Synthetic biology UK: progress, paradigms and prospects

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Abstract: Drawing comparisons with the study of scientific revolutions by Thomas Kuhn over 50 years ago it is possible to frame synthetic biology as a new paradigm, approaching biology and its potential for redesign from an engineering and information management standpoint. This may help relate it to current thinking about potentially revolutionary future developments stemming from the recent and very rapidly progressing convergence of relevant technologies. However, striking differences from Kuhn’s historic examples may also be noted – not only a greater awareness today of potential impacts that highlights the importance of explicitly incorporating broader issues of responsibility and governance but also the rapid growth in numbers of new researchers and entrepreneurs to the field globally which could accelerate the paradigm-shift process. The UK Synthetic Biology Roadmap 2012 and subsequent 2016 Strategy set out to develop a mechanism to respond nationally to this wider perspective, and examples, both UK and global, are drawn upon to help assess current progress towards the realisation of an ‘engineering biology’ paradigm.
hierarchical structure comprising four generic levels: starting with DNA as the basic building block then building up via ‘parts’ – pieces of DNA that encode for a single biological function, ‘devices’ – collections of parts that perform a desired higher order function specified at the design phase, and ‘systems’ – such as a switch, an oscillator or a set of metabolic pathways to synthesise functional components that can be incorporated within an operating system (chassis) [16]. Despite early doubts about the extent to which complex biological systems could ever be designed and constructed with predictable functionality using such a ‘bottom-up’ process [17], numerous working systems have now been developed using this approach.

As emphasised by Kinney and Freemont [18], this synthetic biology approach to assembling a fully functioning system from standard parts should not be misunderstood as delivering a simple ‘plug and play’ approach. A further engineering construct – the design-build-test (DBT) cycle – must invariably be applied to discover, refine and optimise the target system. The ability to design systems with greater predictability significantly reduces the time and cost of empiricism, but does not totally eliminate it.

The co-development and integration of increasingly high-throughput ‘gene foundries’ to perform the relevant DBT cycles with structured and increasingly predictable design protocols not only speeds up (and reduces the cost of) identifying and improving solutions but facilitates greater opportunities for the application of machine learning and AI to explore much greater range of design space than would otherwise be feasible. The process not only helps make the path to discovering solutions quicker and more affordable in the less complex, more conventional, design space (e.g.involving just a small number of gene manipulations) but also provides a systematic platform from which to tackle increasingly challenging and complex systems. The greater than Moore’s law rate of reduction in DNA sequencing cost per base this century is well documented – and is now eight orders of magnitude lower than at the end of HGP in 2001. The cost of synthesis has fallen steadily at a slower rate – by a factor of around a hundred, but many other relevant technologies are also contributing to overall cost reductions and hence increasing accessibility to synthetic biology researchers and developers, such as microfluidics which offer a low cost alternative to robotics as well significantly reduced reagent costs due to the low volumes required [19].

2004 marks the year in which multiple publications explicitly containing the term ‘synthetic biology’ start to appear in the Web of Science (with just four papers in the previous 13 years applying the term, before its more systematic structure had been set out at SB 1.0, for example by Hobom [20]). A more extensive survey of publications applying techniques closely related to the synthetic biology concepts of design and engineering, even if not explicitly using the term, by Shapiro et al. [21] notes an average of about 170 publications per year fitting this broader scope were generated from 2000 to 2005, rising to over 1000 per year 2011–2015. The absolute number is subject to these semantics, but either approach shows a significant rate of increase since 2004, currently running at around 20% per annum (Fig. 1). The bulk of this documented research is concentrated in just a few countries, such that over half the research publications have been produced by the USA (42.4% publications) and UK (10.1%), followed by Germany and Japan and a rapidly increasing contribution from China. However, interest is becoming truly global: Shapiro et al.’s 2000–2015 dataset identifies over 25,000 authors at 3700 organisations located in 79 countries (including papers co-authored by researchers from more than one country). A similar yet differently designed study (including publications and patents) by Oldham et al. [22] published in 2012 identified research investigations consistent with synthetic biology being carried out in 40 countries, supported by over 500 funding organisations and being pursued by an estimated 300 researchers.

