White Paper

The ascent of digital biomanufacturing – creating a new manufacturing industry through the development of synthetic biology standards

bsi.

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Standards and Innovate UK

Innovate UK - the new name for the Technology Strategy Board - is the UK's innovation agency. Our aim is to accelerate economic growth by stimulating and supporting business-led innovation.

Timely, consensus-based use of standards plays a vital role in ensuring that the knowledge created in the UK's research base is commercialised and brought to market and plays an important part in driving innovation.

Innovate UK is working with BSI, Research Councils and Catapults to establish new standards earlier in the development of technologies, to provide UK businesses with a competitive "first mover advantage." We are focusing particularly on four emerging technology areas: offshore renewable energy, assisted living, cell therapy and the subject of this report, synthetic biology. Here the primary objective of the project is to enable computer aided design, manufacture, and verification using digital biological information.

We have also joined with the Engineering and Physical Sciences Research Council and Biotechnology and Biological Sciences Research Council to create SynbiCITE, a pioneering Innovation and Knowledge Centre dedicated to promoting the adoption and use of synthetic biology by industry. The centre is focused at Imperial College, London and will help turn academia and industry-based research into commercial success. For more information see http://synbicite.com/

More widely, health and care is a key priority area in our work - with major innovation programmes to stimulate the development of new technologies, products and services, building on the UK's world-class science and technology base and its global presence in the biopharmaceutical and health technology sectors. Read more here: https://www.innovateuk.org/healthcare.

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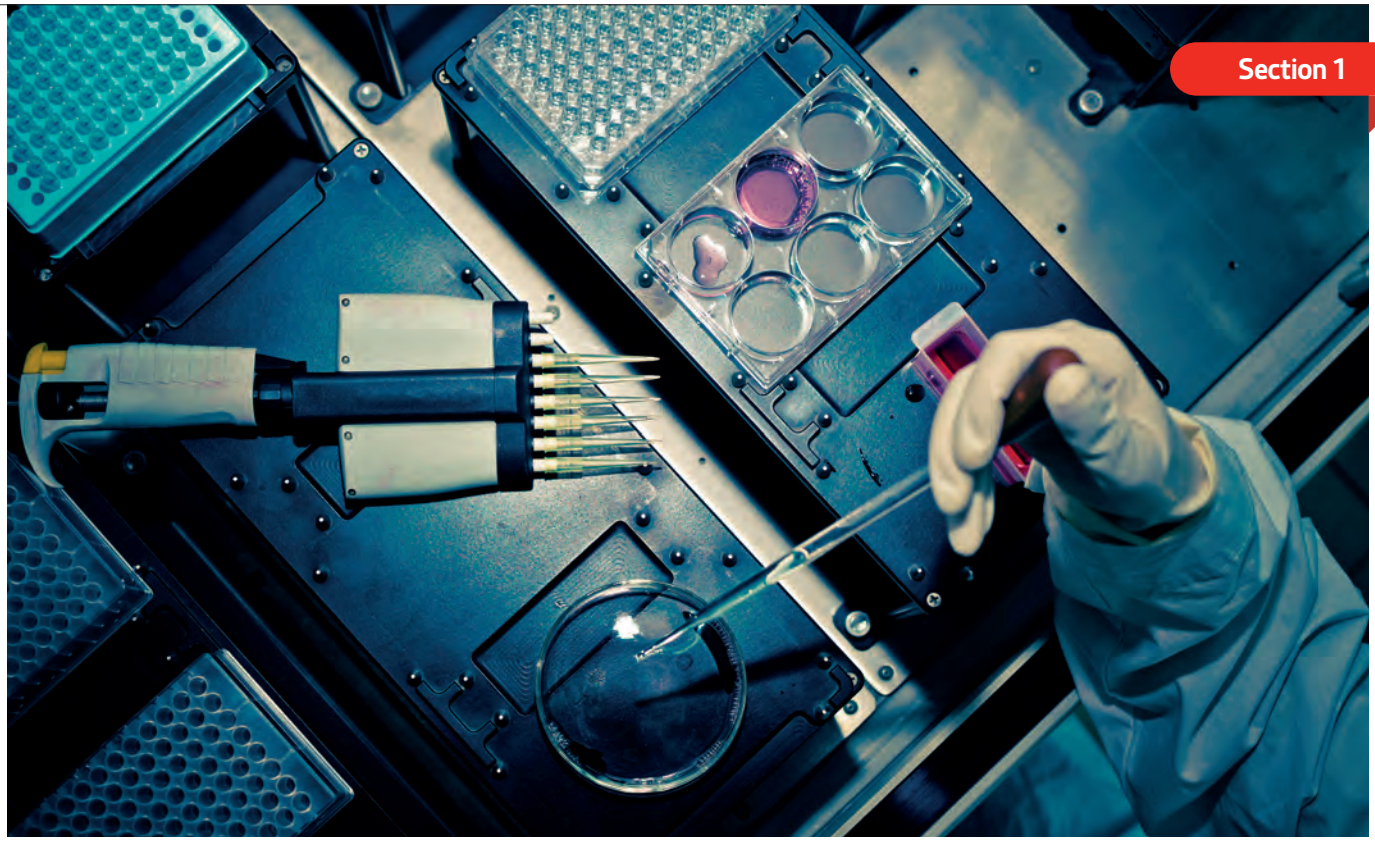


