Note: This is a rough “internal notes” document, which we’re making public in case it’s useful for people. Megan and I (Ben) **don’t necessarily have a high degree of confidence in any particular claim made in this document**, and we don’t guarantee internal consistency or that what’s written here reflects our current beliefs.

Genetic Circuits

Author: Megan Kinniment

Timeline of Development

(Format is a bit different to other techs because this was one of the earlier ones I did - sources as footnotes instead)

Year	Events	Notes	Source
1949	“This idea of programming cellular functions into gene circuits has an impressive historical pedigree. In 1949, even before the discovery of the double helix of DNA, Max Delbrück described a general scheme for obtaining bistability in a biochemical system”		Synthetic Biology: evolution or revolution? A co-founder's perspective
1953	Double helix structure of DNA discovered - copying mechanism		DNA double helix wiki
1957	The concept of artificial cells was first proposed by Dr. Thomas Ming Swi Chang in 1957.		
1961	“Landmark publication” Francois Jacob and Jacques Monod publish theory that molecular regulatory circuits underpin response of cell to its environment after studying the lac operon.		Jacob and Monod theory of molecular regulation

(“next few years”)	after jacob and monrads landmark publication a more concrete picture of what was going on materialised after bacterial transcription was better understood i.e the regulatory circuits interact with how DNA is expressed		
1970s-1980s	the concept of re-usable parts for designing biological systems was well-recognized by the pioneers of modern genetic engineering in the 1970s It wasn’t really the same concept though - they used genetic engineering for all human design in formulating new genes. Source contrasts it with modern genetic circuit research which is rooted in programmability instead PCR and cloning in the 1970s-1980s (mostly just cloning and recombinant gene expression) Techniques to make creating designed DNA easier essentially. In 1977 “a research team had spliced a rat insulin gene into a bacterium that then produced insulin” - an early application of something similar. Later in the 70s they managed this with human insulin genes		Synthetic Biology: evolution or revolution? A co-founder's perspective DNA spliced Bacteria making insulin
1980s - 1990s	Rise of high throughput biology		
1985	C H Bennet and R Landauer publish ‘The Fundamental Physical Limits of Computation' apparently think about using DNA to compute things but there was uncertainty about whether enzymes could compute mathematical functions at all - not super sure of this.		Aldeman Bio
1988	1988: First DNA amplification by the polymerase chain reaction (PCR) using a thermostable DNA polymerase is published in Science by Mullis et al.[17] This obviated adding new DNA polymerase after each PCR cycle, thus greatly simplifying DNA mutagenesis and assembly.		Synth bio wikipedia
1990s	Automated DNA sequencing and complete genomes for model organisms ecoli and s.cerivisae		A brief history of synthetic biology

	"By the mid - 1990s, automated DNA sequencing and improved computational tools enabled complete microbial genomes to be sequenced, and high-throughput techniques for measuring RNA, protein, lipids and metabolites enabled scientists to generate a vast catalogue of cellular components and their interactions. This 'scaling up' of molecular biology generated the field of systems biology , as biologists and computer scientists began to combine experimentation and computation to reverse-engineer cellular networks "		
1994	Leonard Aldeman publishes work on solving NP complete problems with molecular computing. He originally got this idea from realising the similarity of DNA reading to a simple turing tape computer.		Synthetic Biology: evolution or revolution? A co-founder's perspective Aldeman Bio
~1995	by mid 1990s automated DNA sequencing and better computers meant they could measure and categorise vast quantities of DNA in very high detail Systems biology emerges - biologists and computer scientists working together to reverse engineer cellular networks. They find a hierarchy of cellular logic "modules", like other engineered systems. Bottom up approaches now look a bit more manageable "What emerged from this enormous and continuing basic research effort was a view that cellular networks, although vast and intricate, were organized as a hierarchy of clearly discernable functional modules, similar to many engineered systems 10 . Gradually, it was recognized that the rational manipulation of biological systems, either by systematically tuning or rearrang - ing their modular molecular constituents, could form the basis of a formal biological engineering discipline 11 . As a complement to the top-down approach of systems biology, a bottom - up approach was envisioned, which could draw on an ever-expanding list of molecular 'parts' to forward-engineer regu - latory networks."		A brief history of synthetic biology
1997	"DARPA announced a new funding program called Hybrid Information Appliances in 1997 which sought to advance research in hybrid biological/electronic computing systems." Apparently this was stimulated in part by the	Leonard Aldeman's work influences DARPA 1997 funding	Synthetic Biology: evolution or revolution? A co-founder's perspective

