Creating an Environment to Support Investment and Innovation in Synthetic Biology

Summary of a Joint Meeting organized by the
UK Synthetic Biology Leadership Council and US National Academies' Forum on Synthetic Biology[1]
October 28-29 2014, Imperial College, London

Within a decade, synthetic biology has emerged as one of the most promising fields of research for the new century. Today, the United Kingdom and United States are each leaders in enabling and realizing the potential economic benefits of synthetic biology. Both governments are providing support to university researchers and engaging in discussions of regulatory and societal issues as it becomes clear that a balanced policy framework and sustained funding for basic and applied research are necessary to attract private capital and to develop innovative products.

At this early stage in the development of synthetic biology, the UK and the US have the unique opportunity to take note of the scientific and engineering advances made, the investment strategies developed, and the business and regulatory frameworks applied; these questions are core to whether the field is sufficiently well grounded so as to encourage increased private investment and the transformation of today's predominantly petrochemicals based manufacturing processes to biologically based processes, starting materials and new product development.

This joint meeting represented an opportunity for high-level discussions among UK and US government officials, academia, industry, and policy-makers to share approaches, challenges, and best practices that may not only strengthen respective domestic programs but also set the stage for future collaboration to establish mechanisms that further each country's interests and help insure sustained leadership in this increasingly important field. See Appendix 1 for a more complete workshop outline and mission.

The workshop was structured around three key areas that would benefit from US-UK discussion:

- Economic Case and its Viability
- Safeguarding the Bioeconomy
- Standards and Metrology

Throughout the three sessions, participants identified understanding the limits and opportunities presented by existing regulatory frameworks and the need for concerted focused educational programs as integral to moving forward on these three key areas --- suggesting the need for future in-depth exploration of both of these issues.

Session leads from the US and UK provided discussion papers as pre-reading and introduced each session. Discussions were conducted via a combination of plenary and syndicate sessions. See Appendix 2 for the workshop agenda. A total of 37 invited participants attended the two-day workshop (including 11 from the US - see Appendix 3 for attendee list).

The workshop was enabled through the generous support of the Alfred P. Sloan Foundation and Imperial College.

[1] While the US National Academies' Forum on Synthetic Biology assisted in supporting and organizing this meeting, it did not author this summary, and the views expressed here do not necessarily represent those of the Forum or the US National Academies. Responsibility for the content of the summary rests with the UK Synthetic Biology Leadership Council. The Council appreciates the many valuable contributions made by the organizing group and the participants during the UK meeting.

Summary

Following the meeting, a small group of meeting participants summarized the presentations and key issues raised during the meeting. These were then circulated to all participants for comment and contribution. Two main themes emerged:

Synthetic Biology has the potential to become a rapidly increasing contributor to the bioeconomy, (spanning healthcare, industrial biotechnology and agritech). Benefits from synthetic biology will arise not only from its capacity to generate entirely novel solutions to tough challenges, but also through the valuable insights it provides into the operation of known biological systems. Synthetic biology is generating tools and techniques that are already helping advance our understanding of basic science and the biology of complex organisms and ecosystems, which may down the road lead to unanticipated advances in food security, water, energy, health, and improved welfare for all.

a. The bioeconomy is already a significant and growing part of the overall economies of the US and UK. Actions that can accelerate the translation and uptake of synthetic biology within the bioeconomy and thus generate substantial opportunities for future jobs and growth were identified.

b. Although the US and UK currently have a leading role in the development and commercialization of synthetic biology, **the nature of synthetic biology lends itself to more distributed operations potentially including developing regions of the world**. To help realize the opportunities and benefits associated with more globally distributed activities, the development of skills, sharing of good practice principles, establishment of appropriate standards and metrology, regulatory frameworks and other essential underpinnings should be pursued with this future transnational perspective in mind.

The meeting focused on policies that would help provide a supportive framework for synthetic biology to flourish and to deliver envisaged benefits. The majority of recommendations arising are therefore framed in these terms, whilst recognizing that the main engine of progress derives from the efforts of individuals and teams within the research community.

Opportunities to address issues arising from these themes may be summarized as follows:

1. Economic Benefits from Increased Alignment

1a - Funding

Adequate funding is key to delivering envisaged benefits, but uncoordinated activities are unlikely to be as efficient or effective as they could be; coordinated efforts could enable each country to advance complementary, synergistic programs in tandem that would provide mutually beneficial advancements towards accelerated competitive leadership and economic benefit. Growing synthetic biology in both the US & UK will leverage complementary investments at each side, lead to economic growth and job creation, and help retain global leadership in this technology. Engaging globally will be also important to ensure continued ability to trade, develop a broader range of potentially valuable applications and

expand commerce in this technology. A number of joint funding mechanisms between the US and UK and Europe already exist, but potentially more may be achieved through greater alignment of strategic research goals. **It is recommended that action be taken to determine where yet greater alignment of funding initiatives in the US and UK could be established and would clearly drive economic benefits**, for example:

> US-UK should seek joint funding mechanisms to engage international partners in collaborative research and educational training. In order for synthetic biology to create economic opportunities in the US and UK, it is critical that international partners also participate in the development of technologies that are in synchrony with societal challenges. Joint research programs between the UK, US and other countries provide opportunities to establish an international network of researchers that can pursue research that takes into account global opportunities for synthetic biology. Joint educational programs, for example providing support for educational exchange programs with countries interested in setting up synthetic biology programs, also provide mechanisms for broader international engagement.
>
> US-UK should work together on mid-scale research initiatives to build shared expertise in both countries, either promoting synthetic biology topics into existing funding mechanisms[2] or identifying new approaches.

1b – Standards and Metrology

Establishing a framework of appropriate standards and metrology is essential to the acceleration of knowledge into commercial activities, with consequent benefits to jobs and growth. Effective standards and metrology underpin the infrastructure for commercial transactions and property rights, including those that are governed by open source. Poor experimental reproducibility hinders shared learning and impedes the rate of progress. Lack of adequate data standards, including 'metadata' provided with the reporting of *in vitro* or *in silico* studies, compounds these issues by obscuring problems and inhibiting integration of results. Establishing rigorous bases for the generation of reproducible results between different laboratories within and across institutions is critical to sharing data, developing common understanding, tackling technical challenges efficiently, more effectively sharing labour and enabling business-to-business transactions. It requires a more consistent approach towards reference materials and the capturing of representative metadata, and should build on already established standards in the biotechnology industry.

One method for accelerating progress could be the provision of Digital Biological Information (DBI), which comprises more than the sequence alone but also data relating to function and composition. The key to unlocking its value is the establishment of a common, standard language and protocols to enable humans and machines to exchange DBI in such a way that reflects the practices of the synthetic biology community, and also allows processes to be industrialised efficiently and effectively. There are already

[2] Such as the MURI – 'multi-disciplinary university research initiative' – in the US.

activities in place, including the development of standards, such as SBOL and DICOM-SB, that form part of the solution to enabling the routine and trusted provision of DBI. Additionally BSI is building on these developments, and is working with a number of major innovators in the field to extend this best practice and develop guidance on how best to use DBI to systematically design biological systems. This will be published in early 2015.

The US and UK should lead an international discussion to define a framework for the application of Digital Biological Information (DBI) in the bioeconomy - what is it, what is the business model, what are key parameters and points of inflection, what are the most pressing needs for standards and interoperability, over time as the field develops.

Standards are necessarily limited by what can be measured, and without better metrology the entire field will not develop and evolve as effectively as it could. **The development of an appropriate metrology infrastructure to understand better the biological systems under investigation is an urgent requirement,** and this will improve the ability of users to quantify and differentiate products and systems based on their performance. **It would be helpful to generate a joint white paper to outline a strategic approach to the application of metrology, and eventually standards, to aid the commercial development of synthetic biology, to provide context for the wider community, to achieve greater alignment between the various agencies, and to lay the foundation for prioritizing activities.** To assist in this effort, it is recommended that closer working relationships be developed between NIST (National Institute of Standards and Technology, US) and BSI (British Standards institute, UK), together with the NPL (National Physical Laboratory, UK), academics and other individuals and groups working in this field. Mutual understanding derived from these activities would provide a valuable first step towards the development of internationally accepted standards that may only be established through subsequent engagement with relevant agencies globally.

2. Training and Skills

Synthetic Biology as a broadly encompassing field spanning multiple disciplines and core to bio-engineering is a relatively recent development, enthusiastically embraced by a large and rapidly expanding student community in addition to practicing academics, industrialists and even capturing the imagination of the public at large, most notably 'DIY-ers'. Training to increase awareness and skills will be critical to the future success of the themes of synthetic biology as a driver of the bioeconomy and distributed operations including developing regions of the world. This in turn relies on the establishment and sharing of best practice throughout the entire academic, industrial and stakeholder communities.

Training should not only address standard technical guidance such as good laboratory practice and safety, but should also embrace a broader curriculum of issues aimed at raising awareness of Responsible Research and Innovation (RRI) and the global importance of safeguarding the bioeconomy.

Significant social and economic benefits may be derived from the bioeconomy. To effectively secure these benefits it is important to avoid unintended downsides or to prevent deliberate misuse of technology. The development of a Responsible Research and Innovation (RRI) culture through training

and protocols minimizes the likelihood of unintended consequences through raising awareness of broader issues and engagement with a wider mentorship circle of experts especially during the planning and funding phases of research. Potential issues associated with existing natural and conventional biological systems have been, and continue to be, addressed extensively through measures that apply equally to products from synthetic biology.