1. Digital Biomanufacturing – the role of synthetic biology

Synthetic biology has the potential to achieve genuine advances in terms of wealth creation and solving emerging global issues. The government sponsored roadmap highlighted the potential role synthetic biology could play in improving water, food, and energy security, enabling the better use of natural resources, improving disease detection, and providing personalised healthcare.

Indeed the roadmap references an assessment performed by BCC Research on behalf of Global Information Inc. that stated that the value of the global synthetic biology market will grow significantly, from $1.6bn in 2011 to $10.8bn by 2016. Synthetic biology may also enable new products for new, as yet unenvisaged markets, as the potential of the technology emerges.

Markets that are likely to benefit from the use of synthetic biology include biopharmaceuticals and industrial biotechnology. A recent report concluded that biopharmaceuticals now comprises around 20% of new medicines, a percentage that has doubled in a decade.It is likely that this upward trend will continue throughthe application of synthetic biology.

The main impact of the technology will be felt through the creation of digital biomanufacturing industries, which will enable products to be brought to market more quickly, and in greater number, than ever before. This will bring significant economic value to the UK, and solve many of the problems highlighted above. Synthetic biology will do this in a number of ways, including:

- Driving up productivity of biological manufacturing processes, this making products manufactured in this way more readily available at an affordable price;
- Reducing costs of development through the creation of flexible and adaptable processes;
- Enabling the use of renewable feedstocks.

This will be driven by the continuation of a trend identified elsewhere that synthetic biology is emerging through the increasing specialisation, or decoupling, of disciplines into design, synthesis, and characterisation. The division of labour between these disciplines will be enabled by the adoption of digital capabilities, and will further enable the emergence of Computer Aided Design, Computer Aided Manufacture, and Computer Aided Verification for synthetic biology.

Section 1

The successful development and deployment of synthetic biology to meet these digital biomanufacturing challenges in the UK faces a number of risks, however, and not acting to address these may lead to the technology not evolving as predicted, or giving rise to economic success in other parts of the world. These challenges include:

- Driving the decoupling of design, manufacturing, and characterisation in synthetic biology. The successful emergence of synthetic biology depends critically on the efficient and effective specialisation in design, synthesis, and characterisation. Each of these disciplines, however, are mutually interdependent, and if biological information and knowledge cannot be shared easily, then the productivity gains promised by synthetic biology will not happen. There is currently poor data quality and a lack of compatibility between data used and generated at the design, manufacturing and verification stages. The increasing commoditisation of DNA sequencing is creating a plethora of information that needs to be integrated into the design and characterisation stages for it to realise its true value. Additionally there is work to be done in understanding the meaning of biological measurements, and how to make these machine readable. If these issues are not addressed, synthetic biology will not develop into a productive manufacturing discipline, and will not enable the scale-up and innovation that it could deliver.
- Designing extensible manufacturing processes. Much effort so far has been focussed on product design, and the desirable attributes of the final outputs of a process. The approach taken so far is time-consuming and expensive, and to achieve the increases in productivity promised by the technology, innovators need to understand the role of good process design. A major issue in sectors that use synthetic biology is that poor process design leads to expensive and inflexible processes that often struggle to meet regulatory approval. Synthetic biology has the promise to allow actors to design highly extensible processes that can not only scale up to mass manufacture, but also design new outputs from existing processes with the minimum amount of modification. Manufacturers will have processes that are cheaper to develop, and will be more easily scaled up
- Aligning the behaviour of market actors. The synthetic biology industry is comprised of actors from a wide range of disciplines, and therefore traditions. This has led to a variety of approaches within the sector taking place simultaneously, meaning there is a lack of coherence in the approach to intellectual property, responsible innovation, and the desired role of government. Such incoherence is slowing progress in the development of the technology, and there is a need to align and codify principles and expectations of the people looking to innovate to unlock the potential of synthetic biology.

We propose to convene the UK synthetic biology industry and establish consensus on the desired approaches to overcoming the challenges described above, and to make this available to our innovators. This will help the industry emerge more quickly than it would have done otherwise, and, importantly, ensure that the UK leadership opens the global markets up to UK participation. If we allow our competitors to do this before the UK, we run the risk of the UK being excluded from the major markets, thus wasting the significant R&D investments that have already been made, and promise in future.

