNA Synthesis

Ansa
Biotechnologies

nuclera

 **MOLECULAR
ASSEMBLIES**

Design Considerations for DNA Writing Platforms



DECREASE
TURNAROUND TIME



DECREASE COST



INCREASE YIELD



INCREASE
ACCURACY



ENSURE FIDELITY

Industry Challenges

1. Technical Challenges

- a. Synthesis Fidelity and Error Correction
- b. Purification and post-processing

2. Market Challenges

- a. Large, entrenched players dominate the market - may be difficult for newcomers upon entry

3. Ethical, Biosecurity, and Regulatory Challenges

- a. Primarily related to applications of synthetic DNA which include gene therapy and genetic engineering
- b. The field is in its infancy and approval frameworks are evolving

Emerging Applications

- **DNA Storage**
 - Cost of synthetic DNA is prohibitively high for DNA storage applications
 - New technology resulting in low-cost, high fidelity, accurate synthesis can enable growth in DNA storage
- **Personalized Cancer Treatment**
 - Limited by high turnaround times and accuracy of DNA synthesis
 - Faster synthesis can enable personalized gene therapies to be developed and administered more quickly
 - Lack of robust delivery technology limits potential
- **DNA Origami Nanoparticles**
 - Takes advantage of molecular interactions within DNA to form ordered structures for biosensing, bioelectronics, and delivery
 - DNA writing enables faster R&D cycles for DNA origami and formation of new structures

Conclusions

Vertical Strengths	Vertical Weaknesses
<ul style="list-style-type: none">• There is a large market for biological production (and DNA writing) spanning industries including chemistry, food and agriculture, medicine, and basic sciences research.• Advances in DNA reading have set the stage for the DNA writing field in terms of demand.• Increasing competition in the DNA writing space is expected to lead to increased productivity and decreased price of oligonucleotide and gene synthesis.• Improvements to the speed, cost, and accuracy increase the accessibility of DNA writing and reduce barriers to entry for startup companies, small labs, and independent entrepreneurs.• The market is expected to rapidly expand due to increased capabilities and applications enabled by better DNA writing platforms (i.e. DNA storage, novel cell and gene therapies, DNA origami etc.).	<ul style="list-style-type: none">• Until recently, there has been little technological development in the field. This has allowed entrenched players to dominate the market based on development of 35 year old technology.• Currently, emerging technology for DNA synthesis falls short of the “better, faster, cheaper” requirement for synthesis platforms. Further, technological development is necessary to accomplish these goals to scale.• Falling prices of DNA writing may limit profit margins and incentives for DNA synthesis companies to invest in developing new technologies.

Investment Theses

1. **Core technological innovation with highly defensible IP:** Because synthesis technology has remained more or less the same for over 35 years, the market is primed for startups to become leaders in the field based on a core technological innovation.
2. **Better, faster, cheaper oligonucleotide synthesis:** The key to unlocking the potential of the DNA writing space is improving oligonucleotide synthesis specifically; that is first synthesizing smaller sequences of DNA better, faster, and cheaper to then better enable assembly.
3. **Automated platform technologies (desktop):** Of the above goals of the DNA writing space, speed of synthesis is one of the most limiting bottlenecks. Automation of the synthesis process such that it can be accomplished in-house may be paramount in reducing turnaround time for oligonucleotides and genes.