Certain specific additional technical measures have been introduced such as the monitoring of synthesis requests by commercial suppliers of DNA.[3] However, the development of broad-ranging training programmes for the rapidly expanding community of practitioners, devised to include awareness of potential biosecurity issues and to help build and sustain trust, would provide an additional practical and effective approach to complement such technological measures, particularly if a simple and trustworthy mechanism were to be provided for individuals to raise any concerns they may have regarding their own or others' activities, for example via their RRI mentorship circle.

To establish a best-practice approach that could be built into training programmes, **it may be helpful to hold Inter-academy council discussions on Responsible Research and Innovation, and also on Biosecurity** – including national security and law enforcement agencies, social scientists and technologists from across the DIYbio Garage to professional industry/academia continuum.

A good first step might be for the US and UK to adopt a biosecurity code for synthetic biology to be applied on a voluntary basis, and then rolled-out more broadly through common training programmes. This could include efforts to complement ongoing activities on biosecurity undertaken by various national academies and international organizations, identify best practices on research conduct and mechanisms for ongoing learning and refinement. There are good starting points for a synthetic biology biosecurity code in DIY and other communities, as well as models for responsible conduct in research such as the National Academy report 'On Being a Scientist: Responsible Conduct in Research' (National Academies Press, 2009).[4]

3. Global Dissemination

Recognizing the potential for increasingly globally distributed operations, and the mutual benefits that may arise, it was noted that the US and UK should take proactive steps to embrace and work with the wider international community to establish common standards and support expanding opportunities.

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[3] Department of Health and Human Services, Office of the Secretary, "Screening Framework Guidance for Synthetic Double-Stranded DNA Providers," *Federal Register*, vol. 74, no. 227 (November 27, 2009), pp. 62319-62327.

[4] See for example National Research Council, *Understanding Biosecurity: Protecting Against the Misuse of Science in Today's World* (2010); *Challenges and Opportunities for Education About Dual Use Issues in the Life Sciences* (2010); and *Research in the Life Sciences with Dual Use Potential: An International Faculty Development Project on Education About the Responsible Conduct of Science* (2012).

iGEM is well established in the US, UK and numerous other developed and developing markets, and could make a useful contribution towards democratizing synthetic biology throughout the world. iGEM provides a proven mechanism for inspiring and harnessing, and for disseminating knowledge and know-how, especially when in conjunction with local educational programs. Indeed, it is unsurpassed in the depth and diversity of its global reach within the field of synthetic biology, and so its future merits further consideration.[5]

At the same time, there are additional mechanisms that should be considered. For example, the Synthetic Biology Leadership Accelerator Program (LEAP) is another example that brings together young leaders in synthetic biology and provides them with mentorship, practical skills, and a sustaining network to help them guide a socially responsible future for synthetic biology. The UK has recently joined the LEAP team. One of the main sponsors for the program is the UK's Synthetic Biology Industrial Translation Centre (SynBiCITE) who will be hosting the LEAP Program in 2016 in the UK.

A more holistic approach to the effective uptake of synthetic biology in other developed and developing countries needs to be adopted – including consideration of the capacity to provide effective support of regulatory systems, RRI initiatives, infrastructure etc. In addition to initiatives such as iGEM and LEAP, other models of public-private partnerships to build capacity and help tailor the delivery of benefits in developing markets should be explored such as the Higher Engineering Education Alliance Partnership (www.heeap.org).

The world's academies of science and medicine have established several global and regional networks in order to advance their collective work, and further interaction with these networks should be explored as a mechanism for greater international engagement. In particular, an umbrella organization, the InterAcademy Partnership IAP (www.interacademies.org) based in Trieste Italy, comprising 130 members, was formed earlier in 2014 to better support the role of science in seeking solutions to the world's most challenging problems. This brings together two relevant networks – the IAP Science[6] and the InterAcademy Medical Panel (IAMP)[7] - together with the InterAcademy Council (IAC), created by the IAP to provide expert advice to international bodies such as the United Nations and other institutions[8]. In 2014, IAP, IAMP and IAC formed The Network of African Science Academies[9]

[5] At the recent iGEM Jamboree in Boston, there were 220 teams from leading universities around the world, together with their advisors. iGEM is now becoming much more than just a student competition and is a very important vehicle for driving the field forward in both educational and research terms. The role of iGEM in shaping the future of synthetic biology could be increasingly significant, and may therefore merit increasing consideration from funding agencies.

[6] Formerly known as the InterAcademy Panel, this works with its member academies "to strengthen the role that science plays in society and to advise public officials on the scientific aspects of critical global issues".

[7] A network of academies with members from the medical communities who work to improve health worldwide.

[8] The IAC is currently hosted by the Royal Netherlands Academy of Arts and Sciences in Amsterdam.

[9] NASAC is headquartered in Nairobi, Kenya, and currently has 21 members (nasaconline.org).

(NASAC) is one of four IAP regional networks. The IAP released a statement on synthetic biology in 2014.[10]

It would also be timely to re-stimulate the successful 'Six Academies' process for engaging China in a trilateral US-UK-China appraisal of synthetic biology opportunities. Strong consideration should be given to extending this approach to engage the academies in other developing countries. The IAP global network of science academies is one possible venue for this broader engagement, with the US and UK taking the initiative to establish a dialog through the IAP and host initial meetings on this topic. As a part of the National Academies Committee on Science, Law and Technology, the Synthetic Biology Forum would be a natural group to initiate this conversation, with the goal of hosting a first meeting in 2016.

A fundamental pre-cursor to the wider dissemination of synthetic biology values is the establishment of an engaged and supportive social environment within the US and UK. Public engagement and mutual understanding must be effective, and actively shape the future vision and application of synthetic biology.

The delegates to the meeting recommended that the US and UK should continue to take a proactive approach to public engagement, as the field progresses and provides fresh examples of emerging opportunities. Regular meetings to share learnings and best practice would significantly enhance understanding and guide future steps. The US National Science Foundation recently sponsored an international workshop in Arizona on establishing a research agenda for social aspects of synthetic biology to further discuss public engagement. It is already clear that public awareness, engagement and guidance is required for synthetic biology to move forward in terms of research directions, commercial investment, and the substantial opportunity for future jobs, economic growth and quality of life.

Because, in view of time and resources, the meeting deliberately focused on a selected number of areas only, it is recognized that numerous other topics, not addressed at the time, may also benefit from future discussions. For example, the status of regulations and standards related to workplace safety. Intellectual Property is another important topic that has already been addressed jointly in previous discussions[11].

[10] http://www.interacademies.net/News/PressReleases/24059.aspx

[11] For example: 'Ownership and Sharing of Synthetic Biology: Imagining a regime that Makes the Promise of Synthetic Biology a Reality' Workshop held under the auspices of the US National Academy of Scinces' Commmittee on Science, Technology and Law , Imperial College London 28-29 Jan 2013.

Appendix 1 Meeting Concept Paper

Meeting Overview

Over the past decade, synthetic biology has emerged as one of the most promising fields of research for the new century. Today, the United Kingdom and United States are each leaders in enabling and realizing the economic benefits of synthetic biology. Both governments are providing support to university researchers and engaging in discussions of regulatory and societal issues as it becomes clear that a balanced policy framework and sustained funding for basic and applied research are necessary to attract private capital and to develop innovative products.

In 2013, the UK government announced that it would be investing an additional £60 million to become a world leader in synthetic biology. The US government supports a range of synthetic biology projects with funding provided by numerous agencies including DoE, DOD, NIH, NSF, NASA, and NIST. The largest US investment is the DOD-DARPA Living Foundries Program that will provide over $100 million.

At this early stage in the development of synthetic biology, the UK and the US have the unique opportunity to take note of the scientific and engineering advances made, the investment strategies developed, and the business and regulatory frameworks applied; these questions are core to whether the field is sufficiently well grounded so as to encourage increased private investment and the transformation of today's predominantly petrochemicals based manufacturing processes to biologically based processes, starting materials and new product development. This joint meeting represents the first of a series of small high-level discussions among UK and US government officials, academia, industry, and policy-makers to share approaches, challenges, and best practices that may not only strengthen respective domestic programs but also set the stage for future collaboration to establish mechanisms that further each country's interests and help insure sustained leadership in this increasingly important field.

Desired Outcomes, Agenda and Pre-Work

The Summit will be a closed meeting that includes representative members of the UK SB Leadership Council and National Academies' Forum on Synthetic Biology, together with invited guests. The delegation will discuss areas of highest challenge and opportunity in advancing the Bioeconomy and identify areas where the US and UK can each benefit by working together to advance our respective and collective goals. The agenda will be divided into sessions led by US and UK co-leads highly knowledgeable in those areas. In order to maximize the value of time together for discussion at the Summit, session leads will prepare pre-meeting briefing papers for their respective topics, highlighting areas that would benefit by US-UK discussion and the identification of compelling next steps that could be jointly driven forward. Topics are as follows:

- Economic Case and its Viability
- Safeguarding the Bioeconomy
- Standards and Metrology

The briefing papers and meeting discussion will be summarized in a report for SBLC and Forum member consideration. We expect this will be the first in a series of excellent discussions that catalyze important joint initiatives across the United Kingdom and United States in advancing the Bioeconomy.