The past half-century is often characterised in terms of an IT or digital revolution. There is a mounting body of opinion that the future will be shaped by the convergence of technologies. To quote Steve Jobs: ‘I think the biggest innovations of the 21st century will be at the intersection of biology and technology. A new era is beginning’ [23]. As expressed by the World Economic Forum [24]: ‘…The Third [industrial revolution] used electronics and information technology to automate production. Now a Fourth Industrial Revolution is building on the Third, the digital revolution that has been occurring since the middle of the last century. It is characterised by a fusion of technologies that is blurring the lines between the physical, digital, and biological spheres’. Could synthetic biology could find itself at the revolutionary heart of some future ‘age of biology’? Consistent with this view, in 2016 the WEF released a list of its ‘top 30 Technology Pioneers’, no fewer than five of which were synthetic biology companies [25].

**Fig. 1** Worldwide publications, drawn from web of science

*a* Only using the search term ‘synthetic biology’

*b* Including a broader range of publications reflecting core synthetic biology concepts of design and engineering, from Shapiro et al. [21] The cost of gene sequencing dropped by eight orders of magnitude during the same period
The term ‘revolutionary’ can have both positive and negative connotations and should be applied with care, both to avoid raising Unrealistic expectations and to avoid unwarranted concerns regarding the scale or speed at which change may occur, or regarding its likely impact. In practice, the pace of change will be constrained by the rates of technological progress and of regulatory adaptation [26]. Optimising the delivery of effective solutions requires that these two factors are broadly in sync with each other and with recognised needs. The term ‘revolutionary’ is often applied to scientific breakthroughs, even when their full significance may only be apparent to specialists in the relevant field. The concept of an ‘industrial revolution’ is more far-reaching and may only become fully apparent retrospectively many years in the future. Nevertheless, acknowledgment of this potential, arising from the ongoing convergence of biological and physical sciences and technologies, appears to be increasing and should therefore play a role in helping set future policy as, for example relevant to the bioeconomy.

Thomas Kuhn’s seminal treatise of 1962, ‘The Structure of Scientific Revolutions’ [27] provides a useful baseline against which to compare current developments. Drawing from an extensive analysis of numerous scientific developments documented over many centuries Kuhn established a basis for understanding and appreciating scientific revolutions not in terms of ‘discoveries’ that may initiate the process but in terms of ‘paradigm shifts’ that may signal the resolution of the intervening conflict of viewpoints. Kuhn discusses at length his use of the term ‘paradigm’ – to paraphrase at the risk of greatly oversimplifying: it reflects the mindset of the scientific community at large. Scientific endeavour is characterised by periods of stability during which ‘normal science’ (one might reasonably extend this to include ‘engineering’) proceeds following the prevailing paradigm, punctuated by ‘crises’ provoked by failure of the established norm to explain new observations or to solve persistently tough problems. An alternative, potentially disruptive, approach may be discovered yet face many years establishing its validity and significance during which it will co-exist with the working methodologies of the former paradigm to address common problems. Kuhn observed that a new paradigm tends to be more effectively embraced not through arguing theories but rather through the presentation of working models and examples.

Kuhn restricted his analysis to the domain of the physical sciences, but its potential relevance to the significant advances subsequently arising in the biological domain is noted by Hackam in his introduction to the 50th anniversary edition of the original published in 2012 [28]. Comparing the historical nature of scientific endeavour analysed by Kuhn and the pursuit of synthetic biology in the world today highlights interesting similarities but also notable differences that may have significant implications.