	success of Leonard Aldeman in solving NP complete computational problems using DNA as the computer and worries that Moore's law was slowing down and a new change in computing would be needed to keep up the same pace of improvement. "The DARPA program began to bring members of the community together." "The Hybrid Information Appliances program led to the initiation of a similarly minded Office of Naval Research funding program, led by Eric Eisenstadt, with a focus on engineering gene regulatory networks for cellular computing . This program funded the development of the genetic toggle switch. Soon to follow was the DARPA Biocomputing program which funded DNA memory research and the BioSPICE initiative to build a CAD system for gene circuit engineering. "		
1998	The concept of being able to computationally "program" cells through their DNA is fleshed out. In 1998, this concept was termed 'cellular computing' by Tom Knight and Gerald Sussman [20] at MIT. In the same year, such cell-based programs were called 'genetic applets' by Tim Gardner and Jim Collins at Boston University [5,7,21]:		Synthetic Biology: evolution or revolution? A co-founder's perspective
1999	"The DARPA program began to bring members of the community together. The Hybrid Information Appliances program led to the initiation of a similarly-minded Office of Naval Research funding program, led by Eric Eisenstadt, with a focus on engineering gene regulatory networks for cellular computing. **This program funded the development of the genetic toggle switch**" (genetic toggle switch was one of the big papers that came out in 2000) Office of naval research biocomputing funding under Eric Eisenstadt "He also served as a program manager at DARPA (1999–2005), where he developed and managed basic and applied interdisciplinary research programs in various biotechnology areas, such as genomic sequencing of pathogens, neurobiology, synthetic biology, and protein design. Before	DARPA work leads to eric einstadt naval office funding which in turn funds first genetic toggle switch	Synthetic Biology: evolution or revolution? A co-founder's perspective Eric Eisenstadt bio

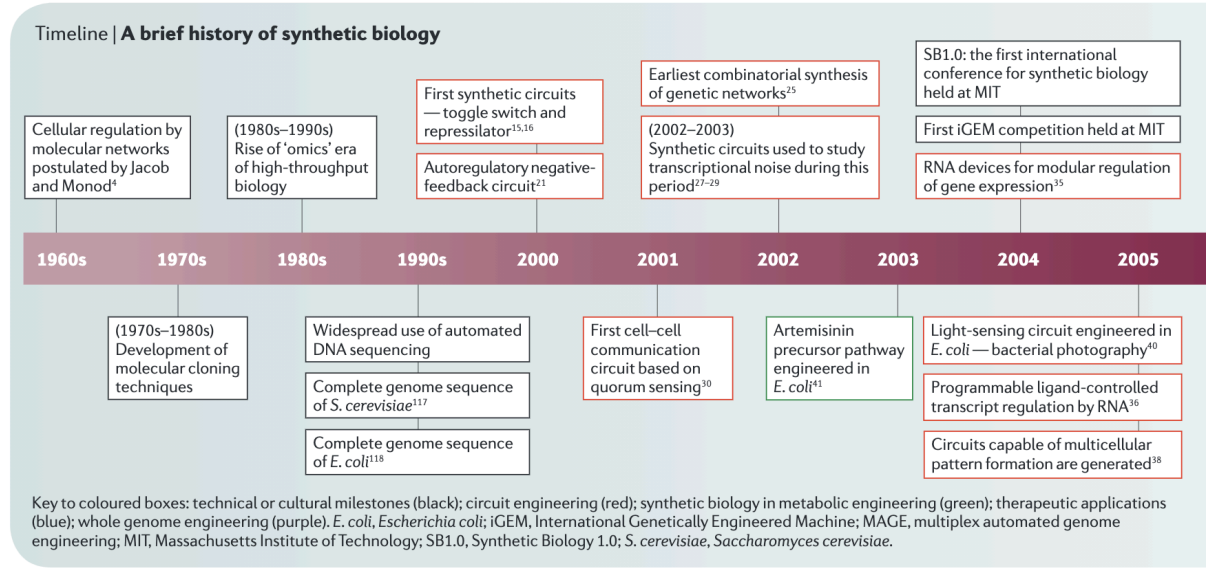
	joining DARPA, Dr. Eisenstadt was a program officer at the Office of Naval Research (ONR) from 1988 to 1999, where he developed and managed basic research programs in marine biotechnology (including a focus on life at high temperature and pressure), systems biology (with a focus on developing novel computational approaches to modeling biological systems), anaerobic bioremediation processes, and biomineralization"		
End of 1990s	Recognising the opportunities that being able to harness these cellular regulatory networks would provide, small groups of engineers, physicists, computer scientist recognise opportunity presented and try research in this area In the late 1990s a new surge of effort to explore cellular computing gained momentum. Genetic toggle switch by Gardener, Collins and co and the bacterial oscillator (by elowitz and leibler) appeared in the same issue of nature using very similar techniques to each other. Many other scientists doing similar work at the time ○ Fussenegger, Bailey and their team pioneering gene regulation circuits for gene therapy control ○ Becksei and Seranno developing noise suprresion circuits for bacteria ○ Sayler and Simpson demonstrating bioluminescent biosensors intergrated with a microchip ○ Church and team exploring high density dynamic memory in living cell DNA "This convergence of activity in cellular computing at the end of the 20th century was not coincidence. Many of the early whitepapers and grant applications at that time cite the unprecedented availability of biological data in structured databases — that is, 'parts catalogs' — as a key driver for their thinking. These were databases built, in part, to capture the data from the human genome sequencing project. The tools of molecular biology had themselves become more standardized and accessible with the emergence of reagent kits, expansive restriction enzyme catalogs, and overnight (or		A brief history of synthetic biology Synthetic Biology: evolution or revolution? A co-founder's perspective