Thank you to our sponsors: Alfred P. Sloan Foundation and Imperial College

Appendix 2: Workshop Agenda

Agenda: Creating an Environment to Support Investment and Innovation in Synthetic Biology

Day 1: Tuesday, 28 October

8:30 Light Breakfast

9:00 Welcome / Opening Remarks (David Willetts, Lionel Clarke, Richard Murray)

9:30 Introductions

9:45 Session I: Economic Case and Its Viability Session Leads: Tom Connelly, Ian Shott and Steve Bates

- Panel Remarks to Delegation Moderator: Lionel Clarke
- Discussion
- Potential UK-US Opportunities

12:15 Lunch

1:15 Session II: Safeguarding the Bioeconomy Session Leads: William So and Piers Millet

- Panel Remarks to Delegation Moderator: Richard Murray
- Discussion
- Potential UK-US Opportunities

3:30 Break

4:00 General Discussion

- Preliminary Summary Statements for Sessions I and II
- Feedback on Day 1

5:30 Break

6:30 Networking Reception and Dinner

Day 2: Wednesday, 29 October

8:00 Light Breakfast

8:30 Welcome Remarks (Alice Gast)

8:40 Session III: Standards and Metrology Session Leads: Marc Salit and Ben Sheridan

- Panel Remarks to Delegation Moderator: Dick Kitney
- Discussion
- Potential UK-US Opportunities

10:00 General Discussion

- Overall Summary Statements for Summit
- Next Steps
- Summit Feedback

11:30 Break

12:00 Lunch/Adjourn

Appendix 3: Workshop Participants

Shami Ahmed, Department of Business Innovation and Skills
Jim Ajioka, Synthetic Biology Research Centre – Cambridge
Steve Bates, BioIndustry Association
Helen Bodmer, Synthetic Biology Leadership Council/Department for Business, Innovation and Skills
James Brown, Synthetic Biology Leadership Council/Knowledge Transfer Network
Steve Chambers, SynBiCITE – Innovation and Knowledge Centre
Lionel Clarke, Synthetic Biology Leadership Council
John Collins, SynBiCITE – Innovation and Knowledge Centre
Amanda Collis, Synthetic Biology Leadership Council/Biotechnology and Biological Sciences Research Council
Tom Connelly, Dupont
Tim Dafforn, Synthetic Biology Leadership Council
Genya Dana, US Department of State
Luke Davis, Engineering and Physical Sciences Research Council
Mike Edbury, Department for Business, Innovation and Skills
Sharon Ellis, Department for Business, Innovation and Skills
Tim Fell, Synthace
Paul Freemont, SynBiCITE – Innovation and Knowledge Centre
Alice Gast, Imperial College
Theresa Good, National Science Foundation
Rick Johnson, Global Helix
Chris Jones, Synthetic Biology Leadership Council/Innovate UK
Richard Kitney, Synthetic Biology Leadership Council/SynBiCITE – Innovation and Knowledge Centre
Steve Laderman, Agilent
Claire Marris, Kings College London
Anne-Marie Mazza, National Academy of Sciences
Piers Millett, United Nations Disarmament Research Institute
Sarah Munro, National Institute of Standards and Technology
Richard Murray, California Institute of Technology
Anne Osbourn, Synthetic Biology Leadership Council/Synthetic Biology Research Centre
Petra Oyston, Defence Science and Technology Laboratory
John Perkins, Department for Business, Innovation and Skills
Kristala Prather, Massachusetts Institute of Technology
Marc Salit, National Institute of Standards and Technology
Ben Sheridan, British Standards Institute
Ian Shott, Shott Trinova LLP
William So, FBI
Darlene Solomon, Agilent
Guy Bart Stan Centre for Synthetic Biology and Innovation, Imperial College
Scott Steedman, British Standards Institute
Joyce Tait, Synthetic Biology Leadership Council/Innogen
David Tew, GlaxoSmithKline
David Willetts, Member of Parliament

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Session I: Economic Case and Its Viability. Pre-reading

Market Pull and the emergence of Synthetic Biology

'The Bioeconomy' is predicted by many to play a significant role in the 21st century. It may be defined as an economy in which the building blocks of materials, chemicals and energy are derived from renewable biological resources, but it also reflects the anticipated benefits arising more broadly from significant underlying advances in biotechnology. These stem from numerous developments through the latter half of the last century to the present day including:

- The discovery of the structure of DNA and subsequent advances in understanding of biological processes at the genomic level, including their relationship to health issues
- Societal awareness of mounting global environmental challenges and resource constraints, and increasing demands for more sustainable (bio-related) solutions
- revolutionary increases in computational power and speed, data storage and sharing capacity, micro-miniaturisation and high throughput and sensitive analysis systems, enabling biological systems to be modelled and assembled with increasing predictability at a parts level.

This rapidly increasing predictive capacity to design and engineering biologically based parts, novel devices and systems as well as the redesign of existing, natural systems is the basis of the new field of 'Synthetic Biology'[1]. The application of increasingly predictive design principles is set to transform the speed, cost-effectiveness and robustness with which new and improved applications may be developed.

Synthetic biology is still at an early stage of its development, but holds great promise as an underpinning platform technology, helping to facilitate the cost-effective development of a potentially vast range of beneficial applications, and assisting greater efficiency of resource use.
Parallels have been drawn both with the development of synthetic chemistry in the 19th & 20th centuries which allowed the development of the pharmaceutical industry[2] and also with the emergence and development of micro-electronics over the past century and its transformatory impact on communications and the knowledge-based economy[3].

[1] UK Synthetic Biology Roadmap July 2012
[2] Such as production of the synthetic drug Aspirin in 1897 by the Bayer Company in Germany
[3] The Knowledge-Based Economy, OECD 1996 OCDE/GD(96)102

The Bioeconomy – Some Financial Dimensions

Technological contributions to the Bioeconomy can be divided into three constituent parts:

- Health – Biologics ('Red')
- Primary Production – Agricultural ('Green')
- Industry - industrial biotechnology ('White')

Analysis of the Bioeconomy in the US by Rob Carlson, presented to a Congressional Hearing in Dec 2013 estimated that the bioeconomy had delivered around $300 bln to the US in 2010, rising at around 7.5% per annum growth rate to around $350bln (or 2.5% GDP) in 2012. The split between the three constituent sectors in 2012 was:

- Biologics $100 bln
- GM crops $125 bln
- Industrial Biotech $125 bln ($66bln chemicals; $30bln biofuels, $16bln biologics feedstocks, $12bln food and ag, $1bln emerging)

Significance of these figures includes:

- By 2012, the total US bioeconomy already exceeded the total global semiconductor industry ($322 bln)
- The growth rate, at >7% p.a. (Carlson defines as 'GMDP' - Genetically Modified Domestic Product) significantly exceeded the underlying growth in GDP (2.5% pa) during the same period, and translated to 7% US growth

The entire European bioeconomy (defined to include food, agriculture, paper/pulp and forestry/wood industries was estimated in 2009 to total euro 2 trillion, relating to 22 million jobs)[4]. At the time, a total of euro 57 bln, ($75 bln) less than 3% of the total bio-related economy was assigned to knowledge-based developments, split between:

- chemicals and plastics euro 50 bln,
- biofuels euro 6 bln,
- enzymes euro 0.8 bln.

An ongoing biotechnology study in Europe (Bio-TIC – in draft) has narrowed down the estimated value of IB demand in the EU to euro 29 bln ($36 bln). Regarding hurdles to IB growth a wide spectrum of views were gathered from over 100 respondees, the average opinion split fairly evenly between R&D, Policies and Regulations, and Market Entry[5].

Advances in the biosciences have played an important role over the last three decades in these developments, but more recent advances in synthetic biology since the human genome project have opened up enormous potential for a huge increase in accelerated development and massive economic impact. The establishment of these major channels to market provides clear pipelines for the rapid commercialisation of ever more effective new synthesis pathways and diverse device and product design and manufacture.

In 2011 BCC Research[6] estimated the global value of synthetic biology (subdivided between the provision of the underpinning technologies of synthetic biology itself and the products enabled by synthetic biology) to be around $1.6 bln in 2011 (0.5% of the Carlson US bioeconomy estimate) rising to $10.8 bln by 2016, representing an effective growth rate of >30% pa., well above the bioeconomy as a whole, but maybe not unrealistic given the very low starting level.

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[4] The Knowledge-Based Bioeconomy in Europe (Sept 2010) http://www.bio-economy.net/reports/reports.html

[5] Overcoming hurdles for innovation in industrial biotechnology in Europe, Market Roadmap DRAFT Bio-TIC

[6] 'Synthetic Biology: Emerging Global Markets' Global Information Inc; 8 Dec 2011

What could inhibit or enhance progress?

'..to obtain the full benefits of the bioeconomy requires purposive goal-oriented policy. This requires leadership… to establish goals for the application of biotechnology to primary production, industry and healthcare, to put in place the structural conditions required to achieve success such as obtaining regional and international agreements; and to develop mechanisms to ensure that policy can flexibly adapt to new opportunities' [7]

'..To advance a competitive and sustainable bioeconomy…[should also pay attention to] two important themes: participatory governance that engages the general public and key stakeholders in an open and informed dialogue as well as a commitment by government and industry to innovation that drives concerted efforts on sustainable development of the bioeconomy'[8]

Issues for which a sharing of US/UK views could be constructive:

- Broadening and securing the feedstock supply chain
    - Renewable energy options, waste streams…
    - Commodity intermediates
    - Could new bio-derived building block markets aid commercialisation?

