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Synthetic biology in the UK — An outline of plans and progress

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ABSTRACT

Synthetic biology is capable of delivering new solutions to key challenges spanning the bioeconomy, both nationally and internationally. Recognising this significant potential and the associated need to facilitate its translation and commercialisation the UK government commissioned the production of a national Synthetic Biology Roadmap in 2011, and subsequently provided crucial support to assist its implementation.

Critical infrastructural investments have been made, and important strides made towards the development of an effectively connected community of practitioners and interest groups. A number of Synthetic Biology Research Centres, DNA Synthesis Foundries, a Centre for Doctoral Training, and an Innovation Knowledge Centre have been established, creating a nationally distributed and integrated network of complementary facilities and expertise.

The UK Synthetic Biology Leadership Council published a UK Synthetic Biology Strategic Plan in 2016, increasing focus on the processes of translation and commercialisation. Over 50 start-ups, SMEs and larger companies are actively engaged in synthetic biology in the UK, and inward investments are starting to flow.

Together these initiatives provide an important foundation for stimulating innovation, actively contributing to international research and development partnerships, and helping deliver useful benefits from synthetic biology in response to local and global needs and challenges.

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1. Introduction – the potential of synthetic biology

1.1. The emergence of synthetic biology

The sustainable manufacture of products, ranging from medicines to materials, and from foodstuffs to fine chemicals, is a critical factor in supplying the present and future needs of society. Such needs will continue to expand alongside rising global human population, as its impact upon the environment and its demand upon planetary resources continues to increase. Synthetic biology, at the heart of a bio-industrial revolution, is beginning to provide fresh options to address such needs, spanning feedstocks, processes and products.

Manufacturing processes have continued to evolve over the centuries. Chemical synthesis methods have delivered important products ranging from aspirin to synthetic polymers and dyes in the nineteenth century to fertilisers and synthetic rubber in the early twentieth century. Gradually replacing coal tar and whale oil by crude oil as the major feedstock during the later half of the nineteenth century inspired the development of petrochemical processes that supply a vast range of products we currently benefit from, spanning fuels to fibres and small molecule drugs to food flavourings. Fermentation, the basis of bread and beer making for thousands of years, advanced in the nineteenth century through the development of additional microbial processes and the discovery of the role of enzymes as biological catalysts with very specific function. Important medicinal products have been extracted or semi-synthesized from plants and animals for centuries, but since 1982, when the first approved ‘biologic’ – ‘human’ insulin produced using recombinant DNA – reached the market, an increasing proportion of therapeutics are now being synthesized.

Significant global challenges necessitate the development of even more effective manufacturing solutions – for example, how to produce fuels, foods and materials more sustainably? How to continue improving human and animal health and wellbeing? Synthetic biology delivers the capability to manufacture complex molecules and smart biological systems that to date have been too expensive, very difficult - or impossible - to produce. The underpinning techniques being developed may enable radically new functionalities to be incorporated, such as the incorporation of ‘smart switches’ into biosensors, or to produce more specific or bespoke drugs and therapies. It can be applied, for example, to support advances in regenerative medicine by providing more precise techniques for drug discovery, cell therapy and tissue repair [1]; to engineer bacteria for human digestive and environmental health [2]; to engineer new traits in plants to assist nitrogen fixation or to produce natural products [3], or to design fermentation processes that can deliver high value biopharmaceuticals at greater scale and affordability.

By improving the productivity of bio-manufacturing processes, synthetic biology can help generate more sustainable materials, chemicals and energy. Prospects for the advanced manufacturing of larger-scale industrial chemicals are also increasing – industrial production of 1,3 propanediol (PDO), lysine and 1,4 butanediol (BDO) using engineered *E. coli* provide early demonstrations of commercial viability [4]. It is generally recognised that the experience gained from developing such products – for example for related product families such as terpenoids related to artemisinin by Amyris [5] - combined with ongoing advances in available biological toolkits and improved industrial chassis (other than the ubiquitous workhorses *E. coli* and *S. cerevisiae*) will continue to reduce development times and costs and hence enhance prospects for future industrial uptake.

Noting certain parallels with the development of the microelectronics industry through the second half of the 20th century, it is also possible to envisage these innovative developments heralding in new generations of biological computers [6], information archiving systems [7] and in decades to come many other applications as yet unimagined.

Whatever the envisaged application, by applying core design and engineering principles of characterisation, standardisation and modularisation to biological systems within a core build-test-analyse-learn cycle, synthetic biology can increase predictability and development speed, and reduce costs. Solutions can be more robust and compete effectively with more established processes, or introduce new functionalities previously too difficult or expensive to consider. The development of better, faster, easier toolkits is itself a significant aspect of synthetic biology. As the field becomes more automated and predictable, developers will be able to focus more on the design of outcomes than on the implementation of laboratory processes themselves.

It is in reflection of such prospects for the delivery of significant benefits to health, economy and security that the UK has placed particular emphasis on the pursuit of research and development of synthetic biology, framed within the broader scope of stakeholder interests as outlined within the original UK Synthetic Biology

Roadmap [8].

1.2. Context - evolution of revolution?

Assessing the potential future significance of any innovative technology is necessarily beset with uncertainty, and the history of technological development is littered with lists of unfulfilled expectations. However, synthetic biology is not defined narrowly in terms of any specific outcome, but instead describes a platform technology with multiple possible applications, some of which are already delivering useful results, whilst others may take much longer or indeed never materialise. It provides core capabilities to accelerate and commercialise ideas within a much broader context of developments in the biological and life sciences that are evolving rapidly and to which the term 'revolutionary' is increasingly being applied. Such developments are likely to expand the opportunity space rather than constrain the possible options.

A reasonable argument can be made to support the view that a scientific ('Kuhnian') revolution in genomics and the life sciences has been taking place since the turn of the 21st century [9]. The foundations for this extraordinary acceleration in progress were set in the middle of the last century, notably with the discovery in 1953 of the structure of DNA by Crick and Watson in Cambridge. As Sidney Brenner, amongst the very earliest students to recognize the significance of Crick and Watson's discovery, and himself subsequently awarded a Nobel prize for his own major contributions to the field, stated upon the 60th anniversary of the discovery that "… the real paradigm shift stemmed from the fact that it introduced of the idea of information and its physical embodiment in DNA sequences of four different bases" [10]. But it took a further half a century before the investment in developing high-throughput instrumentation and associated software capable of extracting the complete structure of the human genome emerged from the Human Genome Project (HGP) 1992–2000 [11]. Within a decade of the completion of the HGP, a succession of further instrumental developments has transformed sequencing to a widely affordable and broadly applicable technique, enabling an explosion in gene-level data generation. This has coincided with a parallel 'revolution' in information technologies – hardware and software - capable of handling and analysing such enormous amounts of data, enabling understanding of the relationship between biological form and function at the gene level to be progressed [12]. Such developments continue to proceed alongside a raft of rapid and complementary scientific and technological advances and discoveries – including micro-fluidics, increasingly sensitive and rapid analytical techniques and increasingly precise gene-editing techniques such as CRISPR-Cas9 [13,14] – collectively contributing towards increasing predictability and cost reduction, transforming prospects for the widespread delivery of commercially viable solutions.

The convergence of biological and engineering concepts as a basis of a new technological revolution was mooted in the report 'Synthetic Biology' by the Royal Academy of Engineering (RAE) in 2009 [15]. It has subsequently been proposed by Prof. Schwab of the World Economic Forum [16] that the broader fusion of physical, digital and biological breakthroughs heralds the dawn of a 'Fourth Industrial Revolution'. The economic consequences may also be associated with the growing 'Knowledge Economy' anticipated by Deming as long ago as 1993 [17].

In summary, it remains to be determined whether future historians will view current progress in such broad terms, but there is no doubt that the term 'scientific revolution' is not misplaced with respect to the digitization of biology, the development of toolkits that enable rapid and effective translation, and the opportunities that are opening up as a result. If in scientific terms the 19th century is considered to have been the age of chemistry, and the 20th century the age of physics, only time – and persistent research effort - will determine whether the 21st century will deliver the age of biology, with synthetic biology at its leading edge.

