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The synthetic biology future

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Herein, I track the evolution of synthetic biology from its earliest incarnations more than 50 years ago, through the DIYbio revolution, to the next 50 years.

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 timekeeping. 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 devices[15-17] 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 Jacob[21] 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 analogies[22,23] and mathematical models[24-27] 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,[19,31,32] and in some cases, entire consortia.[33,34]

The discovery in 1970 of the first Type II restriction enzyme by Hamilton Smith[35] (providing the molecular scalpels necessary to cut DNA at specific sites), coupled with Herb Boyer and Stanley Cohn'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] Infergin (interferon alfacon-1), on the other hand—a wholly synthetic type-I interferon generated from the consensus sequence of several natural interferon α subtypes[44]—is truly a product of synthetic biology.

The 1990s marked the beginning of the "-omics" era,[45] the defining moment of which was the initiation of the human genome project[46,47] and, laterally, the emergence of metagenomics[48]—the genomic view of an entire environmental niche, e.g., the human microbiome.[49,50] 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.[51] Thus, the 2000s marked biology's silicon age, punctuated by the development of bioinformatics[52] and systems biology.[53] 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 page[54] and the first synthetic biology

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conference[55]—its origins, as I have outlined above, can be traced back more than 50 years.

So what of the next 50 years? The possibilities are endless: new pharmaceuticals, biologically produced ("green") fuels, as well as new drugs and vaccines against emerging microbial diseases, are all in the pipeline.[56] However, while many of these high impact discoveries are likely to come from dedicated research centers, such as the J Craig Venter Institute (named for another of our Associate Editors), there exists a counter culture, a new and emerging group of independent researchers who are making synthetic biology their own. These self-styled biohackers (or biopunks) apply the computer hacker ethos to the biological sciences, advocating open access to genetic information and manipulation. This new era of DIY biology[57] originally evolved as a non-institutional pursuit with practitioners—many of whom having little or no formal training—operating out of garages or modified kitchens.[58,59] However, increasingly more organized groups have begun to emerge, including Genspace,[60] a non-profit organization dedicated to promoting citizen science.[61] 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,[62] 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[63] (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.[64] However, even these obstacles are being gradually eroded. Locked out of traditional funding mechanisms, many of the early adopters have turned to crowdsourcing platforms[65-67] 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 Biologigaragen (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.[64] 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.[64] 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,[68] 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.[69] More sophisticated devices include Amplino,[70] 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,[71] 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.[72] 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,"[73] 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.[74]

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,[75] two leading third-level institutions (CIT[76] and UCC[77]), 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.

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