The synthetic biology future

Roy D Sleator

Department of Biological Sciences; Cork Institute of Technology; Cork, Ireland

On March 13, 2014, some of the world’s leading biological science researchers will converge on Cork, Ireland, to discuss the synthetic biology future. Defined loosely as a trans-disciplinary field at the intersection of science and engineering,1 the genesis of synthetic biology can be traced to two milestone papers, published back-to-back in the same January 2000 issue of Nature;2,3 detailing the design and construction of the first synthetic gene networks. The first synthetic biological oscillator (“repressilator”) and bistable gene regulatory network (“toggle switch”) demonstrated, for the first time, that engineering principles could be successfully applied to biological systems—engineering the biological equivalents of electronic memory storage and time-keeping. Over the past 14 years, this approach has been applied to the synthetic engineering of increasingly more complex genetic switches,4-8 memory elements,9,10 and oscillators,11-14 as well as other electronics-inspired genetic devices15-17 up to, and including, synthetic life itself.18,19

Although arguably one of the hottest emerging areas of biological science research,20 the origins of synthetic biology can be traced as far back as 1961 to a paper by Mono and Jacob21 on telenomic mechanisms in cellular metabolism. This seminal paper described the circuit-like connectivity of biological parts, a discussion which spawned several studies on the application of electrical circuitry analogies22,23 and mathematical models24-27 to biological systems. Indeed, from these humble beginnings, each successive decade has helped shape the evolution of the field, providing the material and tools necessary to design and assemble biomolecular parts,28-30 whole entities,31-33 and in some cases, entire consortia.33,34

The discovery in 1970 of the first Type II restriction enzyme by Hamilton Smith35 (providing the molecular scalpel necessary to cut DNA at specific sites), coupled with Herb Boyer and Stanley Cohen’s experimentation on recombinant plasmids,36 made it possible to clone genes from one organism (or species) and express them in another.37 This marked the birth of recombinant DNA technology and with it the golden age of molecular biology. By the 1980s molecular biology had spawned the biotechnology industry, facilitated by Diamond vs. Chakrabarty, 447 US 303 (1980), a landmark ruling by the US Supreme Court, which, for the first time, afforded genetic engineers the same protections for their inventions enjoyed by conventional engineers. The Supreme Court case was heard on March 17, 1980 and decided on June 16, 1980. The patent was granted by the US patent office on March 31, 1981, providing Ananda Chakrabarty (an Associate Editor of Bioengineered) with the first patent on a genetically engineered organism,38 a Pseudomonas strain capable of breaking down crude oil, a biological invention with obvious applications in large scale oil spill cleanup.39 The remainder of the 1980s saw the continued growth and development of the biopharmaceutical industry, punctuated with large scale heterologous production of recombinant human protein therapeutics,40 most notably insulin—DNA technology’s first drug.41 But where does our definition of biotechnology end and synthetic biology begin? For Serrano,42 the introduction of exogenous genes to a host organism for the production of new compounds is more synthetic biology than biotechnology. I disagree with this assertion; for me, synthetic biology involves the use of wholly synthetic constructs (not previously seen in nature). Applying this logic to the insulin example—simply expressing human insulin (e.g., Humulin) against an Escherichia coli background—represents classic biotechnology.43 Inferferon (interferon alfacon-1), on the other hand—a wholly synthetic type-I interferon generated from the consensus sequence of several natural interferon α subtypes44—is truly a product of synthetic biology.

The 1990s marked the beginning of the “-omics” era, the defining moment of which was the initiation of the human genome project46,47 and, laterally, the emergence of metagenomics— the genomic view of an entire environmental niche, e.g., the human microbiome.48,49 In addition to facilitating advancements in so-called wet lab technologies (e.g., large scale DNA sequence and synthesis), the resulting sequence information led to biology’s “big data” revolution and with it, the era of in silico biology.50 Thus, the 2000s marked biology’s silicon age, punctuated by the development of bioinformatics51 and systems biology.52 Again, distinctions must be drawn between systems biology and synthetic biology; while both disciplines consider modeling and simulation as important tools, systems biology is focused on understanding biological systems, while synthetic biology aims to engineer new and improved functions.