1.3. Conceptualisation of synthetic biology

A strong legacy of academic research achievements set the foundations for the development of synthetic biology in the UK. Examples highlighted in the 2012 Roadmap include:

"The discovery by James Watson and Francis Crick of the structure of DNA in 1953 and seminal follow up work by Crick in 1961 which cracked the DNA-to-protein code, laid the foundations on which all Synthetic Biology designs now rely. UK expertise led to the discovery of reverse transcriptase (now an indispensible part of molecular biology) and the development by Frederick Sanger in 1977 of a vastly improved sequencing method. This led to huge scientific advances including the Human Genome Project.

In the 1990s Professor Shankar Balasubramanian and Professor David Klenerman from the University of Cambridge invented Solexa sequencing: an ultrafast method for sequencing DNA which improved cost and speed by 1000 to 10,000 fold on previous technologies. Solexa was sold to Illumina for $600 M in 2007 and is the global market leader in next generation sequencing. This expertise has continued to the present day.

Oxford Nanopore Technology (ONT) has developed a new sequencing technology based on fundamental research from the University of Oxford, which works by running a strand of DNA through a tiny hole called a nanopore. Developments such as these are leading to a point where DNA can be sequenced in real-time opening up exciting new possibilities for medicine and biotechnology [18].

The principles of synthetic biology began to emerge in the UK around the time the Human Genome Project was being published in 2002, funding for networks in synthetic biology awarded from 2007, and in 2009 the Imperial College Centre for Synthetic Biology CSynBi was established. From the outset, the value of collaborative working between research groups across the relevant physical and social sciences was fully recognised and formulated through the formation of the Flowers Consortium in 2010 comprising groups from Imperial College, Kings College, the London School of Economics (LSE), Cambridge University and Newcastle University [19]. The Flowers Consortium set to work on the cohesive development of platform technologies and the integration of tools and methodologies critical to the ability to undertake systematic design. This included the definition and implementation of key emergent metrology concepts and standards (DICOM-SB and SBOL) and their integration into an enabling IT infrastructure (SynBIS) – built to enable efficient information exchange and extraction. Reflecting the rapid uptake of interest in the field, stimulated by support from the UK research councils, synthetic biology research, or research closely related, was also starting to being carried out in numerous other universities across the UK.

Such background developments set the stage for the UK synthetic biology initiative – how to translate this emerging knowledge into benefits for society and the economy? Synthetic biology provides a mechanism to address this challenge by taking foundational research from a range of fields (for example, biochemistry, systems engineering, molecular biology, plant sciences, chemical engineering, informatics, microbiology) and integrates and builds upon these findings through the application of engineering design principles [20]. The resulting discipline may be described as a 'translational field' – helping to extract important benefits from new insights. Synthetic biology sets out to utilise the inherently modular nature of biological systems as a basis for defining discrete 'parts' with context-dependent function, whilst recognising that in practice the development of a robust system will emerge from a design cycle that manages and accelerates the interplay between experiment and theory, and should become more rapid as knowledge continues to unfold. To become an effective basis for design and manufacturing, the formalisation of this approach also requires an increasing degree of new standardisation and interfacing with established standards (e.g. manufacturing standards).

The incorporation and adaptation of engineering principles and techniques, to help translate such opportunities into reliable and robust systems that can deliver benefits as intended, is an integral and vital element of synthetic biology. Rationalising the complex relationship between structure and function permits higher levels of abstraction to be applied, further aiding design speed, consistency and predictability.

The domain of synthetic biology emerging from this perspective is captured schematically in Fig. 1. The increasing ability to predict functional behaviors via information management at the genomic level combined with the application of engineering-type methodologies – in effect shifting the operational foundation from predominantly analogue to digital - leads towards the emergence of a 'biodesign' capability as described below in Section 4.

The principles of Synthetic Biology and a working definition were captured in a report by The Royal Academy of Engineering in 2009 [21], coinciding with the establishment of the UK's first dedicated Synthetic Biology Department 'CSynBI' at Imperial College. A valuable working definition of Synthetic Biology, as expressed in The Royal Academy of Engineering report is: 'the design and engineering of biologically based parts, novel devices and systems as a well as the redesign of existing, natural biological systems'. Although the field itself has progressed substantially over the past seven years, and whilst many alternative definitions have been proposed by others over this period, this working definition has remained relevant and useful, and adopted for consistency in both the 2012 UK Roadmap [22] and the subsequent 2016 UK Strategic Plan [23].

As noted, synthetic biology has defied the formation of an internationally accepted definition, not least because it reflects the convolution of several different disciplines, and represents a constantly advancing frontier of scientific knowledge. Its importance derives from the innovative fusion of scientific and engineering sources into a practical toolkit that facilitates the translation of understanding into the development of practical applications. We have found that our working definition used above is fully adequate to capture the critical elements, and has passed the test of time for this purpose over the seven years since it was first formulated. It is likely that attempts to be more precise will fail to capture the full scope or be rapidly rendered obsolete as new insights and advances continue to enhance the depth and breadth of knowledge, and steadily shift the frontiers of research.

A consequence of this shifting focus is that not all potentially relevant research in the world is described as synthetic biology whilst other studies may use the synthetic biology descriptor but, in fact, have only limited connection to the main technological core. To explore this, an analysis of worldwide scientific publications and IP in the domain of synthetic biology was carried out in 2011 by Oldham [24]. This applied an ontological approach to map the world's scientific literature through the prevalence of terms commonly used in synthetic biology papers, irrespective of the use of the term synthetic biology itself. The study concluded that most synthetic biology-related publications and IP filings were in the US, with the UK second. The combined total of the whole of Europe publications in synthetic-biology-related research was comparable to the US. There was evidence of potentially related research activities in more than 40 countries and 500 funding agencies worldwide, illustrating the breadth of interest and perceived relevance of the field in a broad range of contexts.

As the underlying frontier of knowledge continues to advance, enabling attention to focus on translation and commercialisation, it is reasonable to expect that synthetic biology will persist as the

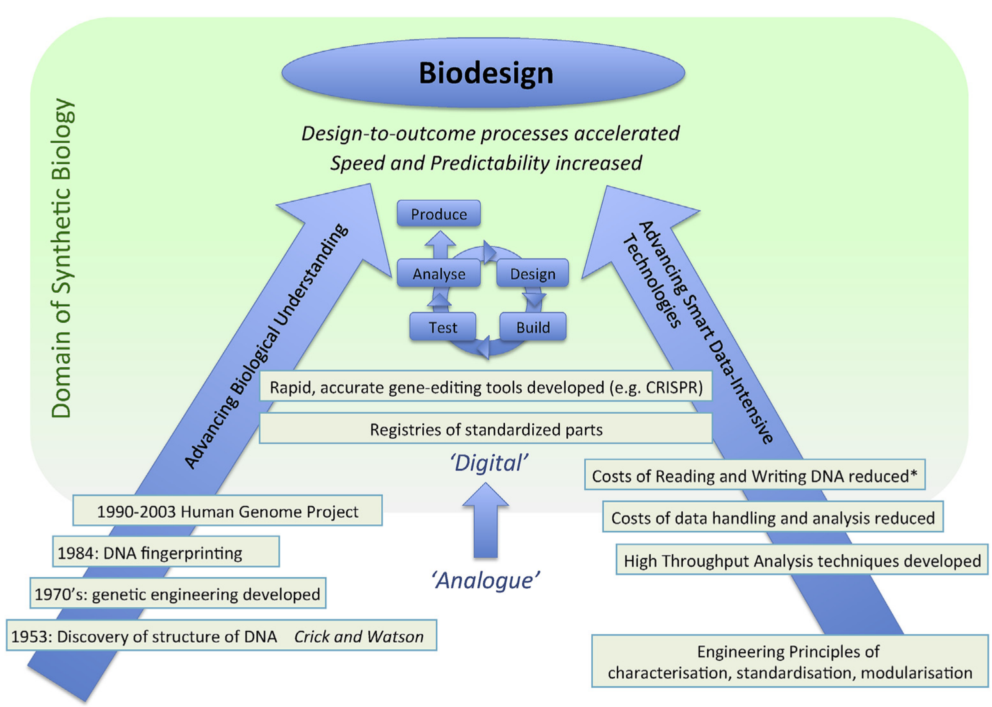

Fig. 1. Schematic illustration of the emergence of the synthetic biology domain via the confluence of advancing biological and informational technologies and the incorporation of engineering principles.

'engine-room' of technique development, enabling ever more predictable and precise techniques to be applied to ever more challenging issues, but that their practical commercial application will in many cases require the additional combination of numerous other techniques separately relevant to the specific field of application.