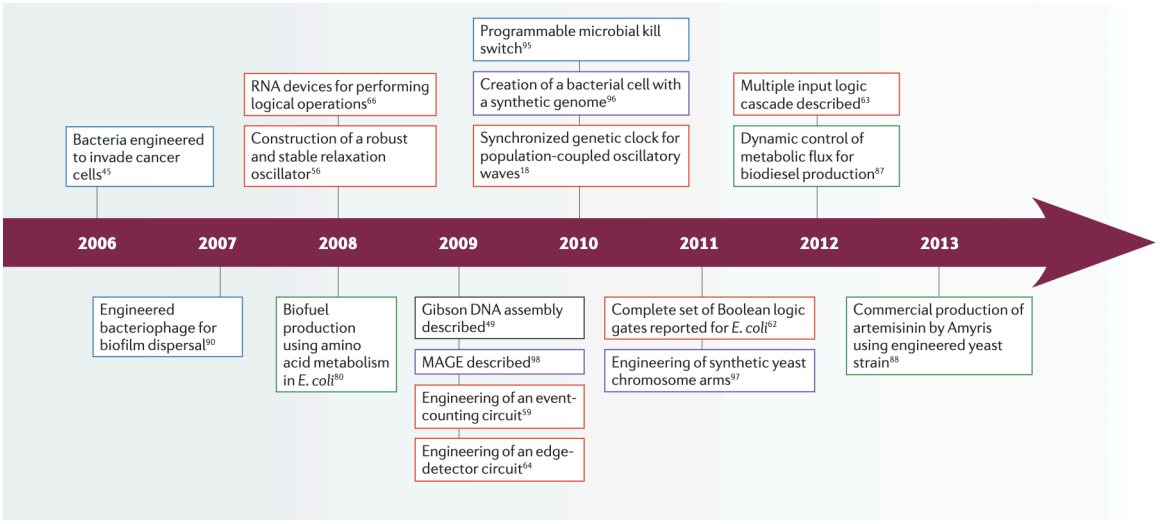
	even same-day) reagent delivery from supplier companies, thereby creating a supply chain for DNA fabrication akin to an electronics supply chain. The availability of cheap Sanger sequencing enabled the delineation of design rules and part boundaries for gene regulatory elements. And standardized genetic componentry was beginning to emerge, such as the tac, tet and ara promoter systems still popular today." "At the same time, trends in other scientific disciplines, such as the scaling back of funding in the physical sciences, were pushing non-biologists to look afresh at biology."		
Jan 2000	In the first month of the new millennium (January 2000), the first reports of genetic circuits that had been engineered to carry out designed functions were published. "Two early examples of synthetic biological circuits were published in Nature in 2000. One, by Tim Gardner, Charles Cantor, and Jim Collins working at Boston University, demonstrated a "bistable" switch in E. coli. The switch is turned on by heating the culture of bacteria and turned off by addition of IPTG. They used GFP as a reporter for their system.[3] The second, by Michael Elowitz and Stanislas Leibler, showed that three repressor genes could be connected to form a negative feedback loop termed the Repressilator that produces self-sustaining oscillations of protein levels in E. coli."		Synth bio wikipedia
2001	DARPA biocomputing program (more funding) "DARPA Biocomputing program which funded DNA memory research and the BioSPICE initiative to build a CAD system for gene circuit engineering."		Synthetic Biology: evolution or revolution? A co-founder's perspective
2000-2003	Foundational period of synthetic biology		
2002	BIOSPICE initiative funded by DARPA		
2003	Biobrick is established (a standardisation of genetic parts for use in circuits - aimed to solve the problem of new parts having to be by each scientist and these parts having unpredictable properties in different situations to the one they were made in).		BIOSPICE announcement