- Mechanisms to support the development of sustainable solutions:
    - What is the impact of continuing fragility of carbon floor price?
    - Do mechanisms that attempt to manipulate the market - e.g. ROCs and RINs – introduce too many unintended consequences?
    - Could a 'damage impact' levy encourage better solutions?
    - How to derive global benefits rather than be inhibited by local cost penalties?

- Balancing societal demand for goods and services against societal concerns over potential unintended consequences –
    - responsible innovation and the need for equally responsible and adaptive approaches to regulation and stakeholder participation
    - Addressing the GMO legacy in Europe

- International regulatory frameworks
    - Role of international treaties such as CBD, Nagoya – ensuring balanced discussion and outcomes

- IP – more haste, less speed…?
    - Finding a better balance point between open source accelerating the field and IP safeguarding investments?
    - Pros and cons of US and UK approaches
    - MTAs and other enablers/inhibitors

- Multi-disciplinary approaches – overcoming cultural interfaces, celebrating diversity, sharing success

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In Session 1 we shall begin by identifying the highest priority issues for joint discussion. This list is simply to inspire further thought, and we encourage delegates to suggest modifications, or contribute other more critical issues that have not been included above.

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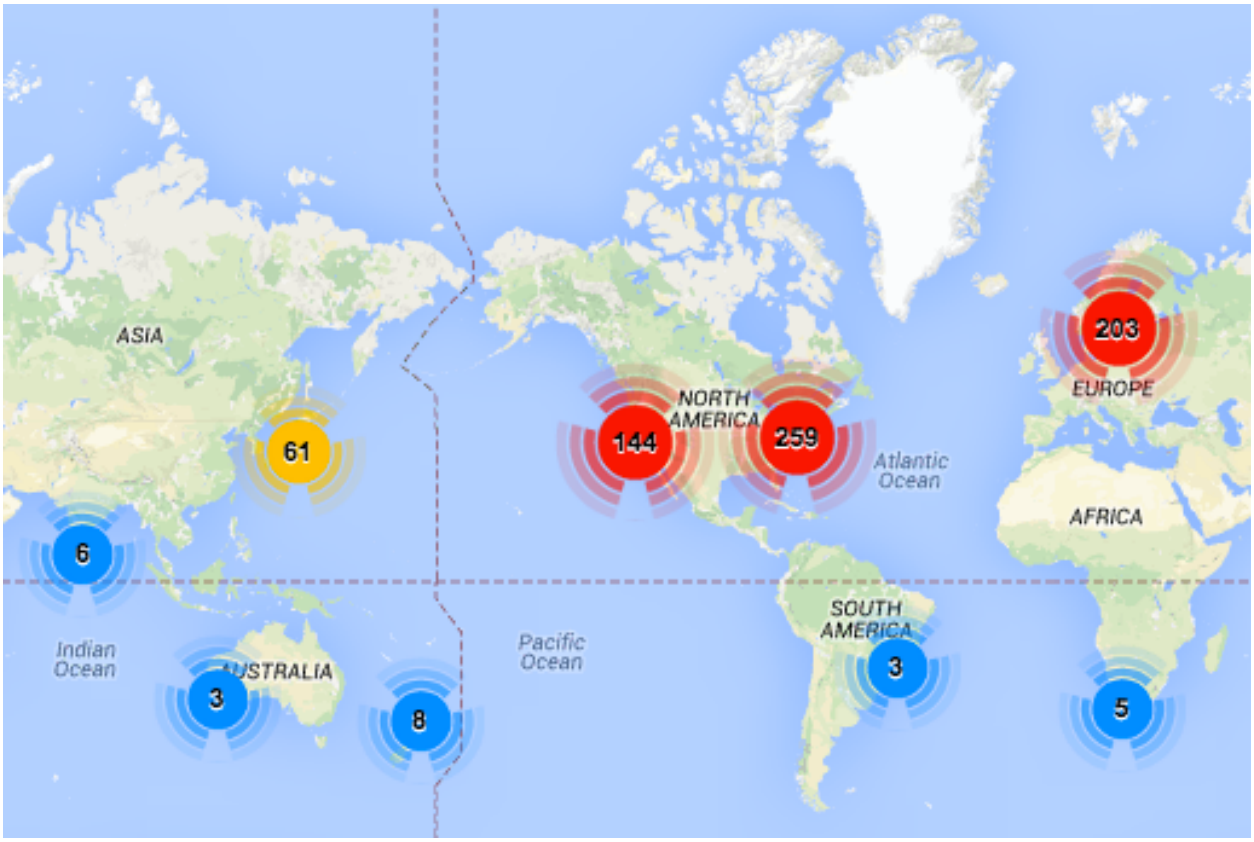
[7] The Bioeconomy to 2030 OECD 15 April 2009

[8] McCormick, K and Kautto, N. The Bioeconomy in Europe: An Overview; Sustainability 2013, *5, 2589-2608*

A Background Paper on Safeguarding the Bioeconomy

The deep inter-disciplinary integration between biology and engineering has led to significant shifts in who and how biological science is being practiced and developed.

Synthetic biology is spreading around the globe. For example, as of 13 October 2014 the global map maintained by the Synthetic Biology Project detailed almost 700 relevant institutions, with 403 in North America, 3 in South America, 203 in Europe, 5 in Africa, 78 in Asia-Pacific.[1]



Screenshot of the SybBio Map of the Synthetic Biology Project, 13 October 2014.

There continues to be a rapid expansion of biotechnology where relevant capacity is to be found. While countries like the US and UK continue to dominate, significant progress is being made elsewhere. For example, in the most recent version of Scientific American's WorldVIEW, which ranks innovation in biotechnology, Puerto Rico climbed 22 places to be placed 30th, Qatar rose 13 places to be 25th, the UAE rose 13 places to be 27th, and Saudi Arabia rose 12 places to be 33rd. Other countries, such as Singapore ranked 2nd and Malaysia ranked 29th continue to hold their own.[2]

Synthetic biology is spreading across sectors. A 2012 survey of products that exist, or which are currently under development, identified 68 products spanning chemicals (25), medicine (18), biofuels (13), food

[1] http://www.synbioproject.org/sbmap/
[2] http://www.saworldview.com/scorecard/2014-scientific-american-worldview-overall-scores/

(6), materials (3), energy (1), and others (2). Seventeen products were already on the market or had been demonstrated, for another 17 a pilot plant or joint ventures were being created or were in clinical trails, and another 11 were pending commercial development from laboratory research. [3]

Synthetic biology is being utilized by people from a variety of backgrounds. Historically, there have been strong relationships between the synthetic biology community and those revitalizing the amateur biology community. As the citizen science movement developed community laboratories, they too began to look towards and teach classes in synthetic biology. A November 2013 report highlighted that "few DIYers are using sophisticated synthetic biology" but noted the potential for this to expand in the future.[4] These movements, and the resulting shift in capacity, are not confined to the US and the UK but can also be found further afield; for example, there is a burgeoning citizen biology movement in Singapore. [5]

Historically, safeguarding synthetic biology was addressed by focusing on the engineering of pathogens, environmental impact of GMOs, and adulteration of the food supply.

The 2014 OECD publication 'Emerging Policy Issues on Synthetic Biology' notes:

> "To date the regulation of synthetic biology is effectively the regulation of genetically modified organisms (GMOs). The thinking on whether this is adequate is polarized. The over-riding opinion of the synthetic biology community itself is that regulation is currently sufficient."[6]

However, a March 2014 legal review of relevant US regulations, suggests that "synthetic biology will place great strain upon the extant regulatory system due to three atypical characteristics of this nascent technology: (i) synthetic organisms can evolve; (ii) traditional risk structures do not apply; and (iii) the conventional regulatory focus on end-products may be a poor match for novel organisms that produce products." [7]

Regulating GMOs

Research by Bar-Yam *et al* for SynBERC and iGEM (ANNEX) has been used by the OECD to demonstrate that "international regulation is virtually at the level of the Cartegena Protocol, which governs the trans-boundary movement of genetically modified organisms".[8] Such regulations cover:

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[3] http://www.synbioproject.org/site/assets/files/1326/synbio_applications_wwics.pdf

[4] Synthetic Biology Project, Seven Myths and Realities of Do-It-Yourself Biology, Woodrow Wilson Center for International Scholars, November 2013, see: http://www.wilsoncenter.org/publication/seven-myths-and-realities-about-do-it-yourself-biology-0

[5] http://diybiosingapore.wordpress.com/

[6] OECD, Emerging Policy Issues on Synthetic Biology, 4 June 2014, p115, see: http://www.oecd-ilibrary.org/science-and-technology/emerging-policy-issues-in-synthetic-biology_9789264208421-en

[7] Mandel & Marchant, The Living Regulatory Challenges of Synthetic Biology, Iowa Law Review, Vol. 100, 2014, Forthcoming, see:

http://papers.ssrn.com/sol3/papers.cfm?abstract_id=2410179

[8] OECD, Emerging Policy Issues on Synthetic Biology, 4 June 2014, p120

- Transfers of genes;
- Mutations, evolution and proliferation;
- Effects on ecosystems and other species;
- Effects on biodiversity;
- Consumption risks;
- Risks to laboratory workers; and
- Accidental release of laboratory strains.