As an important evolutionary step along the path towards increasing application, it is clear that the underlying techniques of synthetic biology are becoming 'higher level' (i.e. offering a simpler coding system that is separated from the details of the operating systems and are therefore easier for humans to understand). The development and adoption of 'higher-level' languages to instruct the required operations will start making the technology accessible to a broader range of non-specialists who can then focus more on the intended outcomes than on the mechanics of the underlying build-test-analyse processes. This gradual shift in focus towards 'Biodesign' is already becoming a reality for simpler systems, whilst remaining a significant future target for more complex systems [25].

1.4. Commercialisation – from roadmap to policy

In 2011 the UK government commissioned a review of significant technological advances, strengths and opportunities within the UK emerging from its academic base. This was led by the Technology Strategy Board (subsequently renamed InnovateUK). The objective was the development of a policy that would better address the so-called 'valley of death' between scientific discoveries and commercial development, and the selection of a small number of R&D-intensive 'general purpose' technologies with significant implications, around which to focus such a policy [26]. In the study it was recognised that the UK possesses considerable breadth and excellence of R&D expertise. Synthetic biology was just one of 170 candidate technologies initially screened during this study. That synthetic biology was eventually selected as one of the 'Eight Great Technologies' arising from this exercise can be largely attributed to the combination of extensive legacy in related world-class research and biotechnology commercialisation, the rapid expansion of R&D interest specifically in synthetic biology across the UK that had already taken place, and the prospects for substantial growth in relevant product and service markets [27].

Recent data and market analyses support the expectation of rapid market sector growth. For example, biotechnology as a sector is growing substantially faster than GDP as a whole in leading markets. Estimates for the US by Carlson (defining the biotechnology sector in its broadest sense to encompass biologics/biopharmaceuticals, GM crops and industrial biotechnology) suggest annual growth exceeding 10% over the past decade, with revenues already exceeding 2% GDP by 2012 [28]. The global biologics market -including monoclonal antibodies, therapeutic proteins, and vaccines - is growing at a compound annual rate exceeding 10% and expected to grow to £387bn by 2019 [29]. It is estimated that biobased chemicals now make up more than 10% of the US chemicals market [30], with projections for global synthetic biology markets for chemicals to grow to $11bn by 2016 [31] delivering an economic impact of at least $100bn by 2025 [32]. A study by Allied Market Research issued in 2014 predicted a global market for synthetic biology of around $38bn by 2020, growing at a CAGR of 44% during the forecast period 2013–2020 [33]. Although comparative analysis suffers from an inherent lack of consistency in the use of terms such as 'biotechnology', and future projections must necessarily be treated with caution, a consistent pattern emerges - of relative and substantial growth to date and anticipated in future for biobased economies, to which synthetic biology is expected to make an increasingly important innovative contribution.

The global significance of such developments had already been recognised and addressed in a ground-breaking series of international meetings convened under the auspices of the six academies - the United Kingdom's Royal Society and Royal Academy of Engineering, the United States' National Academy of Sciences and National Academy of Engineering, and the Chinese Academy of Science and Chinese Academy of Engineering - between 2010 and 2011 [34]. This series of meetings not only addressed issues directly related to synthetic biology, but could be considered to have paved the way for a new approach to engagement on emerging technologies. Of particular significance was that the series of meetings actively took note of the importance of globalisation and the internationalisation of science – thus engaging as equal parties the US, UK, and China and inviting participation in the meeting from individuals around the world. It also actively took note of the critical need to engage expertise outside of the life sciences/engineering community in fostering an emerging technology – thus engaging with ethicists, social scientists, policymakers, legal scholars, and regulators.

The linkage of synthetic biology research to significant commercial strengths in the UK was also recognised. For example, it was noted that the UK has one of the most dynamic and innovative healthcare industries in the world, comprising around 600 companies and employing some 67,000 people [35]. It has developed over 20% of the world's top 100 selling medicines (second only to the US) - more than the rest of Europe combined. Every one of the top 10 pharmaceutical companies in the world has a presence in the UK. GSK [36] had recently committed an investment of more than £500 m across its manufacturing sites in the UK, to increase production of key active ingredients for its pharmaceutical products and vaccines. Together with AstraZeneca, these two companies alone have reported a combined turnover of £42bn (approx. 9% of the global market). A report by the BIA in 2016 also noted the importance of smaller companies to the pharmaceutical sector in the UK – a R&D powerhouse with 585 pipeline projects in development including the highest number of phase 3 projects, and attracting more than a third of all venture capital funding, in Europe [37]. This provides a significant channel to market for potential biotech applications of synthetic biology.

This, combined with significant strengths in the chemical and petrochemical industries, clinical and health sciences, advanced engineering, manufacturing and design, further supported the decision to shortlist synthetic biology for inclusion as one of the 'Eight Great Technologies' policy.

A feature of synthetic biology distinguishing it from the other 'Eight Great Technologies' as selected in 2012 was its relative 'infancy' as an established sector - having only emerged as a new concept during the previous decade. This is not only evident from the aforementioned discussion regarding a definition, but at the time there were very few worked examples of practical applications approaching market deployment– the development of synthetic artemesinin and Artemisinin-based Combination Therapies by the US company Amyris being a notable example at the time [38]. On the other hand by addressing the challenges and opportunities at such an early stage of its development provided a particularly valuable opportunity to map out an entire framework for the development of the sector without preconceptions. The main challenges faced by the Roadmap Coordination group included issues such as: What is our Vision? How to translate this rapidly emerging body of knowledge and capacity into a form in which the anticipated benefits could be developed? How could this lead to an entire new bio-based industry within the UK?

On the basis that scientific and technological progress provides the opportunity to deliver important benefits to society, and given the wide range of potential applications and radically new solutions that could emerge it was clear that processes for discovering and responding to the views of the public, or more strictly of the many 'publics' should be built in from the onset. A Public Dialogue [39] was commissioned and the results analysed and considered before any decision was made to prepare a Synthetic Biology Roadmap, and so that its findings could inform the Roadmap process.

In November 2011, the UK government requested the formation of a Synthetic Biology Roadmap Coordination Group to review and map out the opportunity in more detail. The group was set up to operate in an independent capacity (advising government, not implementing a pre-defined policy), chaired, as proposed in the Policy, by an industrialist with experience in the commercialisation of ideas from research. The Roadmap Coordination Group comprised representatives from industry, academia (universities and higher education institutes spanning physical and social sciences) and research funding bodies, together with observers from relevant UK government departments (a full list of members is included in Roadmap and also in the acknowledgements section of this report).

The Coordination Group applied a variety of processes to stimulate and collate material for consideration in the Roadmap, including number of workshops at which the views of a broad range of stakeholder groups – academic, industrial, social - were enlisted. An intensive series of discussion meetings convened over several months subsequently drew out the broad themes and main recommendations. The Roadmap was completed and presented to the UK Government in July 2012. As noted in the document, the Roadmap reflected ideas from a wide range of sources but did not purport to represent the totality of views existing within the UK including within the group itself. Nevertheless, it permitted an internally consistent approach to be mapped out that enabled some immediate recommendations to be made. This led to the first steps in what was recognised could become a long-term programme of development. It was also recognised that the precise trajectory would undoubtedly adjust over time in response to new knowledge and experience, and that a subsequent document or documents would be required in due course as the focus of effort would shift from the research environment towards one in which application development and industrialisation would play a more significant role.

2. The 2012 UK Synthetic Biology Roadmap

The UK roadmap is not a conventional project plan. It does not have a specific end-point set in time, such as 'putting a man on the moon'. Instead it sets out a framework that will facilitate the efficient development, evaluation and delivery of valuable options spanning a wide range of possible application areas. This framework encompasses a vision, value system, mechanism to promote underpinning technological development – emphasising the importance of systematic biodesign and industrial translation - and a schematic multi-decade timeline to deliver useful applications and benefits.

A unifying theme may be envisaged in terms of a technological 'pipeline' through which ideas are developed, scaled and deployed as needed. The efficiency with which innovations flow from laboratory to market relies on a wide range of factors, including the operating environment and market readiness, embracing cultural values and effective governance systems relevant to each type of application. The availability of expertise and facilities, the regulatory environment, the ultimate value of the final product or service, all play a role. It recognises that certain enabling technologies and useful applications could emerge in the near future whilst ongoing research will continue to inspire new opportunities and applications for many years to come. Given the rapidity of development, the system must also be agile and responsive to new opportunities and insights as they arise. The resulting need is for an integrated matrix of parallel activities supported by a multi-year funding commitment. The roadmap outlines a set of principles and infrastructures to support this system.