2. Synthetic biology - contributing to wealth creation through manufacturing innovation

Tom Knight of MIT, a pioneer of synthetic biology, stated that "biology is a manufacturing capability". The true value of synthetic biology can be identified by looking at some examples.

Artemisinin.

Artemisinin is the collective name for a group of drugs that are the most effective and fast acting against malaria. Artemisinin was first extracted and isolated in 1972 by a Chinese research group led by Professor Tu Youyou from a natural herbal remedy known as artemisia annua. This research effort was monumental and took over a hundred person-years to achieve. In contrast the drug has been manufactured using a semi-synthetic process by University of California at Berkeley, reducing the cost of manufacture from $2.40 per dose to 25 cents per dose.

Manufacturing biological parts.

In early 2013 experts at Imperial College reported that they had developed a method for manufacturing biological parts that reduced the time taken from 2 days to 6 hours. The main innovation was a new method that removed the requirement to re-engineer a cell every time a new part is needed. This gives rise to the possibility of new libraries of components that could be used to build more sophisticated biological manufacturing processes.

DNA synthesis and sequencing.

Rob Carlson has periodically calculated the number of bases per person day that can be synthesised and sequenced, and how this changes over time. A figure from his blog is recreated overleaf.

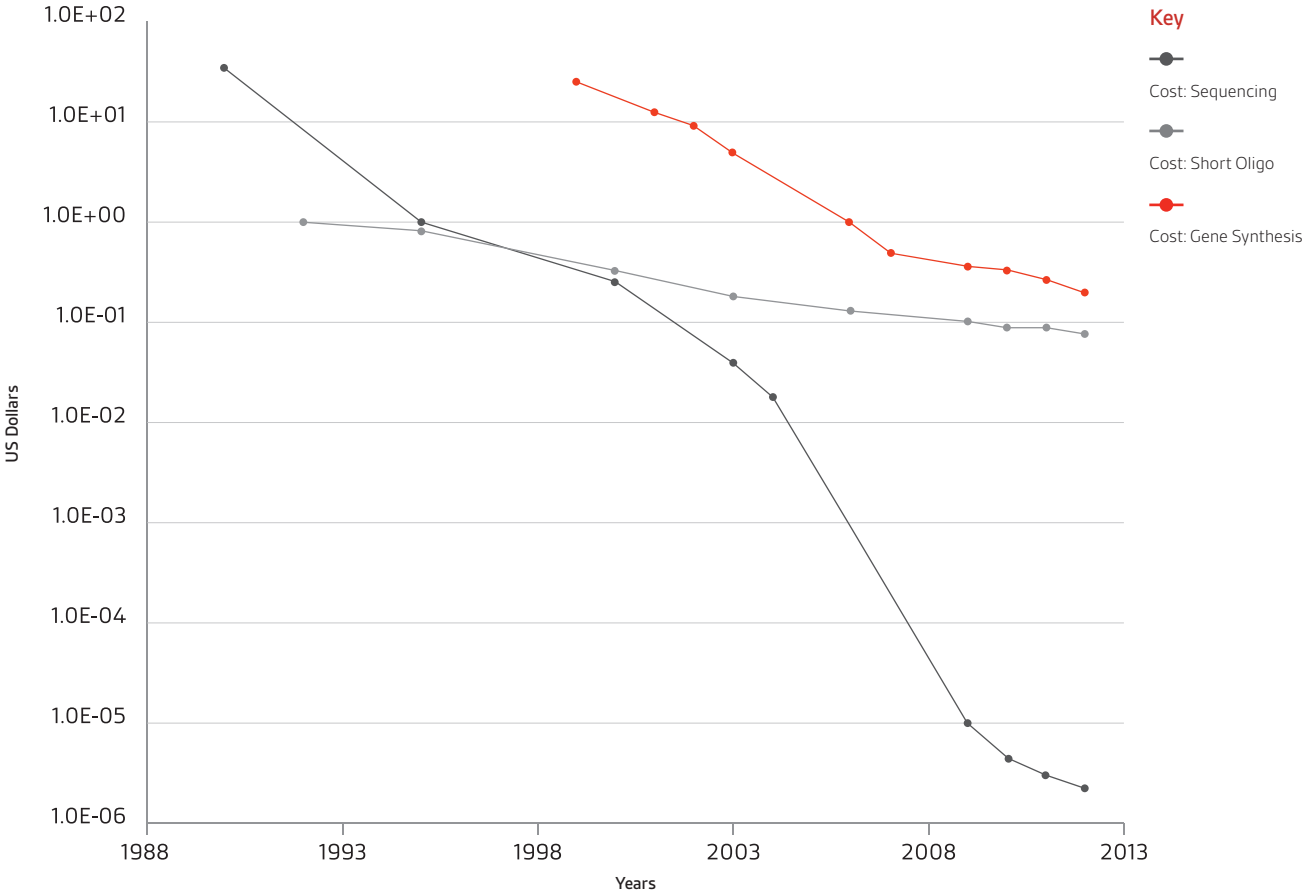
Rises in productivity in synthesis and sequencing compare favourably with the semiconductor industry and Moore's Law. This shows that competition and customer demand is driving up expectations and performance to the point that DNA sequence information, and the services that give rise to it, is becoming commoditised. This is further backed up by another figure taken from Carlson's blog that shows the cost per base of DNA sequencing and synthesis is also rapidly falling to a level where it will become routinely affordable. The developments in synthetic biology are driving towards increasing productivity of production processes, and adding value through greater outputs with lesser inputs, and ensuring greater returns on R&D investment.