The regulation of GMOs marks one significant difference in the approaches taken on either side of the Atlantic:

> "GM concerns have been much more of an issue in Europe than in other regions. It is not a significant issue in much of Asia, the Americas and partner economies, and it not clear whether these regions would agree that new or more regulation is required."[9]

The OECD has detailed a significant difference in approach where the US bases its regulations on environmental impact analysis (a green light approach which allows activities until a risk is identified) While the EU has adopted the precautionary principle (a red light approach which prohibits an activity unless it can be demonstrated to be safe). Given public perception issues in Europe, a 'stringent' regulatory regime has been developed (ANNEX).

There are signs that the potential benefits of GMO approaches more broadly, especially for food security, are being more widely recognized; for example, the suggestion that 'GM crops could be the key to Africa's food security'.[10]

Securing pathogens

The synthetic biology community has a long history of active engagement with concerns that its efforts may result in accidents (addressed through laboratory biosafety) or deliberate misuse to cause harm (addressed through laboratory biosecurity). Relative balancing of these risks has varied over time and geographic location but as a whole the community has been more active than many contemporaries in actively addressing both.

A 2012 UN review of the Security Implications of Synthetic Biology and Nanobiotechnology identified a number of risk scenarios and possible policy options. It focused heavily on risks around the engineering of new, altered or existing pathogens. It found that in the short and medium term, the potential benefits of synthetic biology would likely outweigh security risks but that if synthetic biology was to fully

[9] OECD, Emerging Policy Issues on Synthetic Biology, 4 June 2014, p124
[10] M. Musi, GM crops could be the key to Africa's food security, WorldVIEW: A Global Biotechnology Perspective, Scientific American, see: http://www.saworldview.com/tracking-innovation/growing-optimism/

mature that "there could be a significant risk of hostile applications in the longer term by both state and non-state actors."[11]

Through international obligations under the Biological Weapons Convention (BWC) and United Nations Security Council Resolution 1540, both the UK and the US are bound to prohibit and prevent the acquisition and use of the life sciences and biotechnology for use as a weapon. Both countries have robust legislative and regulatory regimes to meet these commitments, as demonstrated by information provided in annual Confidence-Building Measures[12] and relevant reports to the UN Security Council.[13]

There are also strong examples of industry-led security-based initiatives. For example, commercial gene synthesis providers have developed and instituted screening procedures to screen orders according to what is being requested and by whom. Although two approaches, one largely US-based and the other Europe-centric, have developed; they largely agree on what needs to be done and differ primarily around the amount of human oversight needed.[14] US gene synthesis companies have the additional recourse where they can contact the Federal Bureau of Investigation (FBI) when orders are flagged as being suspicious during the customer-sequence screening. Both the FBI and other US departments and agencies continue to work with synthesis companies to ensure their products are not misused.

The work of two research groups, in the US and in the Netherlands, further confounds policy makers and regulators of advanced and emerging biotechnology such as synthetic biology. The avian influenza gain-of-function research results from these two research groups have had the security, regulatory, and biosafety world communities trying to determine the best balance between the benefits of such research and the potential hazards they present.[15]

This has been paralleled with significant outreach and community building by sectors of the security and law enforcement communities. At the international level, for example, the BWC Implementation Support Unit has been a regular participant in synthetic biology meetings, hosted a series of briefings for the treaty and has long been involved in the policy, practices and safety/security aspects of iGEM.

Broad dissemination and access to synthetic biology technologies, expertise, and products continue to advance basic research and other endeavors. Researchers and individuals outside of the "regulated" and the traditional life-science research communities are leveraging these advances and innovations. This emergent group includes computer scientists, artists, and amateur biologists. Many of whom may not be inculcated in the biosafety requirements while working with either whole or parts of microbes. It is

[11] UNICRI, Security Implications of Synthetic Biology and Nanobiotechnology: A Risk and Response Assessment of Advanced Biotechnology, United Nations Interregional Crime and Justice Research Institute, 2012, see: http://www.unicri.it/in_focus/on/Syntethic_Biology

[12] See: http://www.unog.ch/bwc/cbms

[13] See: http://www.un.org/en/sc/1540/national-implementation/national-reports.shtml

[14] J. Tucker, Double-Edged DNA: Preventing the Misuse of Gene Synthesis, Issues in Science and Technology, 27 November 2013[14]

[15] http://www.whitehouse.gov/blog/2014/10/17/doing-diligence-assess-risks-and-benefits-life-sciences-gain-function-research

with higher confidence to say they have not been inculcated in the culture of biosecurity and the potential implications of their work.

The FBI, in addition to working with the synthetic biology industry, has developed programs that raises biosecurity awareness and supports the development of prevention mechanisms targeted at various levels of education and synthetic biology convergent fields.

The FBI partnered with the iGEM organizers since 2009. Each participating team has had to evaluate their projects for security implications since 2010, and has culminated to an entirely separate judging criterion and award solely for biosecurity focused projects for the 2014 competition. The US and international teams also have the opportunity to speak with FBI representatives each year and attend their biosecurity symposium where they are introduced to topics such as the Biological Weapons Convention and the UN Security Council Resolution 1540 as a means to reinforce scientific stewardship and citizenship.

Issues raised in this paper are discussed at institutional-level and regional workshops, provided by the FBI and hosted by interested academic institutions. These workshops raise the awareness of national and international threats as they relate to the research enterprise and the potential security implications of convergence with advanced and emerging biotechnology, such as the field of synthetic biology.

Biohackers, Do-It-Yourself biology, garage scientists, amateur biologists – all terms interchangeably used to describe individuals and groups who are interested in science –want to know more about science, and just do science. And they have been able to do just that since molecular biology – material, technology, and know-how is more accessible through synthetic biology. Outreach by the FBI to these groups, who see themselves as a counter-culture and have been sensationalized by the media, remain strong. US and international groups of amateur biologists and the FBI maintain working relationships since 2009.

If synthetic biology is to able to make good on its promises for applications, security may need to be assessed in novel ways

Security, whether national or international, is a complex concept and is determined by the interplay of a broad variety of factors, including:

- Access to resources, whether it is oil for energy or industry, water for drinking or agriculture, or land for people and food, has destabilized countries and regions and resulted in wars.
- Access to energy, while related to the resources issue, is a key driver to development and its absence could compound existing disparities, will impact the health, wealth and prospects of those affected, and could lead to domestic, regional or international instability.
- Manufacturing and industrial capacity, again related to access to resources, will play an important role in maintaining and improving both national and international peace and security – both as a

positive, by providing for employment and boosting the economy, but also with potential to be diverted to produce outputs which can be used to cause harm.

- How (and perceptions of how) authorities and institutions gather, handle and use data, especially when it is done in the name of security, remains an issue of contention. Cyber attacks on academic institutions are on the rise and where security performance of some of the major US institutions has not improved commensurate to the threat level.
- Transnational crime, such as the international narcotics trade, destabilizes and challenges governments – to the extent that many countries have 'declared war' on it.
- Maintaining the environment and preserving biodiversity has also been recognized as key to future stability, failing to do so could have significant implications for other factors influencing security promoting insecurity.

Access to resources

Synthetic biology could make it easier to access certain resources and will likely enable a greater number of people, from different sectors, in a wider variety of places to take advantage of resources and translate them into products. Ongoing efforts to stabilize access to artemisinin via a novel, synthetic biology-based, production route is perhaps the most obvious example. Others, such as the ETC Group, have pointed out bio-based production could significantly increase demand for different types of resources, in particular biomass. They have raised concerns that this could further exasperate deforestations and in certain economies, leading to too much needed agricultural land being re-tasked with growing biomass for industrial use. There are certainly examples of efforts to find better uses for biomass currently classified as waste. For example, Malaysia has a national strategy for the biomass left over from its palm oil production. Ultimately, the demand for biomass could result in biomass-export economies. Recent developments in the use of aquaculture for biofuel generation might go some way to minimizing such demands being placed on land use while allowing for increasing total biomass output. Other groups have already raised different environmental concerns over the use of aquaculture.

Access to energy

The International Energy Agency's 2013 World Energy Outlook reported that 1.3 billion people (18% of the world's population) did not have access to electricity in 2011.[16] They noted that while 'modest' progress was being made globally, in some countries access had worsened. The 2014 Africa Energy Outlook highlights the lack of infrastructure and potential for renewable energy sources in sub-Saharan Africa.[17] As bio-based energy sources become more mainstream, their value will increase and reliance on them could translate them into critical infrastructure and therefore potential targets for attack. They will need protecting. This may pose distinct challenges, given the bio-based nature of the processes involved. It is also possible that equity of access to both biomass and bio-based energy production could

[16] IEA, 2013 World Energy Outlook, International Energy Agency, 12 November 2013, see: http://www.worldenergyoutlook.org/media/weowebsite/energydevelopment/WEO2013_EnergyForAll.pdf
[17] IEA, 2014 Africa Energy Outlook, International Energy Agency, 13 October 2014, see: http://www.iea.org/publications/freepublications/publication/AEO_ES_English.pdf

begin to feed into international trade negotiations. As has been witnessed in other sectors, there may be a push by developing countries for the democratization of bio-based energy.