Our approach seeks to reconcile the concept of 'vertical integration' as may be delivered within an a fully integrated private corporation with the recognition that critical decisions along the pipeline within an open-ended national system will generally be made by different public and private entities. Productivity of the system as a whole will be greatest when avoidable delays at interfaces between the various phases are minimised, and the pipeline is supplied with sufficient ideas at the front-end, or effectively linked to complementary ideas as it flows along, to ensure the outputs satisfy market requirements in an affordable and timely manner. Mapping this process and identifying the critical success factors and structural needs specific to the UK is the primary objective of the Roadmap, consistent with the principles set out in 'The Eight Great Technologies' policy document, launched by the then Minister for Science and Innovation, The Rt. Hon David Willetts, in January 2013, which had the express objective of generating more effective links between emerging academic research and the processes of commercialisation and industrialisation.

The UK Synthetic Biology Roadmap Coordination Group identified a package of measures to support and develop the UK-wide research and industrial communities by enhancing the availability of essential resources and information. These were summarized under five main recommendations as listed below. Taken together, they help shape the operating environment in which synthetic biology ideas and applications may flourish and deliver intended benefits. This package of recommendations was supported in full by the UK government in 2012.

2.1. Invest in a network of multi-disciplinary centres to establish an outstanding UK synthetic biology resource

Common themes running through the Roadmap were to facilitate communications and learning, and to generate a network of experts across disciplines with customers, public and private interest groups. Key to achieving this was to provide better access to cutting edge resources for both academic community and industry.

A multi-disciplinary synthetic biology centre had already been established within the UK in 2009 (CSynBI at Imperial College), and it was proposed to establish a number of additional centres, to boost the national research capacity and diversify our expertise, stimulating innovation and facilitating the interfaces with industry and other key stakeholders.

Under the 'Synthetic Biology for Growth' programme, two annual competitions for new centres of multidisciplinary synthetic biology research excellence were held in 2013 and 2014, and three new 'Synthetic Biology Research Centres (SBRCs)' were awarded on each occasion, each with five-year funding commitments. Together with the original CSynBI centre at Imperial this has generated a set of seven major multidisciplinary hubs across the UK.

Each SBRC has its own cooperative network of research groups and smaller centres, collectively comprising more than 30 universities spanning the country, thereby generating a UK-wide research and development foundation of international significance. All centres are committed to research in Ethical, Legal and Social Aspects (ELSA) of their work, with embedded Responsible Research and Innovation (RRI) goals and dedicated staff who link the centres, share experience and develop best practice. This dynamic environment for research and training brings together a critical mass of researchers working across the UK, galvanising the higher education sector to make their own significant investments in synthetic biology, and attracting substantial additional funding from industry and from international grants and partnerships.

Although the centres were selected first and foremost on the basis of individual excellence, the net outcome has been to generate a national research infrastructure that has a broad geographical footprint and spread of academic and potentially commercial interests. Critical mass of facilities and researchers is achieved at both national and regional scales. The primary focus of each centre is summarized as follows, but there are also many examples of collaborative activities between different centres, drawing upon the broad base of resources and expertise available throughout the national network. Each research centre also brings its own set of international partnerships to the overall enterprise.

CSynBI - the Centre for Synthetic Biology and Innovation at Imperial College [40] applies a twin track strategy to engineering biology - the development of platform technologies and applications. Platform technologies include: information systems, standards (SBOL and DICOM-SB), detailed protocols for characterisation (BioParts, devices and chassis) and DNA assembly. Application areas include: biosensors, biocomputing, production therapeutics, cell-based therapies, advanced biofuels and biomaterials, penicillin from yeast and participation in the yeast synthetic genome project Sc 2.0 [41].

BrisSynBio – the Synthetic Biology Research Centre at the University of Bristol [42] seeks to improve the ability to design and engineer biological molecules and systems with a particular focus on proteins, and to apply this knowledge in applications relevant to health and UK industry. Application areas include: producing agrochemicals, pharmaceuticals and fine chemicals in bacteria, new vaccines against dengue fever and other unmet clinical needs, developing new methods to increase the yield of wheat.

SYNBIOCHEM – the Synthetic Biology Research Centre for Fine and Speciality Chemicals at the University of Manchester [43] focuses on the synthetic Biology of fine and speciality chemicals production (including new products and intermediates for drug development, agrochemical and new materials for sustainable bio-manufacturing). Applications are being developed through active collaborations with a large variety of industry partners to propel chemicals/natural products production towards 'green' and more sustainable manufacturing processes.

OpenPlant - a collaboration between the University of Cambridge, the John Innes Centre and The Sainsbury Laboratory in Norwich [44] is accelerating the development of new tools and methods for plant synthetic biology and facilitating their open exchange and application of standard tools for trait development. Application areas include the development of new medicines, chemicals and green energy sources, including enhanced photosynthesis and nitrogen fixation.

SynBio – the Synthetic Biology Research Centre at the University of Nottingham [45] applies synthetic biology to organisms that can digest materials and convert single-carbon gases into more desirable and useful molecules. Applications include the sustainable production of chemicals and fuels to reduce reliance on petrochemicals, utilisation of waste greenhouse gases and thereby to facilitate the emerging waste economy.

The UK Centre for Mammalian Synthetic Biology Research - at the University of Edinburgh [46] is building expertise in cell engineering tool generation, whole-cell modeling, computer-assisted design and construction of DNA and high-throughput phenotyping to enable synthetic biology in mammalian systems. Applications include tools and technologies for near-term commercial exploitation by the pharmaceutical and drug testing industries, diagnostics, novel therapeutics, protein based drugs and regenerative medicine, and participation in the yeast synthetic genome project Sc 2.0.

WISB – the Warwick Integrative Synthetic Biology Centre [47] addresses specific, industrially relevant design challenges across the scales of biological organisation: genetic circuits, pathways, and multi-cellular systems, also providing us with a better understanding of some of the key mechanistic and evolutionary principles underpinning living systems. Application areas include pharmaceuticals, high-value and commodity chemicals, treatments for disease, environmental bioremediation, and food security.

2.2. Build a skilled, energised and well-funded UK-wide synthetic biology community

It was recommended that attention should be given to developing a skilled, energised, responsible and well-funded community, involving the stimulation of cross-disciplinary interactions and sharing of best practice, encouraging innovative research proposals and facilitating the development of valuable applications. This, together with the provision of further guidance on responsible research and innovation and other training initiatives, was aimed at the establishment of an increasingly secure and confident 'can-do' culture, and also to facilitate increased levels of interaction between the research community and other stakeholders and publics.

To provide a central access point for any individual interested to know more about synthetic biology in the UK, and to be able to engage directly in discussions, an online Synthetic Biology Special Interest Group (SIG) was formed immediately following the Roadmap publication in 2012 [48]. Membership registrations grew to over 1000 within the first two years, comprising 44% from academia, 28% from Industry, and 7% public sector, with 26% mixed or unknown background – demonstrating a broad spectrum of stakeholder interests and engagement. In addition to providing up to date information, the SIG provides a mechanism to seek views from a broad spectrum of interest groups via online questionnaires which, for example, have been used to review progress and to seek suggestions for further improvement in the systems we have put in place to help progress synthetic biology in the UK.

Centre for Doctoral Training (CDT). Another important initiative was to further boost the supply and training of synthetic biology scientists beyond that already being carried out in existing and the new research centres, by forming a synthetic biology centre for doctoral training. Typically in the UK PhD students take three years to four years to complete their doctoral research under the supervision of one or more academic advisors within a research group (or possibility more than one group if the project is multidisciplinary in nature). The CDT (otherwise known as a DTC – Doctoral Training Centre) model involves a wider cohort of students, either from one university (or a small number of universities). In the CDT model students are organised into cohorts working within a broad common scientific area. There is, typically, a lot of student interaction and the CDT model also usually involves a considerable amount of transferable skills training. In practice a coordinated three-centre structure was established 'SynBioCDT [49]', comprising a collaboration between the universities of Oxford, Bristol and Warwick, offering a rolling series of four-year doctoral training courses. The third annual cohort of students from this programme is due to start in the Autumn 2016.

iGEM, the international genetically engineered machine competition [50], is recognised in the UK as an integral and very important mechanism for attracting predominantly undergraduate students from a wide range of background and providing valuable training, and in working in multi-disciplinary teams in the production of biologically-based devices. British teams have been highly successful in the competition over the years, including a team from Cambridge being awarded overall winners in 2009. A significant proportion of graduates starting synthetic biology careers have been inspired by taking part in iGEM and ten companies have already formed directly from iGEM projects, with four of these in the UK.