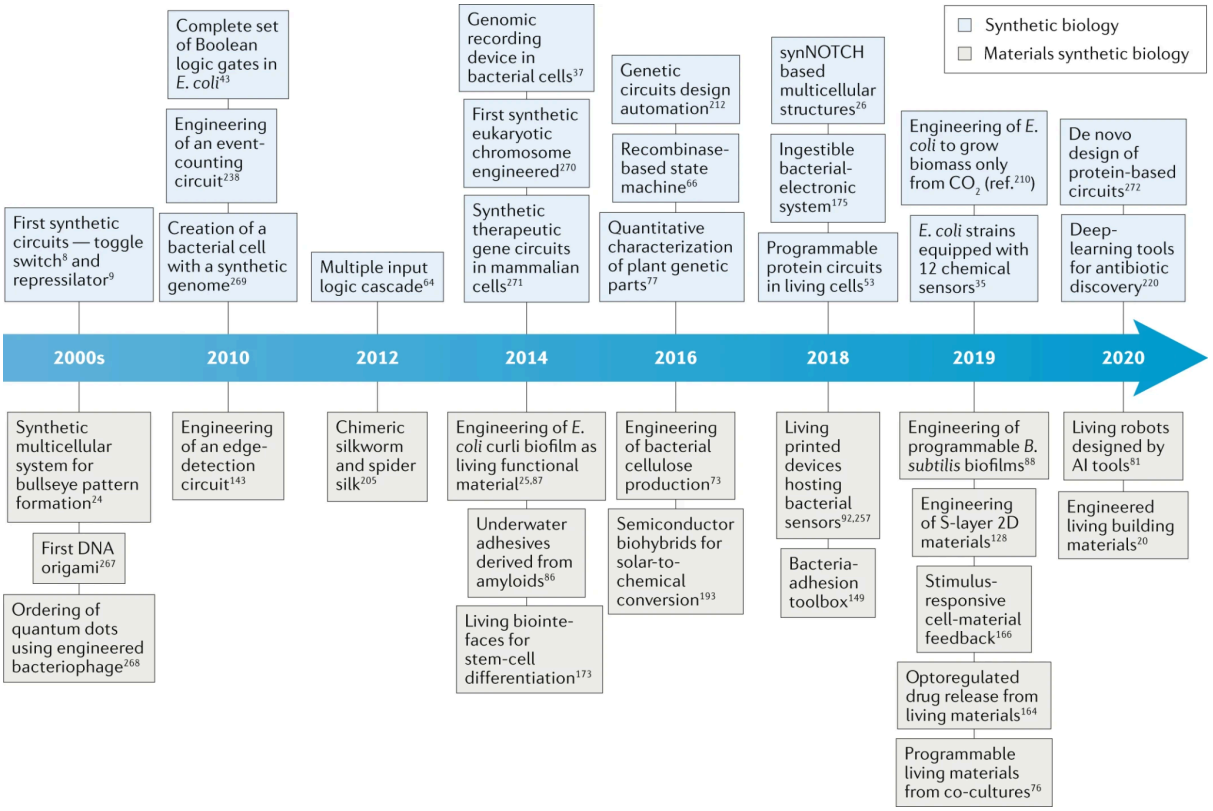
	iGEM competition started: “iGEM began in January 2003 as an independent study course at the Massachusetts Institute of Technology (MIT) where students developed biological devices to make cells blink. This course became a summer competition with 5 teams in 2004 and continued to grow to 13 teams in 2005; it has now expanded to 353 teams in 2019, reaching more than 40 countries. The Competition was originally aimed at undergraduate college students, and has now grown to include graduate and high school students. “		iGEM
2004	“The first international conference for the field, Synthetic Biology 1.0 (SB1.0), was held in the summer of 2004 at the Massachusetts Institute of Technology (MIT), USA”		A brief history of synthetic biology
2005	Review and roadmap for synthetic biology published in nature “Indeed, many of the research groups that entered the field in the earlier part of the decade began to sharpen their craft in the mid - 2000s, making use of better technical understanding, design approaches and construction methods. High-throughput DNA-assembly methods, coupled with the steady decline in gene-synthesis costs, further accelerated the build phase of circuit engineering” “In the mid-2000s, synthetic biology began to receive widespread recognition in both the scientific and popular press, and the rapid expansion of iGEM played an important part in garnering interest in the field within universities and from the general public53,54. Funding agencies also began to follow suit, particularly the US National Science Foundation, which provided funding for SynBERC (Synthetic Biology Engineering Research Project; see further information) — a consortium of synthetic biology laboratories from several leading academic institutions in the United States. The field also became increasingly international during these years, as conferences, such as SB3.0 in Zurich, Switzerland, and SB4.0 in Hong Kong, China, helped to globalize the synthetic biology community.”		A brief history of synthetic biology

2006	Engineered ecoli to selectively invade cancer cells using hypoxia sensor BIOSPICE goes open source after end of DARPA funding		Synthetic biology: an emerging engineering discipline BIOSPICE website
2008	RNA circuit engineering: “RNA-based circuit engineering also underwent an expansion during this period, as biosensing functions gave way to RNA-based computation. RNA devices were built to control the regulatory logic of gene expression66, and RNA design tools were developed to enable the precise, predictable control of heterologous and endogenous gene targets67,68” (2008-2013)	RNA circuit engineering “expansion”	A brief history of synthetic biology
2013	**more efforts to improve part reliablity - BIOFAB reliability score**		
2017	Kymriah approved in US (first FDA approved therapy in US with gene therapy step) (CAR-T) Second generation CAR-T aiming to use genetic circuits, logic gates to try and increase efficacy and reduce serious side effects “Genetic circuit design in mammalian cells is being applied to overcome the limitations of the first CAR-T generation69,74. Targeting a single cancer antigen can lead to off-target toxicity, such as the long-term depletion of healthy B-cells, and resistance emerges if the antigen mutates74. To address these issues, genetic circuits have been designed that integrate information from multiple sensors: AND gates increase specificity and OR gates prevent resistance69,70. CAR-T activity in time and space can be controlled using sensors for small molecules that can be administered as drugs or that react to the tumor environment. Safety switches have been designed to trigger rapid CAR-T depletion in case the patient develops cytokine release syndrome, a common and potentially life-threatening side effect”		Commercial genetic circuits