Therefore, although synthetic biology truly represents a new field—officially emerging in 2004 with the appearance of its own dedicated Wikipedia page54 and the first synthetic biology
Biocurios in the US and La Paillasse in Europe (Paris, France) are establishing hackerspaces that are properly insured and exhibiting wicket, encompassing not only the DIYbio movement but all amateur funding streams, including the Welcome Trust, which funds groups have progressed even further, successfully tapping conventional funding (more specifically, the lack thereof) to establish their own laboratory, or hackerspace. Other DIYbio groups have begun to emerge, including Genspace, a non-profit organization dedicated to promoting citizen science. In 2010, Genspace formed the world’s first community-based biotechnology laboratory, a biosafety level one facility located in Brooklyn, NY. Operating on a monthly subscription basis, the lab offers hands-on courses to the public and encourages scientific entrepreneurship, particularly in the synthetic biology arena (or SynBio in the biohacker vernacular). Although the first, the Genspace laboratory is no longer unique; in the US alone, there are dozens of community biolabs or “hackerspaces” that cooperate among themselves and a loose international confederation of biohackers called DIYBio, which at the time of writing lists 20 organized DIY groups in North America, 16 in Europe, and two each in Asia and Oceania. Many of these DIYbio practitioners actively collaborate and compete in the iGEM (International Genetically Engineered Machine) competition, a worldwide synthetic biology competition open to undergraduate university students, high school students, and entrepreneurs.

Despite experiencing exponential growth following its earliest inception in a Cambridge, MA, pub in 2008, two of the major impediments to the continued development of the DIYbio movement are funding (more specifically, the lack thereof), and continued public fears relating to biosafety and biosecurity. However, even these obstacles are being gradually eroded. Locked out of traditional funding mechanisms, many of the early adopters have turned to crowdfunding platforms to achieve their goals. Indeed, using this approach, Biocurious, a DIYbio group based in Sunnyvale, CA, raised more than $35,000 (from 239 Kickstarter pledges) to establish their own laboratory, or hackerspace. Other groups have progressed even further, successfully tapping conventional funding streams, including the Welcome Trust, which funds Madlab (Manchester, UK) and the FP7 EU project, StudioLab, which funds Biologigarden (Copenhagen, Denmark).

Biosafety and/or security on the other hand remains a sticky wicket, encompassing not only the DIYbio movement but all amateur biology and the democratization of science in general. By establishing hackerspaces that are properly insured and exhibiting documented adherence to safety regulations, DIYbio groups like Biocurios in the US and La Paillasse in Europe (Paris, France) are leading the way in creating safe, secure, and regulated labs for their practitioners. Indeed, DIYbio.org co-founder Jason Bobe believes that, in addition to creating secure work spaces, the DIYbio and iGEM communities combined are best placed to establish a collective code of ethics, enabling global governance of the citizen science culture. In the summer of 2011, the international DIYbio community organized congresses in the US and Europe to establish a collective code of ethics for the community. The following year, DIYbio.org established a “question and answer” platform on biosafety, a free service that allows amateurs to submit questions to professional biosafety experts. While all of the above go some way toward easing public concern and facilitating social legitimacy, regulatory and safety issues still remain the most significant barrier to the continued evolution of the movement.

In addition to funding and policy issues, of most concern (at least for now) is the gap between what is possible in the average hackerspace vs. what is achievable in a typical professional or academic laboratory. With some notable exceptions—such as the La Paillasse bioink project, a non-toxic biodegradable alternative to modern ink—DIY SynBio wetware outputs fall far short of even the most pedestrian of academic labs. One obvious explanation for this is a lack of specialist equipment; while most academic labs are stocked with name brand apparatus and laboratory consumables, biohackers make do with what they have (or in most cases have not). Necessity being the mother of invention, some of these hardware innovations and inventions ironically represent the communities’ first tangible successes. The DremelFuge, for example, developed by Cork-based DIYbio practitioner Cathal Garvey, is a simple component that turns an ordinary Dremel rotary-tool into a lab-quality centrifuge. More sophisticated devices include Amplino, an inexpensive, portable PCR diagnostic system capable of detecting malaria in less than 40 min from a single drop of blood.

Thus, while the DIYbio movement is unlikely, at least in the short-term, to contribute significantly to our fundamental understanding of biological processes, disruptive technologies like Amplino have the potential to significantly impact global health improvement, particularly in developing countries where access to expensive and delicate diagnostic equipment is a significant limitation. While some use these early successes to argue that the stage is set for the “bioscience version of Apple or Google to be born in a dormitory room or garage,” I for one feel that the DIYbio movement is unlikely to morph into a version of the establishment that it currently eschews. For me, the future is more likely to be one of cooperation rather than assimilation. To borrow from the computer jargon which has come to synonymize the field, today’s biohackers are tomorrow’s “bioApp” developers, no longer a subversive group to be feared and derided, but an essential component of biology’s future development.