Manufacturing and industrial capacity

A recent report by the Scientific Advisory Board's Temporary Working Group on the Convergence of Biology and Chemistry of the Organization for the Prohibition of Chemical Weapons started by noting that within the next five years over 10% of the global industry's production will use bio-based processes.[18] This would suggest that there is a significant shift already happening in some industrial sectors to take greater advantage of bio-based manufacturing. Synthetic biology is only likely to speed up and increase the scale of adoption. It could bring with it a range of security issues. It could enable new ways to produce things we already see as dangerous; for example, bio-based production of chemical-explosive precursors. Given the environmental impacts of chemical synthesis and the logistical and security aspects of a centralized manufacturing process, there are a range of arguments as to why such a development makes sense. Research on this potential production pathway has already begun.[19] Concerns over the legal and ethical status of such efforts have also been raised.[20]

A significant shift in industrial and manufacturing capacity towards bio-based solutions could also increase the value of such sites and make them potential targets for those wanting to cause harm. As a result, and given the potential perceptions of a large-scale release from such a facility, there may be an increased need to secure relevant facilities. Should this be paralleled by a trend towards more decentralized production, then the number of facilities needing to be secured could also dramatically increase.

At the international level, the blurring of the boundaries between biology and chemistry are already complicating efforts to verify that facilities are not being used to produce prohibited items. Increasing adoption of bio-based solutions, especially if synthetic biology should increase the scale and pace of such adoption, could compound this further. This could challenge international security regimes but could also result in additional levels of regulatory oversight for such facilities.

New uses for data

Modern medicine, and in particular the increasing use of sequencing as a diagnostic tool is generating a great deal of data. There is also growing dependence on big data, large data sets, and open source data to leverage tools being developed in the design phase of synthetic biology. Data protection laws can, to

[18] OPCW, Convergence of Chemistry and Biology, Report of the Scientific Advisory Board's Temporary Working Group, Organization for the Prohibition of Chemical Weapons , June 2014, see: http://www.opcw.org/index.php?eID=dam_frontend_push&docID=17438

[19] Nitration Enzyme Toolkit for the Biosynthesis of Energetic Materials, see: http://www.serdp-estcp.org/Program-Areas/Weapons-Systems-and-Platforms/Energetic-Materials-and-Munitions/Rocket-and-Missile-Propellants/WP-2332/WP-2332

[20] Rob Carlson & Daniel Grushkin, The Military's Push To Green Our Explosives, Slate Magazine, 19 January 2012, see: http://www.slate.com/articles/technology/future_tense/2012/01/synthetic_biology_environmentally_friendly_weapons_and_the_biological_and_toxin_weapons_convention_.html

some extent, protect individuals from their personal data being misused. Studies have demonstrated, however, that anonymization of this data, can in some cases be circumvented. This poses a threat for identity theft, or exploitation of, or discrimination based upon, individual genomic information. More sophisticated use of data mining and metadata analysis could also challenge assumed levels of anonymity. There may be a case for reviewing informed consent and other legal protections in the face of growing interest and application of longitudinal data analysis.

Analysis of large data sets is also opening new avenues of research. For example, recent years have seen considerable progress in genome-wide association studies which examine many common genetic variants in different individuals to see if any variant is associated with a trait. This provides a concrete example of an area in which there is a risk of individual genomic information being misused.

Transnational crime

The international illicit narcotics trade is estimated at $321 billion USD per year. It represents a significant threat to both national and international peace and security. At present, producing large amounts of narcotics requires large amounts of land. This inevitably means that there is a large footprint to detect illicit activities and the products require processing and moving, often long distances, from production sites to the ultimate customers. Both factors provide important points of leverage to detect and interdict prohibited activity.

Synthetic biology has the potential to revolutionize narcotic production and distribution. The metabolic synthesis pathways of relevant compounds, including those from marijuana and certain opioids are known and in the public domain. The metabolic pathway engineering required to produce such active compounds, it can be argued, is no more complex than has already been accomplished for legal drugs. Those potentially motivated to arrange for such research are better resourced than the funders of the original research.

It is unclear at present whether producing such compounds would contravene current laws as in several countries certain narcotics are regulated by the plant which produces them, rather than the active compound. In light of developments in molecular biology, and given the ascent of synthetic biology, it may be necessary to re-examine the taxonomy of compounds our societies decide to control.

In addition, there is a marked trend towards related synthetic products based upon, and related to, the broad range of psychoactive compounds which mimic marijuana, including K2, Spice, Mexxy, Black Mamba, fake weed, Yucatan Fire, Skunk, and Moon Rocks. Some of these synthetic compounds are promoted as herbal products, with labels claiming that they contain "natural" psychoactive materials taken from a variety of plants. Spice products (and the others as well) may contain some dried plant material (not necessarily natural cannabis), but chemical analyses show that their active ingredients are synthetic (or designer) cannabinoid compounds. However, tests have shown that it is not a single product. For example, Black Mamba contains synthetic cannabinoid AM-2001 and oleamide and oleic acid.

As a secondary issue, the potential for synthetic biology to enable, and be enabled by, a distributed production capacity could also impact upon the existing supply chains for illegal narcotics. For example, an engineered-yeast capable of producing such narcotics would offer a very different footprint to agricultural or chemical production approaches. It may even lend itself to relocating production closer to the end user, diminishing the need for illicit trafficking of bulk material, thereby complicating interdiction.

Data security as synthetic biology and other research areas converge and rely on Big Data sets

Cyber attacks have been attributed to nation states, organized crime, and many non-affiliated individuals. Prime targets have been the finance and retail sectors purely for financial gain. Security performance of these sectors has improved markedly because of the effect on the bottom line. There is a trend in moving to softer targets such as the health and academic sectors. Each stolen health credential fetch 10 to 20 times more than a stolen credit card number.[21] Student financial information is certainly the primary reason for cyber attacks on academic institutions, but they are also a wealth of intellectual property and proprietary information. It is said that an attack of one institution could have a domino effect on many others including government research facilities because of the interconnectiveness and the need for collaboration.[22]

The environment and biodiversity

The potential benefits of synthetic biology for biodiversity and the environment are already being debated. Conservationists, are to some extent, keeping an open mind. For example, synthetic biology could prove important in reviving species that are close to, or which have become, extinct. [23,24] Synthetic biology could, potentially, add to the current biosiversity.

The relationship between synthetic biology and efforts to ensure equitable access to the benefits of biodiversity may be less positive. Initial reflections, by vocal members of the community involved with the Convention on Biological Diversity see synthetic biology as a problem. Some of these concerns relate to the relationship between contained use and risks of accidental release discussed in the first sections of this paper. There is potential for the relationship to change again with the completion of the negotiation of the Ngoya protocol. This new instrument creates a legally-binding international framework for equitable benefit sharing from the transfer of biological material. Given the data driven nature of modern biology, and the potential for synthetic biology to drive the movement of such data, the paper-based nature of the licensing system for consent to transfer might be a source for concern.

Conclusion

[21] http://www.reuters.com/article/2014/09/24/us-cybersecurity-hospitals-idUSKCN0HJ21I20140924
[22] http://www.cnbc.com/id/101934801#.
[23] http://www.sciencedaily.com/releases/2013/04/130402182502.htm
[24] http://www.plosbiology.org/article/info%3Adoi%2F10.1371%2Fjournal.pbio.1001530

While advanced research presented challenges, it is also necessary to support the development of countermeasures and mitigation strategies. It is important to align security goals with new research and innovation models. Emerging bioeconomy policy drivers must align with security.

Perhaps redefining security is needed through the integration of security measures and prevention/detection capabilities in an inherently open and massively distributed system.

While much of this paper has been devoted to the need to think more innovatively about the security implications of synthetic biology, there is still a need to engage with the more traditional implications outlined at the start of the paper. While these issues have been considered in countries like the UK and the US, there are strong indications that other parts of the world are only now beginning to consider the implications of platforms such as synthetic biology. At the 2014 Meeting of Experts of the Biological Weapons Convention, for example, Pakistan asserted:

> "The recent advances in synthetic biology raise immediate concerns related to ethics, safety and security. In this regard, States should employ the utmost transparency and confidence building measures during all their activities related to synthetic biology. There is also a need for strict regulation on the development of synthetic biology to ensure that it does not lead to any concerns related to safety and security as well as incidents of proliferation that have no justification for prophylactic, protective or other peaceful purposes."

Other emerging economies, such as Brazil, have also becoming increasingly vocal in such international security forums on the correct balance between open science and national security. There is an urgent need for states, like the UK and the US, to show continued leadership in shaping the international security debate around synthetic biology. If attention is, and resources are, not maintained, others will be shaping how these issues are perceived and addressed. This could have significant implications for access to and realization of potential future markets.