2.3. Invest to accelerate technology responsibly to market

This third recommendation sought to generate an environment in which commercialisation of a potentially disruptive technology could flourish, reflecting the very early and potentially open-ended stage of development of the sector at the time the Roadmap was being generated. Issues to be addressed included mechanisms to attract investment into a relatively unfamiliar topic area from many would-be investors, including building confidence through helping innovators to apply synthetic biology in a responsible way to create new products, processes or services.

The concept of Innovation and Knowledge Centres (IKCs) had already been successfully established in the UK as a mechanism to nucleate new industries, by closing the gap between scientific research and its commercial exploitation. IKCs are a key component of the UK's approach to the commercialisation of emerging technologies through creating early stage critical mass in an area of disruptive technology. It was recommended that an IKC be included within this overall structure to assist the important function of academic/business integration in synthetic biology. The UK's IKC for Synthetic Biology ‘SynbiCITE’ (pronounced synbi-city) was awarded to Imperial College London [51] in 2013, and is one of seven IKCs set up in the UK to facilitate the development of new industries.

SynbiCITE – the UK's national industrial centre for synthetic biology is designed to be an effective industrial translation engine – bridging the gap between university-based research and industrial processes to create products and jobs, through industry. It provides a national centre of expertise in technology development and commercialisation for the benefit of the UK economy - facilitating collaboration of UK's leading academic institutions and industrial partners, ranging from start-ups to large multinational companies, and supporting organisations including the Northern Ireland, Scottish and Welsh Regional Governments and the Greater London Authority. SynbiCITE's extensive network of partners currently includes 20 U.K. universities and over 50 industrial and commercial partners, made-up of multinational companies, SMEs and start-ups.

Working closely with colleagues in the US, SynbiCITE has pioneered the development of industrial translation training in synthetic biology in the UK, including the nurturing of entrepreneurs through the Lean Launchpad programme, and delivering core business skills through the ‘four-day MBA’ programme. A major training programme for future leaders is provided via the one-year synthetic biology Leadership Excellence Accelerator Programme (SynBioLEAP), a joint programme between Imperial College and Stanford University, aiming to develop the skills needed to lead responsible synthetic biology development in a global context.

2.3.1. DNA synthesis foundries

Practical assistance to start-up companies at SynbiCITE is based around its accelerator facilities, including its DNA synthesis and construction Foundry [52]. The Imperial College Foundry was launched in April 2016 [53]. The most recent synthesis centre to be launched in the UK, in July 2016 [54], is the Edinburgh Genome Foundry [55] ‘SynthSyS’.

These initiatives bring the total of DNA Synthesis Foundries recently established in the UK to five - Edinburgh Genome Foundry, Liverpool Gene Mill, MRC Laboratory of Molecular Biology, DNA Synthesis and Construction Foundry at Imperial College and The Genome Analysis Centre at Norwich Research Park. The different foundries have different emphases and designs linked to the main focus of their associated research – for example, the Imperial Foundry is industry facing and modular.

Such foundries will facilitate a step change in productivity because they enable the introduction of extensive automatic, reducing experimental errors and greatly improving reproducibility. Also, they allow massively parallel experimentation and correspondingly faster data generation.

2.3.2. Technical standards

Underpinning the translation of ideas into industrial production is the need to establish a framework of robust engineering principles and practices. Core elements of such a framework include the timely setting of appropriate standards. The development of internationally recognised standards in synthetic biology was recognised very early on as key to the industrialisation of biological ‘parts’ and processes, alongside the need for data format standards required for seamless transfer between laboratories. Biological ‘parts’ are units of biological activity (normally encoded by DNA) that can be assembled into systems or devices. In recent years the Flowers Consortium has achieved major progress in developing information systems, data-mining, CAD standards (SBOL and DICOM-SB), and modeling - as well as detailed reproducible procedures for characterisation (BioParts, devices and chassis) and DNA assembly [56], with joint support from the EPSRC in the UK and NSF in the US.

The emergence of best practice will be best achieved incrementally, reflecting the pace of development and in anticipation of evolving needs. Innovate UK funded The British Standards Institution (BSI) [57] in 2015 to produce the first guidance on the use of standards in synthetic biology (PAS 246) [58]. The adoption of SBOL (synthetic biology open language) standards in 2016 by the journal ACS Synthetic Biology as the basis for depicting genetic constructs and as the basis for recording and sharing the designs of engineered organisms [59] illustrates how such standards can be expected to steadily impact market practice.

This recommendation directly associates the notion of responsibility with the acceleration of technology. This is captured through the introduction of ‘Responsible Research and Innovation’ (RRI) as an essential value system for funders and practitioners alike. This is regarded as a very important and integral aspect of any prospective research activity, including synthetic biology, and is described in more detail in Section 4.4 below.

2.4. Assume a leading international role

Although the UK Roadmap necessarily focused on developing capabilities and realizing opportunities within the UK, it is fully recognised that such activities are enabled and enhanced by progress across the envelope of leading-edge science globally, especially that being carried out in the US. International collaboration is an essential factor underpinning progress in synthetic biology, reflecting the increasingly knowledge-based and interconnected nature of 21st century society. Clear economic benefits derive from increasing scientific activity between countries, and this expectation lies behind a range of initiatives including jointly funded research programmes in synthetic biology spanning the US and Europe and China. International research-level agreements and collaborative working are a characteristic of research at all the major synthetic biology research centres in the UK.

UK funding council investments into synthetic biology have helped place the UK in a prime position to continue its international role, not only technologically but for example in helping establish international standards, both technical and regulatory, sharing experience in Responsible Research and Innovation, and by contributing positively towards the overall international response to global challenges including health and the environment. This is being achieved through a variety of mechanisms, such as participating in trans-national grant funding, hosting international conferences and by continuing to foster coordinated efforts in synthetic biology through research partnerships.

2.5. Establish a leadership council

Due to the wide range of envisaged potential synthetic biology applications and the corresponding number of institutional bodies involved in different aspects of synthetic biology reflected in the Roadmap, it was clear that there would need to be a single body capable of spanning these many interests, to act as a visible and effective point of co-ordination. It was also recognised that, whereas the original roadmap had set a clear vision and value system which should provide the foundations for long-term development, due to the rapid pace of development, the recommendations for research and commercial translation could only provide the first step of an adaptable, responsive system that would need ongoing reassessment. Agility and responsiveness must be built in at the institutional systems level to match the rapid pace of development and learning of the technology itself. It was therefore proposed to establish an *ad-hoc* UK Synthetic Biology Leadership Council (SBLC), to own and oversee delivery of the vision and roadmap recommendations, to assess progress and update recommendations and priorities within the roadmap, as and when needed.

The UK Synthetic Biology Leadership Council was formed in Nov 2012. As subsequently described in the recommendations of the 2013 Policy document, it was co-chaired by an industrialist and a member of government, providing a unique balance of council independence with an effective mechanism to inform the ongoing development of government policy.

The composition of the leadership council has evolved and will continue to do so as the main focus of attention shifts over time. Consistent with the objective of retaining agility and responsiveness, the council has been numerically constrained in size, but supported by the establishment of sub-groups and through engagement with others as and when needed, to reach out to the broader community of experts and interest groups. Two subgroups are of particular importance for the functioning of the leadership council.

The Governance Subgroup (GSG) provides a dedicated forum to influence the development of an agile and supportive policy and research processes for synthetic biology in the UK. Social awareness alongside technological expertise is now embedded in training programmes, through the framework of Responsible Research and Innovation (RRI) as recommended in the 2012 Roadmap. Outreach and community engagement are important and integral to the UK synthetic biology activities at all the research centres, and effective consideration of RRI has become an essential feature of research funding.

The Science and Technology subgroup (STSB) was formed to provide a first-tier engagement mechanism between the SBLC and representatives of each of the new centres. The function and influence of this group has continued to evolve as the new centres have become fully operational over the past two years.