Timeline supplements


Timeline | A brief history of synthetic biology
Cellular regulation by molecular networks postulated by Jacob and Monod[4]
(1980s–1990s) Rise of 'omics' era of high-throughput biology
First synthetic circuits — toggle switch and repressilator[15,16]
Autoregulatory negative-feedback circuit[21]
Earliest combinatorial synthesis of genetic networks[25]
(2002–2003) Synthetic circuits used to study transcriptional noise during this period[27–29]
SB1.0: the first international conference for synthetic biology held at MIT
First iGEM competition held at MIT
RNA devices for modular regulation of gene expression[35]
1960s
1970s
1980s
1990s
2000
2001
2002
2003
2004
2005
(1970s–1980s) Development of molecular cloning techniques
Widespread use of automated DNA sequencing
Complete genome sequence of S. cerevisiae[117]
Complete genome sequence of E. coli[118]
First cell–cell communication circuit based on quorum sensing[30]
Artemisinin precursor pathway engineered in E. coli[41]
Light-sensing circuit engineered in E. coli — bacterial photography[40]
Programmable ligand-controlled transcript regulation by RNA[36]
Circuits capable of multicellular pattern formation are generated[38]
Key to coloured boxes: technical or cultural milestones (black); circuit engineering (red); synthetic biology in metabolic engineering (green); therapeutic applications (blue); whole genome engineering (purple). E. coli, Escherichia coli; iGEM, International Genetically Engineered Machine; MAGE, multiplex automated genome engineering; MIT, Massachusetts Institute of Technology; SB1.0, Synthetic Biology 1.0; S. cerevisiae, Saccharomyces cerevisiae.


Programmable microbial kill switch[95]
RNA devices for performing logical operations[66]
Creation of a bacterial cell with a synthetic genome[96]
Multiple input logic cascade described[63]
Bacteria engineered to invade cancer cells[45]
Construction of a robust and stable relaxation oscillator[56]
Synchronized genetic clock for population-coupled oscillatory waves[18]
Dynamic control of metabolic flux for biodiesel production[87]
2006
2007
2008
2009
2010
2011
2012
2013
Engineered bacteriophage for biofilm dispersal[90]
Biofuel production using amino acid metabolism in E. coli[80]
Gibson DNA assembly described[49]
MAGE described[98]
Engineering of an event-counting circuit[59]
Engineering of an edge-detector circuit[64]
Complete set of Boolean logic gates reported for E. coli[62]
Engineering of synthetic yeast chromosome arms[97]
Commercial production of artemisinin by Amyris using engineered yeast strain[88]



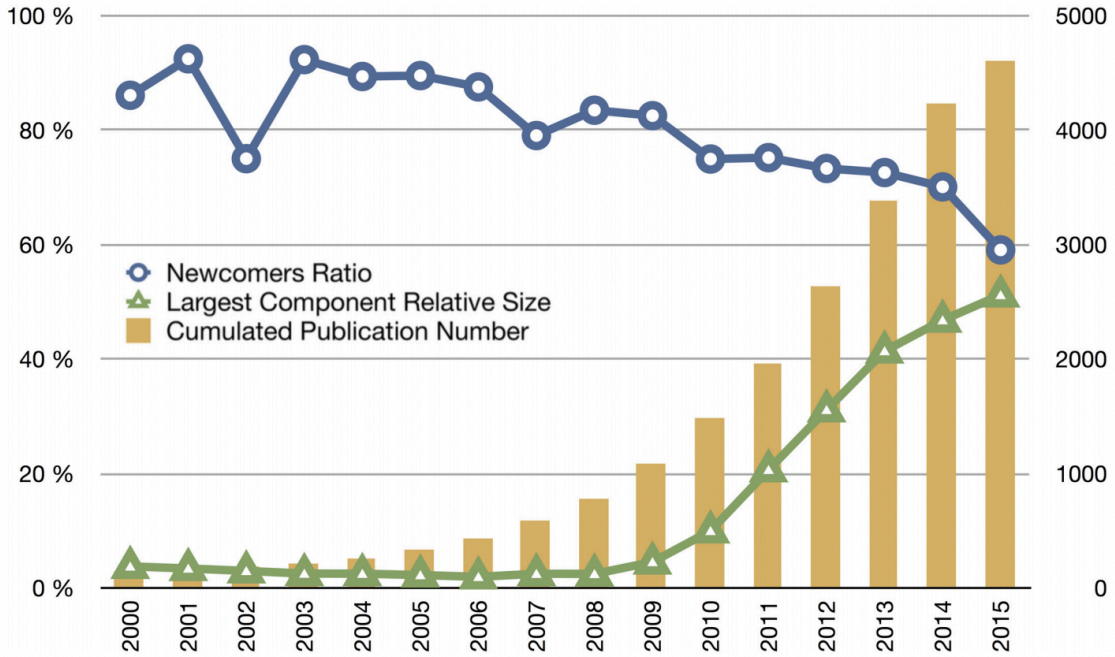
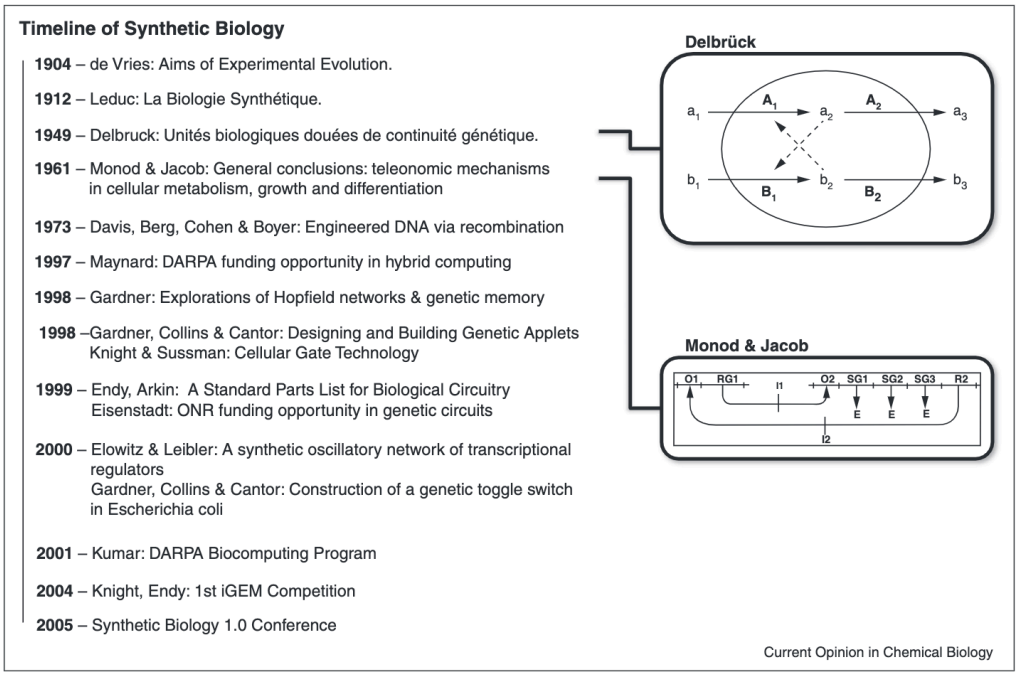