Biological manufacturing is still in its infancy, and may be considered to still be in the 'craft' stage where manufacturing processes are bespoke and created from scratch at each stage. We may find that the first country to succeed in developing new manufacturing paradigms in biological manufacturing will become that economy that beats the rest of the competition and enjoys the fruits of such efforts. To move beyond the craft stage, it is important that the knowledge generated from the improving sequencing technologies can be readily qualified and more easily used for design purposes.

Traditional mechanical and electrical manufacturing disciplines have a strong record of continuous innovation leading to higher productivity, as described earlier. The evolution of a wide range of manufacturing paradigms to improve manufacturing quality, reduce waste, and meet wide ranging customer demand provides an opportunity to learn lessons and apply these to biological processes.

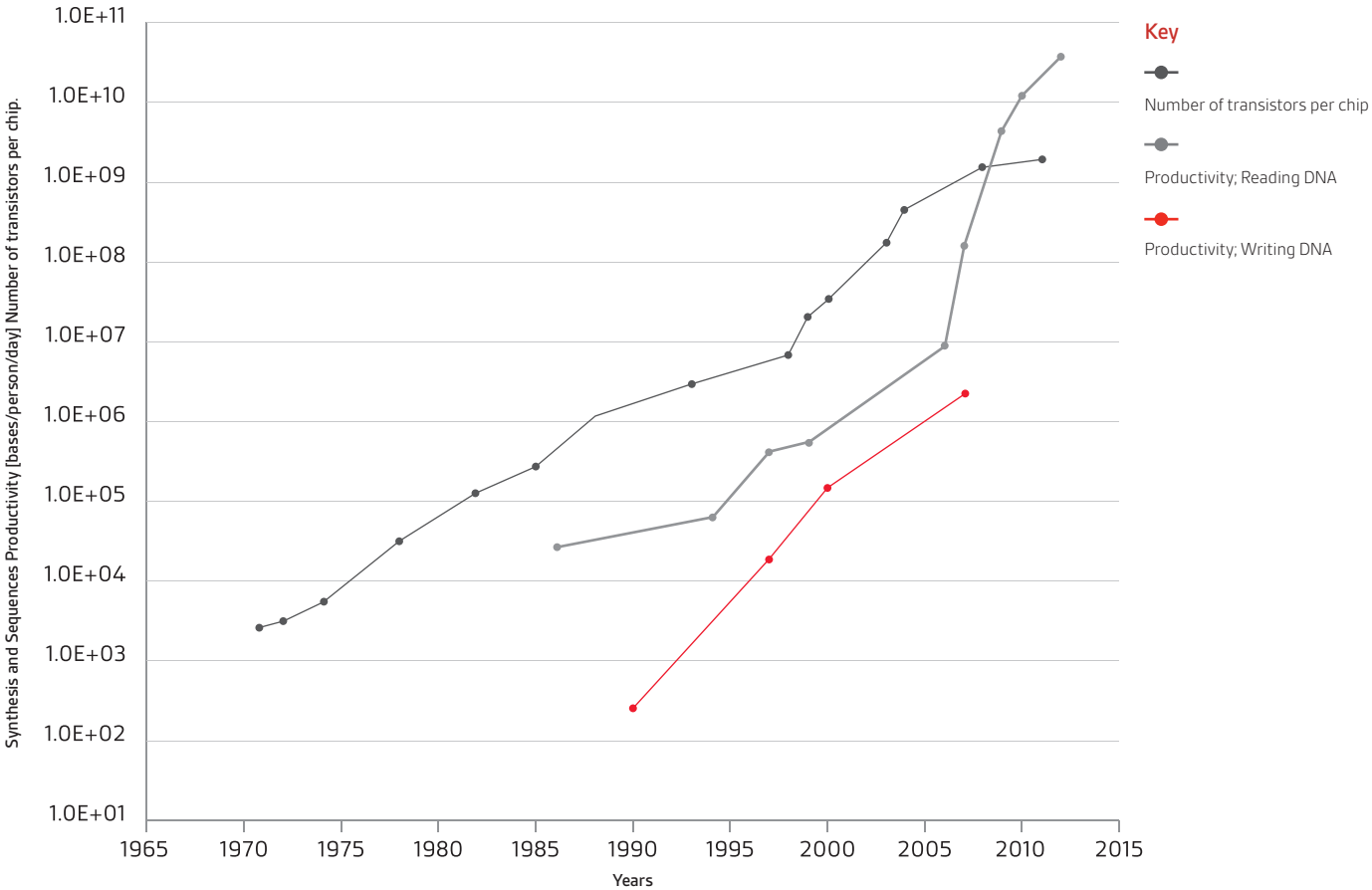
Cost Per Base of DNA Sequencing and Synthesis