3. Progress and achievements

Significant progress has been made towards meeting the objectives of the five core recommendations of the 2012 UK Roadmap. The UK Government's 'Synthetic Biology for Growth' Programme has made significant capital investments in equipment and facilities for foundational research and development from which a broad range of potential applications and commercial opportunities are being generated.

As noted in Section 1.30, rapid advances in information technology and high-throughput analysis and assembly (using automation to conduct huge numbers of experiments in parallel) are making it increasingly possible to address biological system function from a digital rather than analogue perspective. By applying core design and engineering principles of characterisation, standardisation and modularisation to biological systems - allied to a range of innovations in miniaturisation, automation and metrology - predictability and development speed can be increased and costs reduced. This frames the core objectives of synthetic biology. Previously intractable challenges can be readdressed, and the potential to commercialise useful applications enhanced. By enabling concepts to be translated more rapidly and reliably into commercially viable processes, the cost of market entry may be reduced, competitiveness enhanced and the delivery of benefits accelerated.

UK public sector investment has totalled approximately £300 M in the last eight years and is now attracting increasing amounts of private investment as start-ups are formed and joint public-private partnerships are established. Another significant metric beyond funding and investment levels alone is evidence for the dynamic nature of the field. The diversity of background skills and expertise being assembled in the multi-disciplinary centres, stimulating entrepreneurship across a wide range of potential applications – set within a loosely coordinated and broadly inclusive national framework - has generated a highly effective environment within which innovation is flourishing. Synthetic biology in the UK is no longer confined to academic research programmes, but is being actively translated into commercial opportunities, as the following examples illustrate.

3.1. Application examples

Scientists at the John Innes Centre in Norwich have discovered a method to accelerate vaccine production to start within as little as two weeks from the identification of, for example, an influenza virus. They applied their research on the little-known plant virus, cowpea mosaic virus, to produce a non-infective virus-like particle (VLP) that provides the basis for rapid protein expression in plants under greenhouse conditions. Commercialised under licence by the Canadian company Medicago, this technology enabled 10 million doses of H1N1 swine flu VLP vaccine in just a month, outperforming the traditional method that would have taken typically 9–12 months. Increasing the speed of response is critical to the effectiveness of vaccination programmes, enabling them to accommodate and address the most recent naturally mutated virus strains as they become known.

The UK company Prokarium is developing vaccines that are thermostable and can be delivered orally [60]. Increased thermostability – their new vaccine is stable at 4 °C for over 3 years - can be critical to delivering vaccines in places where it is difficult to maintain the otherwise required cold storage conditions. Using synthetic biology to generate their Vaxonella® platform, Prokarium have already brought oral vaccines for *Chlamydia trachomatis* and for *Clostridium difficile* to pre-clinical trial stage. Most recently, it has received funding from the UK and Mexican governments to develop three new vaccines against Zika, bacterial diarrhoea and plague – strengthening response capabilities in the face of emerging disease threats.

As the old adage goes - prevention is better than cure. Oxitec, a spin-out from Oxford University UK, has been developing mechanisms to counter the increasingly widespread transmission of vector-borne diseases such as Dengue-fever, chikungunya and yellow fever, by suppressing their diffusion by the *aedes aegypti* mosquito. This sub-species of mosquito has steadily spread from its native West Africa to well over 100 countries, alongside increasingly global trade, travel and climate change - the WHO recently estimated that the *aedes aegypti* mosquito now lives alongside up to half the world's population [61]. By modifying the genome of *aedes aegypti* mosquito males to render their offspring infertile, the resulting self-limiting OX315A mosquitos can be released to seek out and mate with the local female *aedes aegypti* mosquitos, rapidly collapsing populations in the target areas by over 95% without the need for to use more broadly-impacting insecticides. The potential value of such an approach has been recently highlighted by the recent outbreak of Zika virus initially in South and Central America, spreading to 21 countries by February 2016 [62] and more recently identified in Florida. The US Food and Drug Administration's Centre of Veterinary Medicine (FDA-CVM) recently published a final finding of no significant impact (FONSI) and a final environmental assessment (EA) for an investigational trial of the self-limiting mosquito in the Florida Keys [63].

Another spin-out from Oxford University, Oxford Biotrans, has developed process technologies, based on novel designs of the P450 enzyme, that yield high-value chemical compounds [64]. Their first product nookatone, the flavour and scent of grapefruit, is made by the biotransformation of valencene, the naturally occurring extract from oranges.

Recognising that nookatone is not only a valuable flavouring ingredient, but apparently also an extremely effective insect repellent [65], these examples illustrate how a number of scientific and commercial developments in the UK may be collectively related to disease control, just one of the many application area envisaged for synthetic biology.

It should also be noted that each of these examples draws from many years of legacy research and development. They also reflect an important feature of innovative research — that the technologies subsequently developed may often contribute to addressing fresh challenges and applications beyond what might have been initially envisaged. The potential value or limitations of a particular technology should not be judged solely on the initial application for which it is developed but rather in terms of its contribution to knowledge as a whole.

From very limited numbers ten years ago, over 50 synthetic biology start-ups and more established companies now operate in the UK. Based on start-up company data compiled by SynBioBeta, synthetic biology start-ups in the UK are currently second only to the US in total numbers, and represent more than half the total for Europe as a whole [66]. This is consistent with our own independent assessment of synthetic biology companies in the UK. From 2009 to 2015, the number of synthetic biology companies operating in the UK has been increasing at an average rate of about 20% year-on-year, as illustrated in Fig. 2.

A number of these focus primarily on the development of the tools and techniques that are helping to accelerate progress in synthetic biology, rather than on the end applications. For example, Synpromics [67] (developing promoters that can switch genes on and off in a much more controlled manner than previously possible), Desktop Genetics [68] (developers of DESKGEN, a software system to help scientists design genome editing experiments), Sphere Fluidics [69] (developing micro-fluidic technology that enable the rapid screening and characterisation of single cells and their biological products) and Lab Genius [70] (a gene synthesis company, offering proprietary technology that enables allows the construction of high complexity libraries).

To highlight just one out of the many, it may be noted that Synthace (developer of Antha, 'a high-level programming language for biology, designed to make simple, reproducible and scalable workflows that are easily automated and shared') was recently picked as one of the world Technology Pioneers by the World Economic Forum (WEF) [71]. Five out of the thirty technology pioneers (early-stage companies) awarded this year are associated with synthetic biology, reflecting the view by the WEF that the

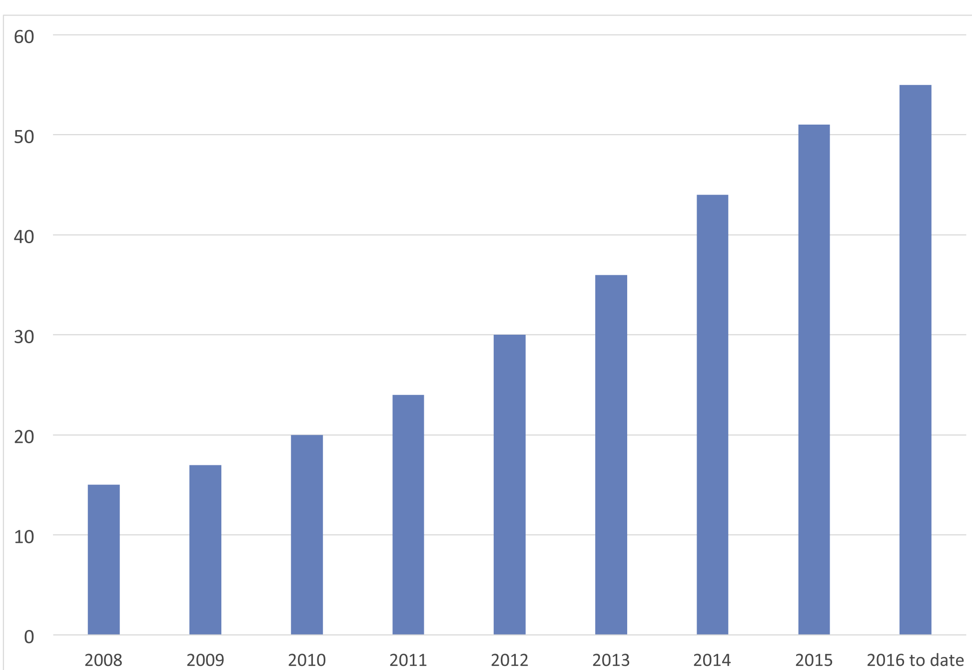

Fig. 2. Number of synthetic biology companies in the UK 2008-present.

sector is 'poised to have a significant impact upon business and society'.