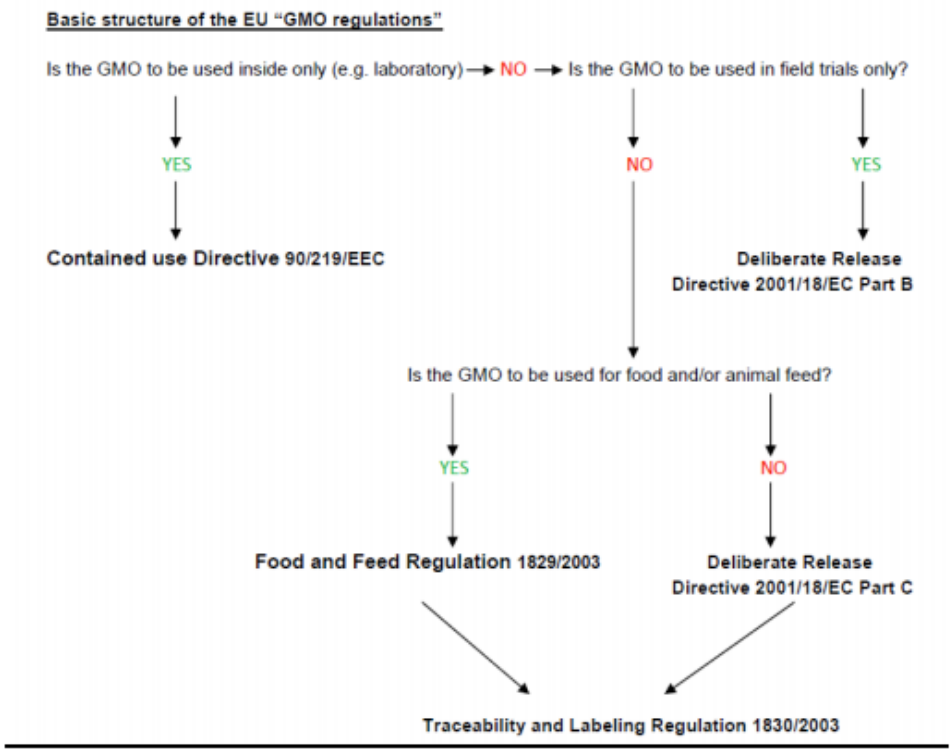
The current biosecurity framework which the end goals at the very least is well agreed upon , remains relevant and impactful because of the physicality of the biological material and technologies. Advanced and emergent technologies, such as synthetic biology, do show that reliance on only the traditional framework is, and absolutely will be in the future, insufficient. Biosecurity is no longer solely minimizing the vulnerabilities of the life sciences. Information technologies, both hardware and software, is more relied upon; collaboration means sending data packets instead of physical material; and life science research is no longer performed solely by life scientists. These factors necessitate the biosecurity framework to be more encompassing and capable to evolve in the near and distant future.

Extracts from: Bar-Yam *et al*, The Regulation of Synthetic Biology: A Guide to United States and European Union Regulations, Rules and Guidelines, SynBERC and iGEM Version 9.1 January 10, 2012[25]

(Reproduced with the permission of the lead author)

Table 5: Analysis of regulatory coverage of safety and environmental risks of synthetic biology.

Risk	International Regulation	US Regulation	EU Regulation
Transfer of genes	Cartagena Protocol on Biosafety	EPA & APHIS	Directive 2001/18/EC
Mutations, evolution and proliferation		EPA	Directive 2001/18/EC
Effects on ecosystem and other species	Cartagena Protocol on Biosafety	EPA & APHIS	Directive 2001/18/EC
Effects on biodiversity	Convention on Biological Diversity, Cartagena Protocol on Biosafety		Directive 2001/18/EC
Consumption risks	`	EPA (only for plant incorporated pesticides)	Regulation 1829/2003
Risks to laboratory workers		NIH Guidelines	Directive 2009/41/EC, Directive 2000/54/EC
Accidental release of laboratory strains		NIH Guidelines	Directive 2009/41/EC



25 http://synberc.org/sites/default/files/Concise%20Guide%20to%20Synbio%20Regulation%20OYE%20Jan%202012_0.pdf

Creating an environment for wealth creation from synthetic biology – the critical role of standards.

Ben Sheridan, BSI & Richard I. Kitney, Imperial College.

1. Wealth creation – driven by manufacturing.

The creation of wealth arising from a new way of manufacturing products is one of the major drivers of investment in synthetic biology. The significant innovations promised by increasing specialisation in design, manufacture, and verification could potentially lead to enhanced economic prosperity for a number of reasons, including:

- Increased productivity of manufacturing processes, leading to products being made more affordable;
- Reduced development costs through the creation of flexible and adaptable processes;
- The use of renewable feedstocks.

Innovation in manufacturing was the primary source of wealth creation arising from the industrial revolution, where populations were liberated from resource constraints and poverty and able to enjoy sustained increases in incomes and prosperity[1]. Innovation in manufacturing systems did not end there, and new ways of enhancing wealth have been developing ever since[2]. Each of these innovations contributes to rises in productivity, either through increased efficiencies in the use of material or time, or responding quickly to changing customer needs. A paper by Griffiths[3] demonstrates how each of these developments critically depended on the emergence of the right standards. For example, the shift from a craft-based system to mass manufacture required interchangeable parts, which requires a significant degree of standardisation. Henry Ford was a major innovator in this regard, and his pioneering of interchangeable parts at the manufacturing stage led to his company revolutionising personal transport, and creating large amounts of wealth at the same time.

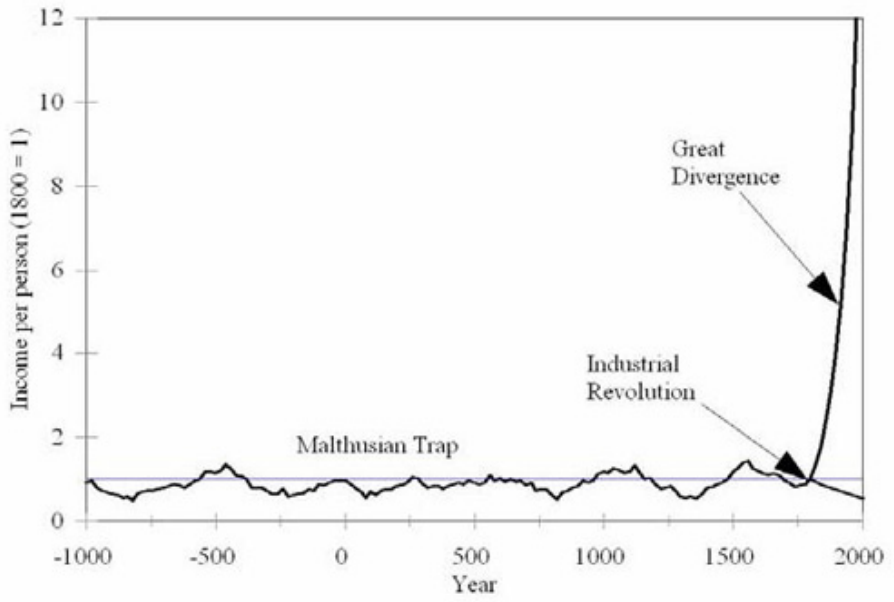


Fig 1. Graph showing average UK income per person from around 1000 BC to the end of the 20th Century[1].

[1] *Farewell to Alms - A Brief Economic History of the World,* Gregory Clark, Princeton University Press (29 Dec 2008).
[2] *Towards a conceptual framework of manufacturing paradigms,* W. G. K. Lee, T. Baines, B. Tjahjono, and R. Greenough, SIMTech technical reports, Volume 7 Number 3 Jul-Sep 2006.
[3] *Manufacturing paradigms: the role of standards in the past, the present and the future paradigm of sustainable manufacturing,* Brian Griffiths, Proc IMechE Part B: J Engineering Manufacture 0(0).

Synthetic Biology has been selected by the UK Government as one of the '8 Great Technologies'[4] identified as being sources of significant wealth creation, and where the UK stands to benefit. Synthetic Biology, developed in parallel with Big Data and Robotics and Autonomous Systems (two more of the 8 Great Technologies) offers great potential in this regard. This paper suggests that without the timely development of the right standards, the wealth creation promised by synthetic biology will not happen, and the investments made to date will go to waste. If we are to attract further investment in the technology, then the appropriate standards infrastructure needs to be in place as a matter of urgency. We also suggest a model that can deliver this infrastructure in a timely and effective way.

2. Synthetic Biology and Manufacturing.

The major impact of synthetic biology will be felt through the creation of new manufacturing industries, enabling products to be brought to market more quickly, and in greater number, than ever before. The specialisms that are emerging will manifest themselves through the adoption of digital capabilities, and will further enable the emergence of biological Computer Aided Design, Computer Aided Manufacture, and Computer Aided Verification.

The emergence of these disciplines will enable the development of autonomous and automated manufacturing processes that use digital biological information. To achieve this, the following technological developments need to be met:

- 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.

Biological processes are notoriously difficult to reproduce[5], and random perturbations introduced through human interventions are a major factor in this. Indeed in industries such as medicinal products, regulatory approval depends critically on being able to demonstrate reproducible manufacturing processes, and failure to do so will result in regulators rejecting market authorisation applications. The commercial success of synthetic biology, therefore requires the development of automated and autonomous capabilities that remove humans from the process as much as possible. The standards and metrology actions that will need to take place to enable these developments include:

- Standards to enable the digital description of genes, proteins, and cells;
- Systematic design guides;
- Standards to enable flow of digital biological information between machines;
- Metrology that enables repeatable processes to be developed;
- Metrology to enable design verification of models;
- Metrology to underpin machine learning and feedback mechanisms.

The timing of these developments is important, and will be critical in driving the success of investments in synthetic biology. Figure 2 is reproduced from a NIST presentation[6]

[4] *Eight Great Technologies,* David Willetts, published by the Policy Exchange - http://www.policyexchange.org.uk/images/publications/eight%20great%20technologies.pdf

[5] *Drug development: Raise standards for preclinical cancer research*, C. Glenn Begley & Lee M. Ellis, Nature **483**, 531–533 (29 March 2012).