Rob Carlson, October 2012, www.synthesis.cc



Productivity in DNA Synthesis and Sequencing Using Commercially Available Instruments

Rob Carlson, February 2013, www.synthesis.cc



3. Wider issues relating to synthetic biology

Standardisation efforts to increase the productivity of synthetic biology-inspired biomanufacturing processes will not ensure success, however. For example, the TSB R&D call for proposals "Advancing the industrial application of synthetic biology" demonstrated the desire for the work to be carried out in a responsible manner and in compliance with all relevant regulations in place. The TSB required applicants to describe the social, ethical and regulatory considerations inherent in their proposed work, and how they proposed to manage these issues.

There is a great deal of generic guidance already in existence, such as that published by the Nuffield Council for Bioethics , the think tank Matter For All, and by the ESRC INNOGEN Centre. However, there is as yet, no consensus amongst synthetic biology stakeholders on what the basic principles are for responsible innovation, and it is possible that the establishment of such a consensus is desirable to support the successful emergence of the technology.

The uncertainties relating to responsible innovations are not simply an academic concern, as there may be risks associated with the emergence of synthetic biology on a large scale. This particularly relates to the fact that industrialising the technology and making the products widely available will mean moving from contained processes to non-contained process ones. Any risks arising in an industrial setting would have to be covered by the insurance industry, and any investments made by the banking and investment sectors. If the potential liabilities or probability of failure are too high, then this may lead to new facilities and manufacturing plants not gaining the finance they require, or such operations not getting adequate insurance coverage for them to be financially viable. It is imperative that the financial services industry is engaged at an early stage and their appetite for risks in this sector explored. If they consider the technology to be too risky at this stage, then we should explore what steps need to be taken to mitigate these risks, and to put into place the appropriate tools that will give the financial assurance it needs to be able to adequately support the growth of the industry.

Section 3

In any new technology there are uncertainties, and it is inevitable that there will be pressure for government to intervene at some point in future and introduce legislation to regulate activities using the technology. Such intervention would become inevitable if the industry allowed a mishap to occur, or if the technology was misused in some way. A major risk in such a situation is that the legislation would be reacting to public pressure, and would not reflect the best scientific understanding of the technology. This may lead to unforeseen and undesired consequences such as the inability of the industry to operate legally in the UK, and companies may choose to relocate abroad. If the legislation is to reflect best practice and the most up-to-date knowledge, it is vital that the industry, and its wider stakeholders, get together and agree on the best practice principles upon which they will operate. This will increase the probability of government intervention being successful in guiding the industry towards an outcome that is both economically successful and publicly acceptable.

A major issue source of cost and uncertainty in synthetic biology relates to IP, leading to delays and unnecessary costs when trying to achieve freedom-to-operate status. The main factors in this is the balance between what knowledge should be made widely available (i.e. standards) and what knowledge should be protected (i.e. patents). Agreement on an approach to this will be a natural outcome of reaching a consensus on the desired shape of the future industry. Additionally, there would have to be an agreement on the basis that patents will be licensed and made available. There is much desire to facilitate 'open access' within the industry, but also a requirement to make a fair return on protected IP. The often stated aim of open access in synthetic biology is often stymied by a lack of consensus on what the definition of the term is, and what it means in practice.

All of these wider issues need to be addressed by the industry in some way. The synthetic biology industry needs to design its own strategy for using different types of standards to address these issues, and the standardisation process is ideal for capturing best practice and making public the agreed solution. In addition to product specification standards, and process standards such as ISO 9001, there exists the category known as 'Framework Standards'. Framework standards are voluntary agreements that reflect the best practice relating to the values, principles, and behaviour of the stakeholders that own them. This model should be adopted by the industry and deployed to overcome the real barriers to progress that are likely to be put into place.