4. UK Synthetic Biology Strategic Plan 2016

This faster than originally anticipated rate of application development and commercialisation within the system stimulated the Leadership Council to initiate, in 2015, a review of progress, initiating a Roadmap refresh exercise giving greater focus on translation and industrialisation aspects than feasible during the original Roadmap exercise 2011–2012. The SBLC engaged with a cross section of UK synthetic biology stakeholders to garner their thoughts on how best to refresh the UK Roadmap for Synthetic Biology. During summer 2015, workshops were held in Edinburgh, Birmingham and London. Further input was encouraged through an online survey and the SBLC discussed their ideas with delegates at their annual open meeting.

Automating the core build-test-analyse cycle, combined with development and adoption of 'higher-level' languages to instruct the required operations, is making it possible to focus more on the intended outcomes than on the mechanics of the underlying build-test-analyse processes themselves. At its core, synthetic biology may be reframed as the facilitating toolbox that transforms possibilities into practical options. Reflecting our working definition - 'synthetic biology is the design and engineering of biologically based parts, novel devices and systems as well as the redesign of existing, natural biological systems' —and can be summarized in the equivalent 'higher-level' term 'Biodesign'. 'Biodesign' technology will become increasingly accessible to a broader range of non-specialists. Translation becomes the process of focussing on and delivering desired outcomes. This is now becoming a practical reality for simpler systems whilst remaining a significant future research and development target for more complex systems.

A new UK Synthetic Biology Strategic Plan 2016: 'Biodesign for the Bioeconomy' representing the outcome of the refresh exercise was launched by George Freeman, MP, co-chair of the SBLC, on 24th February 2016 [72].

Key to fulfilling the UK vision for synthetic biology is maintaining excellent national agility and responsiveness whilst adhering fully to our core principles as set out in the original Roadmap. The new plan complements, not replaces, the original roadmap, which continues to provide the enduring foundation for this refreshed focus on translation and commercialisation. It builds directly upon — reaffirming, not replacing - the core principles and initiatives set out in the original roadmap, seeking to accelerate commercial translation responsibly towards the delivery of products and services of clear public benefit for many years to come.

The Strategic Plan focuses on five key areas of related strategic importance: accelerating industrialisation and commercialisation; maximising the capability of the innovation pipeline; building an expert workforce; developing a supportive business environment, and building value from national and international partnerships (Table 1).

The context of each of these recommendations may be summarized as follows.

4.1. Accelerate industrialisation and commercialisation by promoting investment in, and translation of, biodesign technologies and assets to drive growth in the bioeconomy

The translation of synthetic biology into useful applications is being carried out within large companies and SMEs, but it is the rate of formation of start-ups that provides the clearest evidence of accelerating progress towards commercialisation and support of the bio-economy. An important strategy for ensuring growing companies are funded is to concentrate on supporting businesses through a range of tools such as accelerator schemes, as now established at the IKC 'SynbiCITE' at Imperial College, London. Since its foundation in 2014, SynbiCITE has supported over 50 startup ventures ranging from speciality chemicals to mobile medical devices, helped entrepreneurs, de-risked the science and technology by funding proof of concept (PoC) projects and a development of prototype (DoP) project, and supported ventures in attracting investment from public and private sources. The wider network of Synthetic Biology Research Centres described previously also have a range of industrial partners with clear application development targets and interact directly with the IKC as suitable for training and other translation support.

This recommendation reflects and acknowledges progress made to date but also, noting the UK strength in process engineering (focussing on the design, operation, control, and optimization of chemical, physical, and biological processes) emphasises the continuing need to building links to relevant technology centres with capital intensive plants of value to synthetic biology, such as the CPI [73] Industrial Biotechnology (Wilton) and National Biologics Manufacturing Centre (Darlington) [74] facilities as well as the Catapult network, applying graduated support mechanisms as required.

In many areas of industry the use of standardised components and processes is central to enhancing productivity. Consequently, the development of new metrology and effective technical standards is essential. The synthetic biology design cycle, based on the principles of characterisation, standardisation and modularisation, is now well established. The challenge is to develop techniques and methodology that can be used across a range of applications. This requires accurate metrology, with the comprehensive use of automation (e.g. laboratory robots), interoperability and technical standards. This also underlines the need for reproducibility - i.e. the ability to repeat precisely the same biological system design and its realisation at multiple locations (including BioPart characterisation), using the same protocols. The use of comprehensive automation and high throughput (HTP) techniques in the design cycle helps address the need for accurate reproducibility, and these technologies are becoming increasingly important for the field.

Table 1
UK synthetic biology strategic plan 2016 recommendations.

Recommendations UK Synthetic Biology Strategic Plan 2016
1 - Accelerate industrialisation and commercialisation by promoting investment in, and translation of, biodesign technologies and assets to drive growth in the bioeconomy
2 - Maximise the capability of the innovation pipeline by continuing to research and develop platform technologies that will improve manufacturing efficiencies and unlock future opportunities
3 - Build an expert workforce by developing the skills required for biodesign and implementing them through education and training
4 - Develop a supportive business environment by promoting strong and integrated governance, a proportionate regulatory system, excellent stakeholder relationships and responsible innovation
5 - Build value from national and international partnerships by fully integrating the UK synthetic biology community to position UK research, industry and policy makers as partners of choice for international collaboration

The development of internationally recognised standards in synthetic biology was recognised very early on as key to the industrialisation of biological 'parts' and processes. Biological 'parts' are units of biological activity - normally encoded by DNA - that can be assembled into systems or devices. Internationally agreed standards for 'parts' and the associated metrology materials remain an important goal now supplemented by a need for data format standards required for seamless transfer between laboratories. These include remote gene assembly and data analysis hubs. It is suggested that the emergence of best practice will be best achieved incrementally, reflecting the pace of development and in anticipation of evolving needs. As noted above, Innovate UK funded BSI to produce the first guidance on the use of standards in synthetic biology (PAS 246) [75]. An important goal is to build upon such initiatives to support effective engagement with global standard setting agencies, and through multi-national industries, to facilitate the international development of the field.

Underlining the successful development and uptake of synthetic biology in the UK are government policies that support innovation and industry more generally. It was noted in the 2012 Roadmap that many factors converge favourably to make the UK an excellent place to progress Synthetic Biology. These remain equally valid today:

- Healthy ecosystem for new and established businesses (UK ranked in the top 5% of countries for 'ease of doing business' — defined in terms of business-friendly regulations - by the World Bank [76])
- Strong academic base in Synthetic Biology, linked to a very strong innovative culture and heritage across the life sciences, engineering and physical sciences
- Strong and internationally networked industrial base in application areas for synthetic biology
- Agile and responsive funding agencies
- Proportionate and robust regulatory frameworks that are internationally recognised and well regarded
- Strong UK Government support for the field

To these may be added the 'Patent-Box' initiative, which provides a tax break for corporate income earned through the exploitation of a patented invention, provides a strong incentive to industries to get more involved in the development of qualifying IP within the UK. Opportunities to further enhance the operating environment for innovative businesses in the UK continue to be explored.

4.2. Maximise the capability of the innovation pipeline by continuing to research and develop platform technologies that will improve manufacturing efficiencies and unlock future opportunities

This second recommendation reaffirms the position adopted in the original Roadmap, that commercial development derives from a base of world-class academic science. The development of the platform technologies that form much of the basis of industrial translation in synthetic biology benefits from significant advances in related fields that are also being supported through UK research investments. It is therefore vitally important that the innovation pipeline is supported on a continuing basis through investment in the underpinning science and engineering.

The investments in Synthetic Biology Research Centres noted previously in addition to the broader range of related research programmes in academic and industrial groups across the UK provide an appropriate mechanism to ensure the innovation pipeline remains supplied with a flow of ideas and options. Although sufficient applications are now flowing from this research base to justify the current focus on the processes of translation and commercialisation, it must also be recognised that many tough scientific challenges remain, for example, when considering eukaryotic organisms, or the characterising the behaviours of consortia of microbial communities. A further challenge is the ability to control intracellular function through the deployment of smart, designed, biological information and control systems. This will be enabled by the development of effective, robust biodesign tools that will make the high level design and implementation of synthetic biology solutions more accessible to a wide range of users.