Fig 1. Global population statistics of the SynBio community over time. Cumulated number of publications (bar chart), newcomers' ratio and largest component relative size. While the number of publication follows a typical exponential growth, the newcomers ratio, while very high, is decreasing with time, and the largest component relative size has been significantly growing since 2010 indicating a progressive structuration of the SynBio community.

doi:10.1371/journal.pone.0161522.g001

[1] Mapping the Emergence of Synthetic Biology



Key events in the development of Synthetic Biology. Highlighted are a two-state enzyme circuit described by Max Delbruk in 1949, and a two-state gene circuit described by Francois Jacob and Jacques Monod in 1961, shortly after their discovery of the lac operon system in *Escherichia coli*.

2

Writeup of Development

Our understanding of how cells manage to respond to their environment and regulate themselves is relatively recent, in 1961 Jacob and Monod published their landmark publication, postulating the existence of molecular regulatory circuits using evidence from their studies of the lac operon. “The ability to assemble new regulatory systems from molecular components was soon envisioned”.[3]

In the 1970s, “the concept of re-usable parts for designing biological systems was well-recognized by the pioneers of modern genetic engineering” and molecular cloning and DNA amplification techniques were created. In 1977, a particularly notable application of recombinant DNA was achieved when researchers managed to get bacteria to produce human insulin. I think this constitutes an early success for synthetic biology, and may have also served as evidence of practical applications of the basic research into cell regulation (my interpretation). In the 1980s, PCR made molecular cloning and recombinant gene

[2] Synthetic Biology: evolution or revolution? A co-founder’s perspective
[3] A brief history of synthetic biology

expression (putting segments of DNA into different genomes) much easier and opened up a wider range of cases in which it could be used.[4]

"By the mid - 1990s, automated DNA sequencing and improved computational tools enabled complete microbial genomes to be sequenced, and high-throughput techniques for measuring RNA, protein, lipids and metabolites enabled scientists to generate a vast catalogue of cellular components and their interactions."[5] It was around this time that complete genomes were sequenced for the model organisms E.coli and S.cerevisiae.

"This 'scaling up' of molecular biology generated the field of systems biology , as biologists and computer scientists began to combine experimentation and computation to reverse-engineer cellular networks "[6] They found that many complex circuits are composed of a hierarchy of cellular logic "modules". *"Gradually, it was recognized that the rational manipulation of biological systems [...] could form the basis of a formal biological engineering discipline . As a complement to the top-down approach of systems biology, a bottom-up approach was envisioned, which could draw on an ever-expanding list of molecular 'parts' to forward-engineer regulatory networks.""*[7]

These breakthroughs in sequencing and other techniques were used to collect a vast amount of information. After this data gold rush, there existed a large store of knowledge on individual biological parts, the DNA that codes for them, and their functions. With this new knowledge, investigating how the parts work together, and the possibility of synthesising DNA to create our own circuits seemed quite natural.