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Section 4

4. Existing standards activities in synthetic biology

There are, as yet, no formal standards specific to synthetic biology. However, there are a number of academic pioneers working in the field creating knowledge that could be turned into formal standards. Notable examples are Digital Imaging and Communications in Medicine – Synthetic Biology (DICOM-SB) and the Synthetic Biology Open Language (SBOL). Additionally there are organisations such as the BioBricks Foundation in the US that are working to create registries of standard biological parts, with the intention that end users can procure both the digital representation of the biological part and the physical part itself.

There are an enormous number of existing standards that are not specific to synthetic biology, but could be useful in some way. However, there is no evidence that any attention has been paid to the development of a framework of standards, or what the value of such standards is intended to add. Our search for relevant standards came up with a long list, broken down into the following categories.

Market Sector	Number of standards identified.
Mathematics and Natural Sciences	870
Environment and Health Protection	8,863
Information Technology & Office Equipment	10,161
Food Technology	5,120
Chemical Technology	7,443
Petroleum and Related Technologies	1,708
Rubber & Plastics	5,302
Total	**39,467**

There are, as yet, no formal standards specific to synthetic biology

Section 4

The origins of the standards are broken down graphically as follows:

Country of origin	Number of standards
Austria	545
Belgium	620
Canada	355
Czech Republic	961
European standards body	2,936
Finland	5
France	2,068
Germany	4,923
International standards body	7,452
Italy	1,495
Japan	2,396
Netherlands	388
Norway	239
Poland	1,798
Slovakia	1,407
Spain	1,685
Sweden	185
Switzerland	13
Turkey	2,253
UK	1,706
US	6,047
Total	**39,467**

Around half of these standards have an origin within a European state, although a further quarter of them are published by either an international or European standards body such as CEN, ETSI, ISO, or IEC. The Americas are responsible for less than a fifth of the total, and Japan much less than this.

Out of nearly 40,000 potential relevant standards, none of them were developed specifically for synthetic biology. Every standard identified had a potential application for an aspect of synthetic biology, but there is no consistent synthetic biology theme underpinning the reasoning behind their development. If synthetic biology is to emerge as a coherent technology routinely adding value through the provision of information and goods, then it is critical that this is enabled by a consistent framework of standards. It is apparent that this does not currently exist.

There have already been a number of efforts internationally to start to address standardisation in synthetic biology, and papers by Torrance & Kahl, and Kitney & Freemont catalogues and describe these. Some of these efforts include:

DICOM-SB.

DICOM (Digital Imaging and Communications in Medicine) is a standardised approach in medical imaging to handling, storing, printing, and transmitting information, including file formats and communications protocols. This has been adopted as an international standard and is available as ISO 12052:2006. DICOM-SB is the synthetic biology extension of this work, and its adoption and availability as a formal standard is a priority.

SBOL (Synthetic Biology Open Language).

SBOL is a standard for exchanging biological parts information, and contains a vocabulary and core data model. It is currently not formally linked with DICOM-SB, but there is no technical reason why this should remain an obstacle.

BioBricks.

BioBricks are standard biological parts developed as part of an open innovation process enabled by the BioBricks Foundation. The data forming the basis of these standards, however, are not currently validated so the quality of the standards is not consistent.

Therefore we propose that we, as a matter of urgency, we establish consensus regarding the desired approach to the standardised digital representation and sharing of biological information, develop the standards to support these, and make these internationally available to users.

Section 5

5. Standards in synthetic biology – driving the industry towards full automation

The ultimate aim of synthetic biology is to enable the development of fully automated manufacturing processes that use digital biological information. To achieve full automation, the following criteria need to be satisfied:

- The meaning and accuracy of biological measurements need to be widely understood, and the data made machine readable;
- All processes need to be repeatable;
- Digital biological information and machines for design, manufacture, and verification need to be interoperable.

The status of the technology in 2014, however, is that full automation has not been reached. The technology has reached sufficient maturity to allow each individual machine to be controlled as a robot, but these are not yet able to be integrated into a seamless, efficient design and manufacturing process using digital biological information.

The next 2-3 years will require significant advances in the understanding of metrology of the biological systems under investigation. What will be required by the end of 2017 is a consensus on what needs to be measured to enable repeatability of processes to be achieved. This will enable a single machine to have repeatable processes by the end of 2020.

The standards that need to be developed to achieve this will include:

- Standards that specify how digital biological information should be transferred between different machines;
- Standards that enable the digital description of genes, followed by standards that enable the digital description of proteins;
- A description of the consensus on measurement requirements for repeatable processes.

This will also lead to all machines being interoperable, also by the end of 2020.

During the period 2017-2020, the development of metrology will continue such that it will define how to verify designs of simulation models. And from 2020-2025 we envisage that the metrology challenges will be focussed on understanding the measurement requirements that will enable feedback for machine learning, such that designs can be successfully physically reproduced more often.

This improvement in understanding of biological measurements driving fully repeatable processes, coupled with interoperability of information and machines, will lead to a truly global supply chain, as well as the ability to have full automation of processes.