True to this assertion, the Cork SynBio meeting aims to bring amateurs, academics, and professionals together in a spirit of collaboration—home to Ireland’s first DIYbio group, two leading third-level institutions (CIT and UCC), and playing host to 14 of the world’s top 15 pharmaceutical companies, Cork is the perfect location from which to frame The Synthetic Biology Future.
Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

R.D.S. is coordinator of the EU FP7 grant ClouDx-i.

Acknowledgments

33. Brenner K, Arnold FH. Self-organization, layered structure, and aggregation enhance persistence of a synthetic biofilm consortium. PLoS One 2011; 6:e16791; http://dx.doi.org/10.1371/journal.pone.016791

34. Hu B, Du J, Zou RY, Yuan YJ. An environment-sensitive synthetic microbial ecosystem. PLoS One 2010; 5:e10659; PMID:20485551; http://dx.doi.org/10.1371/journal.pone.010659

35. Smith HO, Wilcox KW. A restriction enzyme from Hemophilus influenzae. I. Purification and general properties. J Mol Biol 1970; 51:379-91; PMID:5312500; http://dx.doi.org/10.1016/0022-5193(69)90149-X

36. Cohen SN, Chang ACY, Boyer HW, Helling RB. Construction of biologically functional bacterial plasmids in vitro. Proc Natl Acad Sci U S A 1973; 70:3240-4; PMID:4594039; http://dx.doi.org/10.1073/pnas.70.5.3240

37. Morrow JF, Cohen SN, Chang AC, Boyer HW, Goodman HM, Helling RB. Replication and transcription of eukaryotic DNA in Escherichia coli. Proc Natl Acad Sci U S A 1974; 71:1743-7; PMID:41002624; http://dx.doi.org/10.1073/pnas.71.5.1743

38. Chakrabarty AM. Bioengineered bugs, drugs and contentious issues in patenting. Bioeng Bugs 2010; 1:2-8; PMID:21327053; http://dx.doi.org/10.4161/bbug.1.4.12465

39. Basu S, Gerchman Y, Collins CH, Arnold FH, Weiss R. A synthetic multicellular system for programmed pattern formation. Nature 2005; 434:1130-4; PMID:15858574; http://dx.doi.org/10.1038/nature4360

40. Leibler S. A synthetic oscillator network of transcriptional regulators. Nature 2000; 403:335-8; PMID:10659856; http://dx.doi.org/10.1038/3502125

41. Gardner TS, Cantor CR, Collins JJ. Construction of a genetic toggle switch in Escherichia coli. Nature 2000; 403:339-42; PMID:10659857; http://dx.doi.org/10.1038/35021231

42. Atkinson MR, Savageau MA, Myers JT, Ninfa AJ. Continuous, non-linear biochemical control networks. J Theor Biol 1997; 183:439-55; PMID:9351743; http://dx.doi.org/10.1016/S0022-5193(97)85006-7

43. Friedland AE, Lu TK, Wang X, Shi D, Church G, Ham TS, Lee SK, Keasling JD, Arkin AP. A tightly regulated inducible expression system utilizing the mini inversion recombination switch. Biotechnol Bioeng 2006; 94:1-4; PMID:16534780; http://dx.doi.org/10.1002/bit.20916

44. Ajo-Franklin CM, Druin DA, Eskin JA, Gee EP, Landgraf D, Phillips I, Silver PA. Rational design of memory in eukaryotic cells. Genes Dev 2007; 21:2271-6; PMID:17875664; http://dx.doi.org/10.1101/gad.158607

45. Fung E, Wong WW, Suen JK, Bulter T, Lee SG, Liao JC. A synthetic gene-metabolic oscillator. Nature 2009; 461:118-22; PMID:19587627; http://dx.doi.org/10.1038/nature08508

46. Stricker J, Cookson S, Bennett MR, Mather WH, Tsimring L, Hasty J. A fast, robust and tunable synthetic gene oscillator. Nature 2008; 456:605-6; PMID:18624793; http://dx.doi.org/10.1038/nature07435

47. Glass L, Kauffman SA. The logical analysis of continuous, non-linear biochemical control networks. J Theor Biol 1973; 39:103-29; PMID:4747904; http://dx.doi.org/10.1016/S0022-5193(73)90208-7