The development of new chassis will also greatly assist the implementation and controllability of biodesigns and to improve manufacturing efficiencies. One example of this approach is the synthetic yeast genome project, Sc2.0, currently ongoing.

Overall, such developments will lead to the more robust and reproducible solutions required for industrial processes.

4.3. Build an expert workforce by developing the skills required for biodesign and implementing them through education and training

The original 2012 recommendation was 'to build a skilled, energised and well-funded UK-wide synthetic biology community'. The original goals have been broadly achieved through the formation of the SIG, the formation of the Synthetic Biology CDT, and the development of a wide range of training courses in the SBRCs, the IKC and elsewhere.

This new recommendation reaffirms the importance of the availability of an expert workforce in supporting the speed and development of an emerging area. Historically the emergence of other "new" scientific disciplines has often been accompanied by an *ad hoc* approach to establishing a trained workforce. It is important to approach this topic in a more structured manner. Synthetic biology has always aimed to innovate in a wider area than just the underpinning science, challenging current approaches in training, innovation and regulation amongst others. Uniquely, from its inception the discipline has always viewed synthetic biology training to encompass other essential skills - including entrepreneurship, communication and high-level group working. As the relevant principles become increasingly clear and established, there is increasing scope to steer relevant training in multidisciplinary science, awareness of alternative viewpoints, and the importance of effective communication between the disciplines not only in further education, but increasingly throughout the education system from higher education to secondary and even to primary education.

Specifically relevant to translation and industrialisation is the role of entrepreneurism. Entrepreneurial skills can significantly accelerate the realisation of economic benefit from synthetic biology. Relevant training courses such as the Lean Launchpad programme to develop entrepreneurial skills in postdoctoral researchers has been established by SynbiCITE. But more entrepreneurial approaches are now being stimulated at and earlier stage of the education system. Young scientists are trained in multidisciplinary team working and commercial awareness through the iGEM competition [77] and Biotechnology Young Entrepreneurs Scheme (Biotechnology YES). These and other examples represent significant capacity building and future UK plans are being aimed at filling gaps and ensuring that this forward-looking trajectory is maintained.

4.4. Develop a supportive business environment by promoting strong and integrated governance, a proportionate regulatory system, excellent stakeholder relationships and responsible innovation

The application of excellent basic science at industrial scale will require an agile, supportive and proportionate governance approach, including government policies, development of standards, regulatory systems and public and stakeholder engagement and dialogue. A responsible approach to research and innovation will be a key component, embedded within that environment. Responsibility in its broadest sense will be crucial to the successful delivery of the benefits of synthetic biology.

It was recognised in the original Roadmap, and reaffirmed in the 2016 Strategic Plan that it is crucial that this technology continues to be developed in a socially responsible fashion, and that relevant stakeholders, regulators and publics be engaged in research and innovation processes from the outset. Such principles of Responsible Research and Innovation (RRI) are not unique to synthetic biology, but broadly apply to all emerging technologies. In consequence, applying due consideration of RRI aspects of individual project proposals has been adopted by funding agencies as an integral part of the assessment process.

RRI is arguably less about following a formulaic approach to justifying a particular programme of investigation than about establishing a critical mindset consistent with the broader value system developing across the sector. RRI is addressed in all pertinent training programmes, including the training for all iGEM teams, who may represent the mainstream of future researchers and entrepreneurs in the field. Each of the UK SBRCs includes social scientists assessing RRI issues associated with the activities of each centre. These RRI groups also form a network across the UK that is helping inform best practice.

The Governance sub-group of the UK Synthetic Biology Leadership Council provides a central point of contact for relevant issues to be raised and discussed in more depth than possible by the full Leadership Council. Issues addressed include linkages to regulatory processes, public engagement and the development of suitable standards and guidelines. A feature of the integrated roadmap process is that relevant issues are being addressed at an early stage – parallel with ongoing research and development, rather than sequentially - allowing greater time for engagement and deliberation before specific ideas evolve into potentially commercial applications.

4.5. Build value from national and international partnerships by fully integrating the UK synthetic biology community to position UK research, industry and policy makers as partners of choice for international collaboration

Synthetic Biology and closely related technologies are being pursued across the world, and international collaborations and partnerships play an important role in its continuing development. The UK synthetic biology research community is highly networked with other world-leaders in the field and has played host to major international synthetic biology events such as one of the three 'six academies' US, UK, China meetings in 2011, SB6.0, held at Imperial College in 2013, and SynBioBeta in 2015 and 2016. The SBLC has engaged with delegations from several countries to compare policies and strategies and share best practice.

The geographical spread of rising interest can already be gauged from the participation of student teams from 30 different countries in recent iGEM competitions [78], and there is an important and increasing opportunity to engage and interact more effectively with research groups in the developing world. A number of early applications directly address developing world needs, such as the development of an arsenic biosensor for drinking water [79] and the development of oral vaccines [80], in addition to the pioneering example of the anti-malarial, artemisinin. Synthetic biology is becoming increasingly suited to distributed operations and this should make it easier not only to develop applications for the developing world, but to co-develop applications through the merging of local knowledge and expertise with centralised expertise and resources.

Ongoing activities that will help lay the foundations for more international development include the establishment of standards and guidelines (as noted under recommendation 1 above), material transfer agreements and internationally recognised governance systems.

4.6. Synthetic biology contribution to the bioeconomy

Recognising this new stage of development of the technology in the UK, increasing attention may now be given to the commercial applications and channels to market. For the foreseeable future, the main applications are likely to fall within the scope of existing business sectors. Within the UK, relevant sectors span the bioeconomy [81]. Combining the expertise and interests of these sectors through representatives of the Synthetic Biology Leadership Council, the Industrial Biotechnology Leadership Council, the Agri-Food-Tech Leadership Forum, a working definition of the UK Bioeconomy is expressed as [82]:

"All economic activity derived from bio-based products and processes which contributes to sustainable and resource-efficient solutions to the challenges we face in food, chemicals, materials, energy production, health and environmental protection."

In this context, synthetic biology and emerging biodesign capabilities can be positioned clearly at the innovative core of the bioeconomy, providing fresh options and opportunities for advancement, ranging from incremental to disruptive, across all these challenge areas.

5. Conclusions

Synthetic biology is capable of delivering new solutions to key challenges spanning the bioeconomy, both nationally and internationally. Recognising this significant potential and the associated need to facilitate its translation and commercialisation the UK government commissioned the production of a national Synthetic Biology Roadmap in 2011, and subsequently provided crucial support to assist its implementation.

Critical infrastructural investments have been made, and important strides made towards the development of an effectively connected community of practitioners and interest groups. A number of Synthetic Biology Research Centres, DNA Synthesis Foundries, a Centre for Doctoral Training, and an Innovation Knowledge Centre have been established, creating a nationally distributed and integrated network of complementary facilities and expertise.

The UK Synthetic Biology Leadership Council responded to the completion of the initial wave of investments and to the rapid technological progress being made nationally and internationally to address the next phase of the Roadmap, via the publication of the UK Synthetic Biology Strategic Plan, in February 2016. The title 'Biodesign for the Bioeconomy' reflects the shifting focus towards translation and commercialisation - the design of applications and the delivery of benefits. Key recommendations include building a skilled workforce, reaffirming core principles of responsible research and innovation, and ensuring effective oversight and governance.

The UK is now well positioned to generate and deliver benefits from the field of synthetic biology, building upon its established science base and structured approach. Over 50 start-ups, SMEs and larger companies are actively engaged in synthetic biology in the UK, and inward investments are starting to flow.

Together these initiatives provide an important foundation for stimulating innovation, actively contributing to international research and development partnerships, and helping deliver useful benefits from synthetic biology in response to local and global needs and challenges.

Disclaimer

This paper sets out to reflect the processes and progress in synthetic biology throughout the UK to date. The authors have attempted to provide a fully representative summary, and have drawn extensively upon the significant contributions of others as expressed in the UK Roadmap 2012 and UK Strategic Plan 2016, often quoting verbatim from such sources to reflect as accurately as possible the original intentions. Any misinterpretations, omissions or errors in so doing are entirely the responsibility of the authors.

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