"In the late 1990s a new surge of effort to explore cellular computing gained momentum." "This convergence of activity in cellular computing at the end of the 20th century was not coincidence. Many of the early whitepapers and grant applications at that time cite the unprecedented availability of biological data in structured databases — that is, 'parts catalogs' — as a key driver for their thinking. These were databases built, in part, to capture the data from the human genome sequencing project.

The tools of molecular biology had themselves become more standardized and accessible with the emergence of reagent kits, expansive restriction enzyme catalogs, and overnight (or even same-day) reagent delivery from supplier companies, thereby creating a supply chain for DNA fabrication akin to an electronics supply chain. The availability of cheap Sanger sequencing enabled the delineation of design rules and part boundaries for gene regulatory elements. And standardized genetic componentry was beginning to emerge, such as the tac, tet and ara promoter systems still popular today." "At the same time, trends in other scientific disciplines, such as the scaling back of funding in the physical sciences, were pushing non-biologists to look afresh at biology." [8]

"DARPA announced a new funding program called Hybrid Information Appliances in 1997 which sought to advance research in hybrid biological/electronic computing systems." [9] Apparently this was stimulated in part by the success of Leonard Aldeman in solving NP complete computational problems using DNA in 1994, and worries about computing

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[4] Synthetic Biology: evolution or revolution? A co-founder's perspective
[5] A brief history of synthetic biology
[6] A brief history of synthetic biology
[7] A brief history of synthetic biology
[8] Synthetic Biology: evolution or revolution? A co-founder's perspective
[9] Synthetic Biology: evolution or revolution? A co-founder's perspective

progress beginning to lag behind Moore's law, indicating to DARPA that a new change in computing would be needed to keep up the same pace of improvement. The DARPA program served as a valuable funding source and also functioned to bring scientists interested in synthetic biology together. In 1999 the Office of Naval Research also created a similar biocomputing funding program under Eric Eisenstadt.

The year 2000 was a watershed for genetic circuit design in synthetic biology, two papers both demonstrated the first examples of human designed and assembled regulatory circuits, and were published in the same issue of nature. The year after in 2001 DARPA created the biocomputing program "which funded DNA memory research and the BioSPICE initiative to build a CAD system for gene circuit engineering."[10]

In 2003 the biobrick standard was established to help with the standardisation of genetic parts used in circuits (which beforehand were often made from scratch for the circuit in question and had unpredictable behaviour when being used in other circuits). In 2005, a review and roadmap for synthetic biology was published in nature and the first synthetic biology conference was hosted. This was also around the time that international funding for synthetic biology and genetic circuits was beginning to come online.

In summary, modern genetic circuits focused synthetic biology seems to have emerged as a field in the late 90s and early 2000s as a result of a gradual improvement in available techniques and supplies for working with DNA, a massive influx of new data on individual parts from newly developed high throughput sequencing, a more systematised understanding of cell parts and functions, and an injection of funding to explore this new area from government programs such as DARPA (because DARPA wanted to speed up computing progress).

Summary of Development

Our understanding of how cells manage to respond to their environment and regulate themselves is relatively recent. In 1961 Jacob and Monod published their landmark paper, postulating the existence of molecular regulatory circuits using evidence from their studies of the lac operon. "The ability to assemble new regulatory systems from molecular components was soon envisioned".[11]

Genetic circuits focused synthetic biology emerged as a field in the late 90s and early 2000s as a result of a gradual improvements in a few different areas in the 70s and 80s, such as available techniques and supplies for working with DNA, a massive influx of new data on individual parts from newly developed high throughput sequencing, and a more systematised understanding of cell parts and functions, and an injection of funding to explore this new area from government programs such as from DARPA in 1997.

"By the mid - 1990s, automated DNA sequencing and improved computational tools enabled complete microbial genomes to be sequenced, and high-throughput techniques for

[10] Synthetic biology evolution or revolution
[11] A brief history of synthetic biology

measuring RNA, protein, lipids and metabolites enabled scientists to generate a vast catalogue of cellular components and their interactions."[12]

"Gradually, it was recognized that the rational manipulation of biological systems [...] could form the basis of a formal biological engineering discipline . As a complement to the top-down approach of systems biology, a bottom-up approach was envisioned, which could draw on an ever-expanding list of molecular 'parts' to forward-engineer regulatory networks.""[13]

"DARPA announced a new funding program called Hybrid Information Appliances in 1997 which sought to advance research in hybrid biological/electronic computing systems." [14]

Apparently this was stimulated in part by the success of Leonard Aldeman in NP complete problems using DNA in 1994[15], and worries about computing progress beginning to lag behind Moore's law. The DARPA program served as a valuable funding source and also functioned to bring scientists interested in synthetic biology together. In 1999 the Office of Naval Research also created a similar biocomputing funding program under Eric Eisenstadt. These programs helped to solidify the community and resulted in the creation of the very first genetic circuits in 2000.