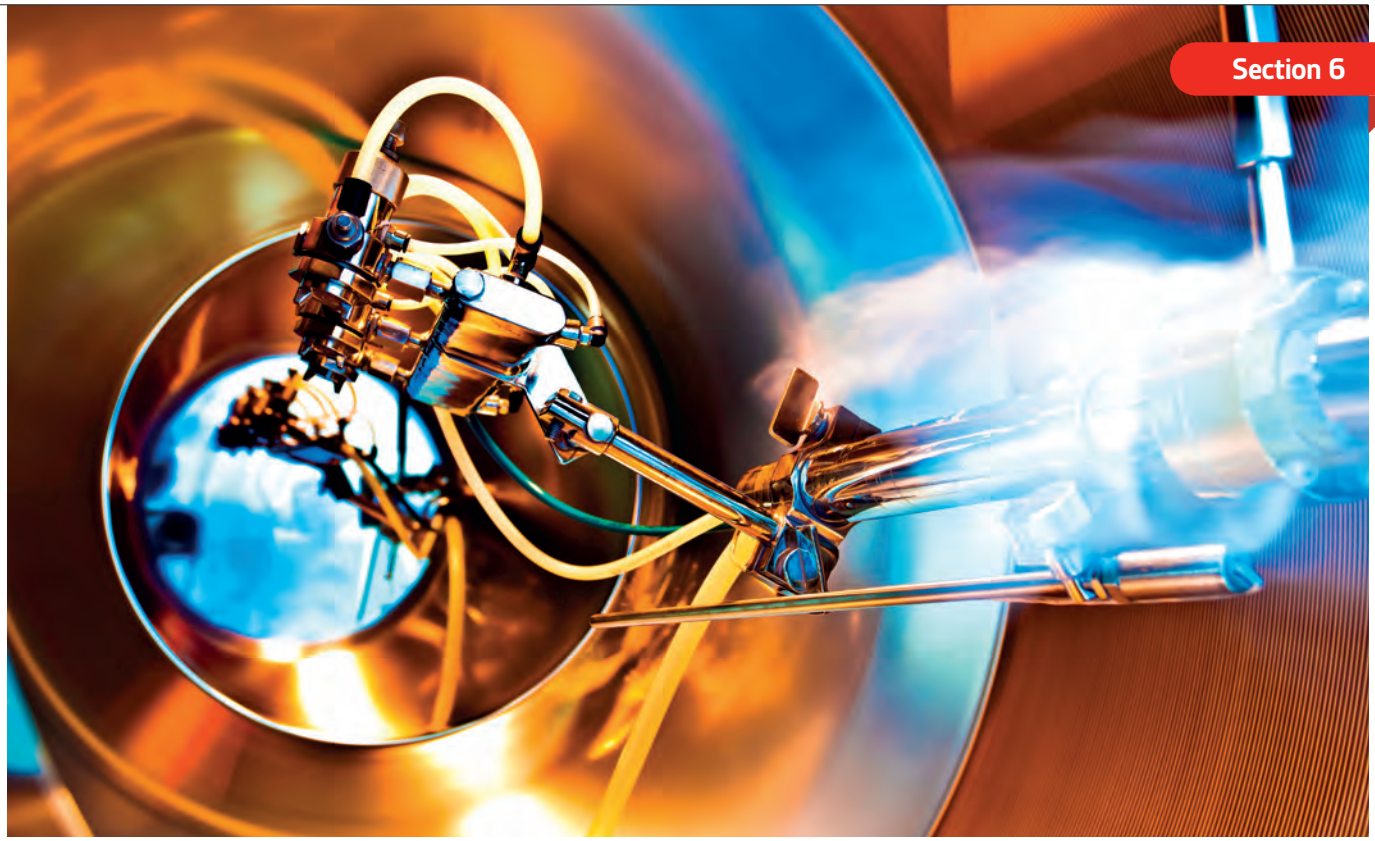
The standards that need to be developed to achieve this will include:

- Standards that specify how digital biological information should be transferred between different machines;
- Standards that enable the digital description of proteins (by 2020), followed by standards that enable the digital description of cells (by 2025).

If the industry is to move quickly towards full automation, then it is vital that all those looking to innovate using digital biological information begin, at the earliest opportunity, to make sure their practices and behaviours reflect the existing best practice. They need to be aware of standards in development, and to start to look to how best to integrate this work into their activities. **We propose that BSI should develop guidance on a systematic approach to the development of manufacturing processes that use digital biological information.** This document would enable organisations looking to develop commercial processes to achieve their goals using digital biological information more quickly than would otherwise be the case. This would be achieved by educating the industry on how best to handle and manage data, and point them towards existing standards and best practice.

As new standards emerged and the industry evolved, this design guide would need to be updated periodically.