The community of relevant thought leaders in the former worlds of Priestley and Lavoisier, or Einstein and Pauli, could – as Kuhn observed – be numbered in terms of tens or at most hundreds. Rates of communication within the community and with the wider lay community at large were severely limited by the technologies of the day. Today, near instantaneous global communications and mutually informed and inspired research programmes may be transformative, as is evident from the recent exponential growth rate in publications. Not only is the global community of practicing scientists enormous by comparison with historical equivalents, but it is consequently open to a far greater cultural diversity of approaches which may more readily stimulate innovation and challenge incumbent thinking.

Kuhn noted that getting to grips with potentially revolutionary changes would often challenge the discoverer as much as the wider community, whilst grappling with the challenge of rationalising the new paradigm through the lens of the old and encountering significant resistance and controversy from peers and the wider scientific and lay community along the way. He observed that it would often require a generation of young scientists, or those entering the domain from outside the discipline and unencumbered by the prevailing mindset, to fully adopt the new paradigm and accept it as the established view from which the next wave of developments and pursuit of ‘normal science’ would emerge.

The year 2004 not only marked the collective envisioning of ‘synthetic biology’ engineering principles in SB 1.0 but also the establishment iGEM: ‘encouraging students to work together to solve real-world challenges by building genetically engineered biological systems with standard, interchangeable parts’ [29]. The iGEM competition has grown steadily year-on-year since. Focusing primarily on multidisciplinary teams at undergraduate level, this has now grown to over 30,000 alumni worldwide all having been introduced to, and having working experience of, the core concept of synthetic biology as a parts-based approach to engineering biology. The fact that iGEM mainly engages undergraduate teams, and that over half of the 30,000 alumni participated in 2012 or more recently, clearly illustrates the development of a large and relatively youthful community of future researchers and entrepreneurs that is already embracing the ‘new paradigm’ of synthetic biology.

However, does synthetic biology actually embody a new paradigm, or is it simply an evolution, albeit rapidly advancing, of technologies emerging throughout and since the second half of the twentieth century? Origins of an emerging new paradigm may be traced back to Crick and Watson’s discovery of the double helix in 1953. Coinciding with the 60th anniversary of their publication in 2013, Sydney Brenner, one of their earliest students and subsequent Nobel-prize-winner, observed ‘...the real paradigm shift stemmed from the fact that it introduced the idea of information and its physical embodiment in DNA sequences’ [30]. Taking the embodiment of ‘information’ in biology as a distinguishing feature from the pre-genetics era, one may draw a direct link with the following statement by Baldwin et al. [16], ‘...two concepts that must be understood: how information flows in biological systems, and how this information flow is controlled. With an understanding of these concepts one can, in principle, apply engineering principles to the design and building of new biological systems: what we call synthetic biology’.

Since the completion of the Human Genome Project in 2002, extraordinarily rapid advances in hardware and software – not only DNA sequencing but also a huge array of high-throughput and increasingly miniaturised sample preparation and handling, analysis and robotics, massive data generation and storage, machine learning and AI, increasingly precise gene editing and genome synthesis, and 3D printing – are all contributing to an explosion in the capability and affordability of tackling increasingly tough challenges. A significant enabler is that automated and digital systems able to generate and handle at speed the quantities of data associated with genome research have only become practically and affordably available within the past decade.