48. Savageau MA. Comparison of classical and autogenous systems of regulation in inducible operons. Nature 1974; 242:546-9; PMID:443516; http://dx.doi.org/10.1038/252546a0

49. Kauffman S. The large scale structure and dynamics of gene control circuits: an ensemble approach. J Theor Biol 1974; 44:167-90; PMID:4595774; http://dx.doi.org/10.1016/0022-5193(74)90037-8

50. McAdams HH, Shapiro L. Circuit simulation of genetic networks. Science 1995; 260:650-6; PMID:7624793; http://dx.doi.org/10.1126/science.7624793

51. McAdams HH, Shapiro L. Theoretical analysis of the stochastic nature of bacterial gene expression. Proc Natl Acad Sci U S A 2001; 98:15112-7; PMID:11451937; http://dx.doi.org/10.1073/pnas.151121298

52. Alon U, Surette MG, Surette SJ, Sherlock G. Singularities in genetic networks: the balanced, nested and core modules. J Theor Biol 2000; 200:153-9; PMID:1076026; http://dx.doi.org/10.1006/jtbi.2000.2005.045

53. Constante M, Grünberg R, Isalan M. A biobrick switch based on RNAi and repressor proteins for heritable sequential genetic memory. PLoS One 2009; 4:e43231; http://dx.doi.org/10.1371/journal.pone.0043231

54. Basu S, Gerchman Y, Collins CH, Arnold FH, Weiss R. A synthetic multicellular system for programmed pattern formation. Nature 2005; 434:1130-4; PMID:15858574; http://dx.doi.org/10.1038/nature4360