The evolution of the technology towards full automation through the development of standards is illustrated in annex 1.



6. Recommendations for framework standards to support manufacturing innovation using synthetic biology

We have described the technical standards that will be required to drive productivity improvements in digital biomanufacturing processes. There is, also, however, a desire to align the behaviour of market actors, and standards have a role to play in achieving this. The synthetic biology marketplace is currently immature with a wide range of expectations and behaviours, and this means access to information and establishing partnerships is complex and costly. By aligning the behaviour of the marketplace, companies will be able to attain freedom-to-operate and thus reach commercial success at a much earlier stage than would otherwise be the case.

We propose that BSI should work with UK synthetic biology stakeholders and develop an insight into where framework standards would be critical in establishing UK leadership in establishing the principles and expectations of the industry.

The value of standards activity will only be realised through a long-term commitment from industry, both in their development and implementation. This will require a sustained partnership over a number of years, and will bear the fruits of collaboration between the leading SMEs, large companies, relevant academics, BSI, and other stakeholders. Additionally, it is imperative that this is not seen as a UK-centric activity, due to the global nature of innovations in synthetic biology. Therefore we would need to ensure international participation, particularly from leading figures in the US.

BSI should lead the creation of an international Synthetic Biology Standards hub, a collaboration of all the leading industrial and academic innovators in synthetic biology, with the intention of creating a broad consensus in priority areas.

Annex 1

Annex 1 - The ascent of digital biomanufacturing – the evolution of synthetic biology through strategic development of standards 2014-2025.

	2014	2015-2017	2018-2020	2020-2025
	Generation 0	Generation 1	Generation 2	Generation 3
Automation	No automation other than robotically-controlled individual machines			**Fully automated processes on a global scale.**
Repeatability	Not yet developed repeatable processes		Repeatable processes within a single machine.	Globally interoperable machines delivering repeatable processes.
Interoperability	Not yet achieved interoperability		Full global interoperability between all machines.	
Metrology	Understanding of biological systems not yet sufficient for development of industrial systems.	Consensus developed on what needs to be developed to enable repeatability.	Metrology to enable design verification of simulation modelling.	Metrology to enable feedback for machine learning.
Systems able to be digitally described	None	Genes	Genes and proteins	Genes, proteins, and cells.
Standards required	Systematic design of manufacturing processes using digital biological engineering (0G).	Standards for: • Enabling flow of digital biological information between machines; • Digital description of genes; • Metrology for repeatable processes; • Systematic design guide (1G).	Standards for: • Digital description of proteins; • Metrology for verification of models; • Systematic design guide (2G).	Standards for: • Digital description of cells; • Systematic design guide (3G);
Framework standards	Framework standards to be developed in line with the consensus view of synthetic biology stakeholders			

Annex 2 - Synthetic biology – a plan to deliver value through standards.

This section describes a multi-year programme that aims to deliver the first part of this vision, with the intention that the UK establishes itself as a leader in the technology though the creation of a standards hub, and starts to receive significant economic benefits from the investments currently being made.

An important part of this work is to encourage the UK to take an international lead in synthetic biology through the creation of standards, but to ensure the international pioneers of the technology engage with and adopt the UK agenda. The work programme is reproduced in a schematic way below.

Activities of proposed synthetic biology standards hub.

2014	2015-2017	2018-2020	2020-2025

• Workshops held on systematic design of processes using biological information.
• Establishment of international steering groups for PAS projects in digital biological information standards;
• International promotion of synthetic biology standards
  • Invitations sent to major international participants, including DICOM and BioBricks.
  • Creation of case studies, research and position papers in each of the areas of interest.
  • Creation of communications material.
	• PAS design guide in use of digital biological information published;
	• Workshops held to review areas and to assess future priorities in:
	  • Digital SB standards;
	  • Framework standards.
	• Establishment of the international Synthetic Biology Standards hub.
	• Impact and future priorities published for:
	  • Digital biological information standards;
	  • Framework standards.
	• Establishment of international steering groups for PAS projects in:
	  • Measurement for repeatability;
	  • Digital representation of genes.
		• International conference on synthetic biology standards held.
		• PAS documents published in:
		  • Measurement for repeatability;
		  • Digital representation of genes.
		• Establishment of international steering group for PAS project in framework standards and in revision of design guide.
			• PAS design guide published.
			• Framework PAS published.
			• Review workshops held.
			• Impact and future priorities paper published.

Footnotes

1. A synthetic biology roadmap for the UK - Published by Technology Strategy Board on behalf of UK Synthetic Biology Roadmap Coordination Group - http://www.rcuk.ac.uk/documents/publications/SyntheticBiologyRoadmap.pdf.
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11. http://www.nuffieldbioethics.org/sites/default/files/Biofuels_ethical_issues_FULL%20REPORT_0.pdf
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