Commercialisation was severely hampered until recently by the limitations of technology, lack of affordable techniques and high costs of development, but has progressed rapidly in the past few years mainly via start-ups and SMEs that can now afford to operate effectively in the field. In the UK alone, recent analysis indicates that upwards of 150 companies are now using or facilitating synthetic biology [31]. An effective ‘service industry’ has emerged, providing tools and components that are helping accelerate the development of finished products by established industries and other start-ups. The embodiment and practical deployment of the core engineering concepts in this service industry context may be illustrated via the open-source ‘Antha’ software language for biology, recently developed by Sanghvi [32], along with an operating system designed to facilitate effective data sharing and hardware interoperability (‘standardisation’), helping overcome the complexities of different hardware protocols by applying higher-level software interfaces (‘abstraction’) and developed with the net objective of providing simpler access to a range of instrumentation and facilities (‘decoupling’). An expanding range of similar commercial examples further illustrates the emergence of a service industry within the UK now available to support the engineering of biology [33].
Current practice of synthetic biology has not been shaped by technological developments alone, but draws upon the rich and increasing needs arising from a growing human population, such as the Club of Rome’s ‘The Limits to Growth’ published in 1972 [34] and concerns over the detrimental impact of certain human activities on the environment and the emergence of the environmental movement [35]. Extensive regulatory frameworks have been established in response, and regulations continue to be updated as needed and as new information is generated. As a platform technology, synthetic biology is being identified with an ever-increasing range of potential applications, but in so doing is also starting to encounter overlapping and even conflicting regulations, stemming from numerous different historical starting points. There are mounting reasons to reassess some of the premises underpinning current regulations, to help ensure that developments of safe and effective solutions are not needlessly inhibited in future [36]. Such experiences have alsoflagged the need to consider and address technical, societal and ethical issues at an earlier stage of technological development and at the point of commercial application than generally considered in the past, via active deliberation and the development of suitable governance structures.

The framing of ‘global challenges’ in today’s world highlights the increasingly pressing needs arising from a growing human population, recognising both its dependence and impact upon global resources. A wide range of political, behavioural and technological responses are required to address these needs. An important part of the technological response can be framed within the scope of the bioeconomy – spanning health, food, sustainable chemicals and energy – and it appears likely that synthetic biology could play an increasingly contributory role in developing the solutions that will be vital to future progress and sustainability.

The practice of synthetic biology today is constantly being enhanced by improved techniques and insights arising from ongoing research spanning multiple application areas, such as the development of increasingly precise gene-editing technologies. It is also informed by past experience with earlier technologies, and from the outset has routinely maintained a broader perspective than solely technological, by also regarding needs and potential outcomes. The decision to publish a UK Roadmap [1] and to include Synthetic Biology in UK Policy as one of the ‘Eight Great Technologies’ [37] was made only after a detailed Public Dialogue exercise [38] had been carried out and assessed. The UK Roadmap makes a clear series of recommendations relating to addressing and building up good practice in Responsible Research and Innovation (RRI) throughout the practicing academic and commercial communities. The evaluation of best RRI practices is being actively pursued by dedicated RRI groups integrated within a number of research centres, and funded projects are now required to have considered RRI aspects at the outset, consistent with the stated Roadmap vision ‘of a UK synthetic biology sector that is... of clear public benefit: an exemplar of responsible innovation, incorporating the views of a range of stakeholders and addressing global societal and environmental challenges within and effective, appropriate and responsive regulatory framework’ (see [1, Vision Statement, p. 4]).

Valuable insights are accumulating from the wide range of initiatives currently underway in the UK, across the EU and beyond, but, given the wide range of approaches being explored, it is important to take some time yet for the increasing awareness to be assimilated into broadly applicable guidelines. The development of the current UK synthetic biology ‘eco-system’ – addressing the wider range of relevant factors, not only the establishment of research facilities – was recently described in detail elsewhere [39] so will not be repeated here.

Anticipation and coordination will be key to steering a smooth path from initial ideas to economically viable solutions. Significant progress over the past 5 years, as outlined above, provides strong endorsement of the UK government initiative to include synthetic biology in policy in 2013, whilst the breath of potential applications across the bioeconomy and the speed of development across a wide range of enabling technologies underpins the value of ongoing coordination spanning a broad range of stakeholder interest groups, as summarised in the 2016 publication ‘Biodesign for the Bioeconomy’ [40].

A synthetic biology ‘paradigm’ may be emerging through the working demonstration of the principles set down at the outset: that biology expressed in terms of information storage is now amenable to redesign and engineering, and proactively embedding awareness and responsibility in research and innovation is recognised as integral to facilitating the delivery of intended economic and societal benefits. In Kubinian terms, the corresponding paradigm shift could be considered accomplished only as and when design-led ‘Engineering Biology’ becomes the accepted norm.

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