The year 2000 was a watershed for genetic circuit design / synthetic biology, two papers both demonstrated the first examples of human designed and assembled regulatory circuits, and were published in the same issue of nature. The year after in 2001, DARPA started the biocomputing program "which funded DNA memory research and the BioSPICE initiative to build a CAD system for gene circuit engineering."[16] The BioSPICE initiative later went on to create some of the first standards and tools for genetic circuit design. By the mid 2000s the US National Science Foundation and many other countries were beginning to get involved with genetic circuit and other synthetic biology research[17]. The field was also rapidly gaining popularity in universities through iGEM, which hosted courses and competitions where students got to try their hand at designing their own genetic circuits.

The next decades would mostly revolve around trying to reduce the unreliability of specific parts by the adoption of certain standards and data collection. In the last decade, these improvements have allowed the design of much more robust and complex circuits than was previously possible.

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[12] A brief history of synthetic biology
[13] A brief history of synthetic biology
[14] Synthetic Biology: evolution or revolution? A co-founder's perspective
[15] Synthetic Biology: evolution or revolution? A co-founder's perspective
[16] Synthetic biology evolution or revolution
[17] A brief history of synthetic biology

Very Quick Summary of My Opinions of How this Field became established

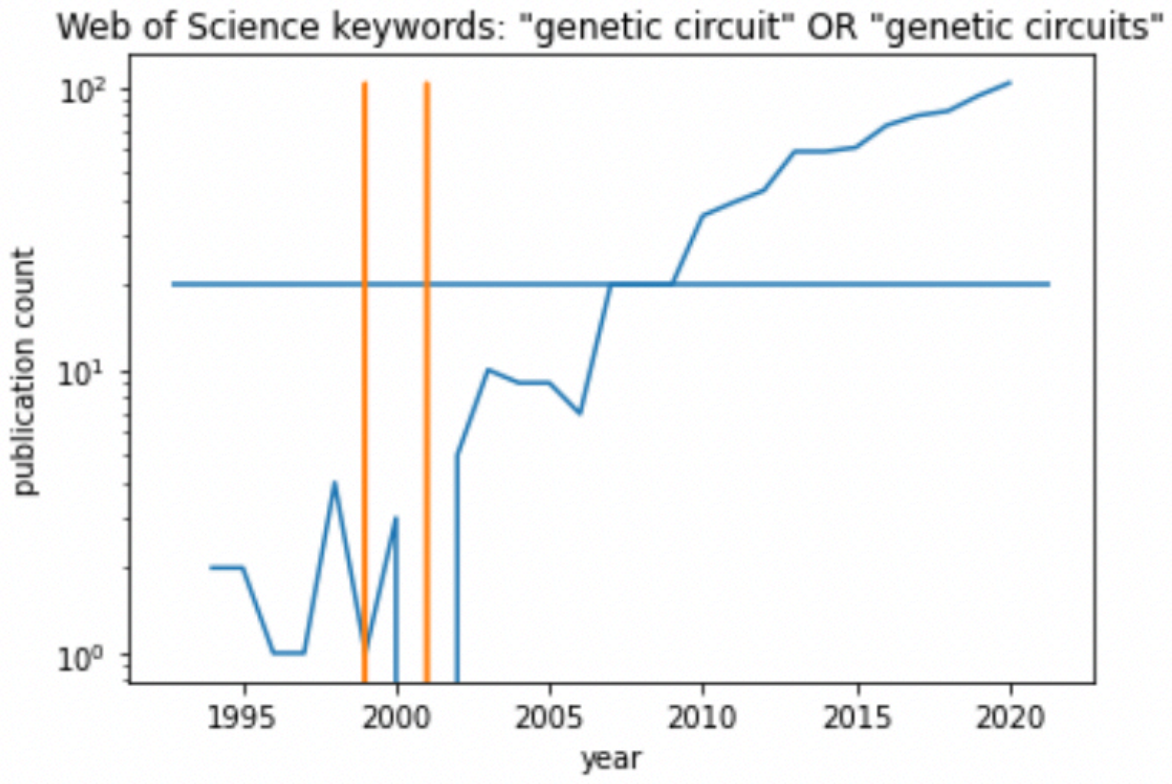
(Short 1-2 sentences on inside view of how tech became thriving, don't have to be sure its right)

Genetic circuits focused synthetic biology emerged as a field in the late 90s and early 2000s as a result of a gradual improvements in a few different areas in the 70s and 80s, such as available techniques and supplies for working with DNA, a massive influx of new data on individual parts from newly developed high throughput sequencing, a more systematised understanding of cell parts and functions, and an injection of funding to explore this new area from government programs such as from DARPA in 1997. US government funding brought together interested scientists and resulted in two high impact papers which put the young subject on the map.

Development Factors

See Spreadsheet (filter for "Genetic Circuits")

Development Measures



The y axis marks papers published in that year for that Web of Science Query
The blue horizontal line marks 20 papers published per year
The orange lines mark years in which the papers published per year had doubled or more year on year, over a 4 year time period (where the year marked is the first year of that 4 year period. Our “early growth metric” just takes the first year that the growth condition is met, or the first year that the field hits 20 papers published per year, whichever is first.

So the early growth year for genetic circuits is 1999

Code Parameters

Query was just articles (as with all that I have done so far)

Threshold = log(1.5) [x 1.5 average year on year growth]
Zero num = 0.5
p = 4
papers = 20