55. Leibler S. A synthetic oscillator network of transcriptional regulators. Nature 2000; 403:335-8; PMID:10659856; http://dx.doi.org/10.1038/3502125
48. Seator RD, Shortall C, Hill C. Metagenomics. Lett Appl Microbiol 2008; 47:361-6; PMID:19146522; http://dx.doi.org/10.1111/j.1472-765X.2008.0444.x
49. Seator RD. The human superorganism - of microbes and men. Med Hypotheses 2010; 74:214-5; PMID:19836466; http://dx.doi.org/10.1016/j.mehy.2009.08.047
50. Feeney A, Seator RD. The human gut microbiome: the ghost in the machine. Future Microbiol 2012; 7:1235-7; PMID:23075440; http://dx.doi.org/10.2217/fmb.12.105
51. O’Driscoll A, Daugelaite J, Seator RD. ‘Big data’, Hadoop and cloud computing in genomics. J Biomed Inform 2013; 46:774-81; PMID:23872175; http://dx.doi.org/10.1016/j.jbi.2013.07.001
52. Kelly MJ. Computers: the best friends a human genome ever had. Genome 1989; 31:1027-33; PMID:2698820; http://dx.doi.org/10.1139/g89-177
53. Ideker T, Galitski T, Hood L. A new approach to decoding life: systems biology. Annu Rev Genomics Hum Genet 2001; 2:343-72; PMID:11701654; http://dx.doi.org/10.1146/annurev.genom.2.1.343
54. Synthetic Biology [Internet]. Wikipedia: c2014 [cited 2014 Feb 21]. Available from: http://en.wikipedia.org/wiki/Synthetic_biology.
55. Synthetic Biology 1.0 [Internet]. Available from: http://syntheticbiology.org/Synthetic_Biology_1.0.html.
56. Khalil AS, Collins JJ. Synthetic biology: applications come of age. Nat Rev Genet 2010; 11:367-79; PMID:20395970; http://dx.doi.org/10.1038/nrg2775
57. Bennett G, Gilman N, Stavrianakis A, Rabinow P. From synthetic biology to biohacking: are we prepared? Nat Biotechnol 2009; 27:1109-11; PMID:20010587; http://dx.doi.org/10.1038/nbt1209-1109
58. Alper J. Biotech in the basement. Nat Biotechnol 2009; 27:1077-8; PMID:20010575; http://dx.doi.org/10.1038/nbt1209-1077
59. Wolinsky H. Kitchen biology. The rise of do-it-yourself biology democratizes science, but is it dangerous to public health and the environment? EMBO Rep 2009; 10:683-5; PMID:19568259; http://dx.doi.org/10.1038/embor.2009.145
60. Genspace [Internet]. Brooklyn (NY): Genspace, New York City's Community Biobank: c2014 [cited 2014 Feb 21]. Available from: http://genspace.org/.
61. Hochachka WM, Fink D, Hutchinson RA, Sheldon D, Wong WK, Kelling S. Data-intensive science applied to broad-scale citizen science. Trends Ecol Evol 2012; 27:130-7; PMID:22192976; http://dx.doi.org/10.1016/j.tree.2011.11.006
62. DIYBio [Internet]. DIYBio: c2013 [cited 2014 Feb 21]. Available from: http://diybio.org/.
63. iGEM [Internet]. Cambridge (MA): iGem Foundation: c2014 [cited 2014 Feb 21]. Available from: https://www.igem.org.
64. Landrain T. [Do-it-yourself biology: challenges and promises]. Med Sci (Paris) 2013; 29:33-5; PMID:23759493; http://dx.doi.org/10.1051/medsci/201329_209
65. Weigmann K. Tapping the crowds for research funding. Crowdfunding, a common practice to support projects in the arts, music or gaming, has also attracted the attention of scientists. EMBO Rep 2013; 14:1043-6; PMID:24201975; http://dx.doi.org/10.1038/embor.2013.380
66. Wheat RE, Wang Y, Byrnes JE, Ranganathan J. Raising money for scientific research through crowdfunding. Trends Ecol Evol 2013; 28:71-2; PMID:23219380; http://dx.doi.org/10.1016/j.tree.2012.11.001
67. Orelli B. Biotech crowdfunding paves way for angels. Nat Biotechnol 2012; 30:1020; PMID:23138287; http://dx.doi.org/10.1038/nbt112-1020a
68. DIYBio.org Question and Answer platform on bio-safety [Internet]. DIYBio: c2014 [cited 2014 Feb 21]. Available from: http://ask.diybio.org/.
69. DremelFuge [Internet]. Brooklyn (NY): MakerBot Industries: c2014 [cited 2014 Feb 21]. Available from: http://www.thingiverse.com/thing:1483.
70. Amplino [Internet]. Den Haag, the Netherlands: Amplino: c2014 [cited 2014 Feb 21]. Available from: http://www.amplino.org/.
71. Anon. Garage biology. Nature 2010; 467:634; PMID:20930797; http://dx.doi.org/10.1038/467634a
72. Seator RD. Probiotics -- a viable therapeutic alternative for enteric infections especially in the developing world. Disoc Med 2010; 10:119-24; PMID:20807472
73. Hacking goes squishy. The Economist Technology Quarterly, 2009.
74. Nash DB. Beware biohacking! Biotechnol Healthc 2010; 7:7; PMID:22478803
75. Cork’s DIYbio Group [Internet]. Google: c2014 [cited 2014 Feb 21]. Available from: https://groups.google.com/forum/#!forum/diybio-ireland.
76. CIT [Internet]. Cork, Ireland: Cork Institute of Technology: c2012 [cited 2014 Feb 21]. Available from: http://www.cit.ie/.
77. UCC [Internet]. Cork, Ireland: University College Cork: c2014 [cited 2014 Feb 21]. Available from: http://www.ucc.ie/en/.
78. Amplino [Internet]. Den Haag, the Netherlands: Amplino: c2014 [cited 2014 Feb 21]. Available from: http://www.amplino.org/.
79. Orelli B. Biotech crowdfunding paves way for angels. Nat Biotechnol 2012; 30:1020; PMID:23138287; http://dx.doi.org/10.1038/nbt112-1020a
80. DIYBio.org Question and Answer platform on bio-safety [Internet]. DIYBio: c2014 [cited 2014 Feb 21]. Available from: http://ask.diybio.org/.
81. DremelFuge [Internet]. Brooklyn (NY): MakerBot Industries: c2014 [cited 2014 Feb 21]. Available from: http://www.thingiverse.com/thing:1483.
82. Seator RD. Probiotics -- a viable therapeutic alternative for enteric infections especially in the developing world. Disoc Med 2010; 10:119-24; PMID:20807472
83. Hacking goes squishy. The Economist Technology Quarterly, 2009.
84. Nash DB. Beware biohacking! Biotechnol Healthc 2010; 7:7; PMID:22478803
85. Cork’s DIYbio Group [Internet]. Google: c2014 [cited 2014 Feb 21]. Available from: https://groups.google.com/forum/#!forum/diybio-ireland.
86. CIT [Internet]. Cork, Ireland: Cork Institute of Technology: c2012 [cited 2014 Feb 21]. Available from: http://www.cit.ie/.
87. UCC [Internet]. Cork, Ireland: University College Cork: c2014 [cited 2014 Feb 21]. Available from: http://www.ucc.ie/en/.