[6] The NIST 2010 Strategic Plan Version 1B June 2004 http://www.nist.gov/director/planning/upload/nist2010_plan.pdf

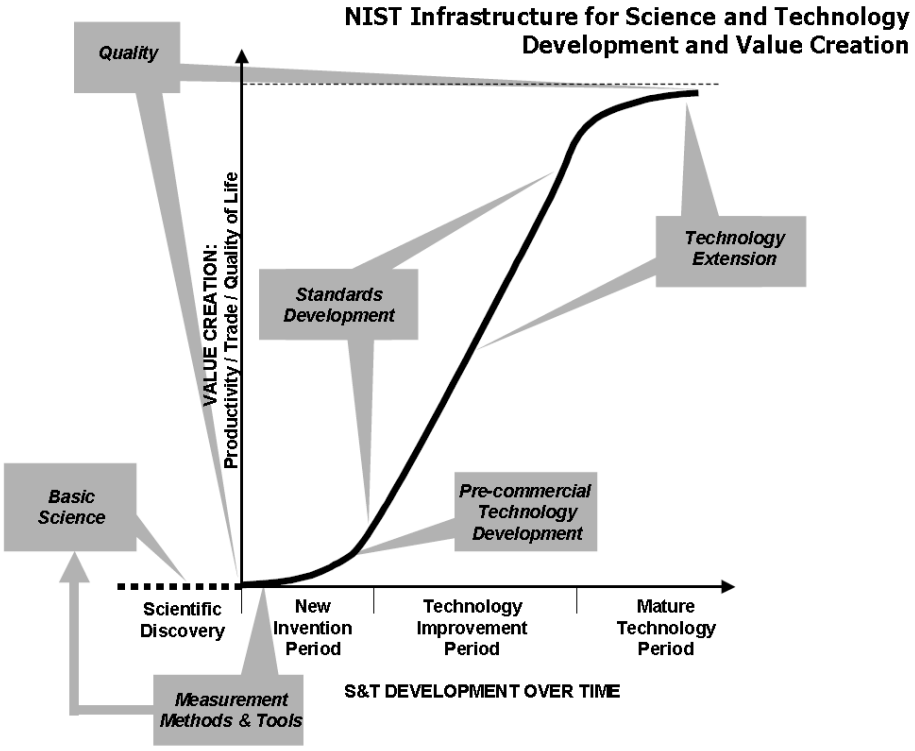


Fig 2. NIST demonstration of role of standards in driving productivity of an emerging technology towards a high quality, wealth creating position.

This shows that without the development of the right standards, the technology will not be translated into a mature and highly productive manufacturing capability and thus will not lead to successful economic outcomes. The appropriate standards and metrology infrastructure is an essential pre-requisite for successful investments in any emerging technology. In the case of synthetic biology, the technology is developing rapidly, and the standards infrastructure needs to be put into place that delivers new and revised standards at a rate that reflects the quickly evolving nature of the technology.

3. A proposal – rapid international development and adoption.

The successful deployment of synthetic biology as a source of significant wealth creation depends on the technology evolving into a manufacturing capability delivering reproducible processes to a high level of quality. The development and adoption of the standards that will deliver this will accelerate innovation and increase the probability of a return on investments in this area.

We therefore propose that an international standards development effort takes place to develop these standards, achieve their acceptance by the international community, and drive their adoption. At the core of these development, acceptance, and adoption activities must be the stakeholders that form the international synthetic biology community. The standards developments must form part of their existing day-to-day collaborations, and be integral in driving their success. The standards must also be revised at the same rate as the technology evolves, so that they remain relevant and valuable.

The major synthetic biology collaborations in both the UK and the US therefore need to partner with organisations such as BSI, and collaborate on quickly developing one set of standards that can be accepted and adopted internationally. We propose that BSI joins forces with UK stakeholders and wider international collaborators, and works with them to deliver this vision for standards. The standards need to be acceptable internationally, and participation in their development would reflect this.

Foundations for Metrology in Synthetic Biology

Sarah A. Munro, Matthew S. Munson, Marc Salit
National Institute of Standards and Technology

Despite billions invested in a commercial ecosystem ranging from startups to well-established publicly held companies, success has been slow and costly. Synthetic Biology will fulfill its potential as a manufacturing technology and a commercial force when it can be engineered in a reliable, scalable, systematic way – metrology is needed to make this possible. Metrology – the systematic science of establishing traceability, estimating measurement uncertainty, and validating methods – will enable engineered biology to define and shape the 21st century just as the semiconductor electronics industry shaped the 20th century. This task is formidable; new challenges are posed by the intrinsic complexity, nonlinearity, diversity, and evolutionary capacity of biological systems.

In 2014, there are successful organizations using systematic approaches to engineer biology, but most are self-contained ecosystems. While each may be a distinct and vibrant terrarium, there is no permeability and exchange amongst the terraria. A vibrant bioeconomy will be a jungle. What interfaces will enable distribution of labor? What metrology products – 'standards' and etalons – minimize the friction at the interfaces? With metrology in place and confident, comparable measurement results at hand, what must be learned to forward-engineer biological systems?

NIST have taken initial steps by convening a stakeholder workshop (July 12, 2013 in London, UK, co-hosted by the National Academy of Sciences, BioBricks Foundation, and Imperial College) to begin development of a *Metrology Roadmap* for the SB Industry, intended to explicitly outline industry capabilities, standards, and technology development[1]. The top priorities identified from that workshop are:

- Measurement technology and method development for high-throughput single-cell analysis
- DNA fabrication standards to provide metrics beyond cost per base
- Standards for comparing performance of engineered biological systems

Figure 1 presents a more comprehensive set of example metrology products and the roles they might play in the SB enterprise. Development of these metrology products will best be done in partnership with the stakeholders who need them.

A Synthetic Biology Standards Consortium, as called for in a 2012 LEAP White Paper[2], is being convened for this purpose. This consortium will act as a standards development organization, providing safe harbor for collaborative work. Figure 2 is a concept diagram of such a consortium. Candidate working group topics include:

- DNA Synthesis Quality
- Strain Performance
- *In vivo* and *In vitro* Test Systems
- Fluidics Interoperability
- Protocol Exchange
- Analytical Metrology
- DNA Watermarking
- …

Informal stakeholder outreach is underway to establish this consortium and an open, public meeting will be convened in Q2 2015 at Stanford University.

Success in this work is critical for SB to fulfill its potential as an engine for value creation.

[1] NIST-ABMS Workshop to Develop a Metrology Roadmap for Synthetic Biology, July 13, 2013, https://sites.stanford.edu/abms/sites/default/files/ABMS_Workshop_Report_Final.pdf
[2] Galdzicki, M., Munro, S., Boyle, P., and Ubersax, J. "A Vision for a Synthetic Biology Standards Consortium", Version 2: March 18, 2013. http://synbioleap.org/wp-content/uploads/2013/05/a-vision-for-a-synthetic-biology-standards-consortium.pdf

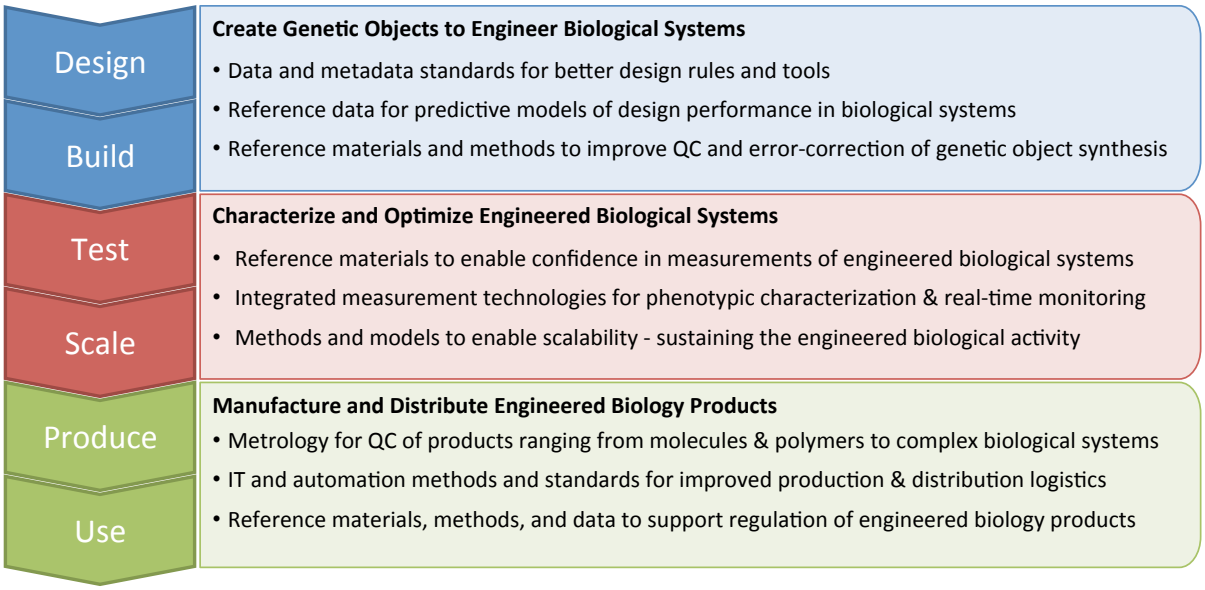


Figure 1. Examples of metrology products and how they might support the SB ecosystem

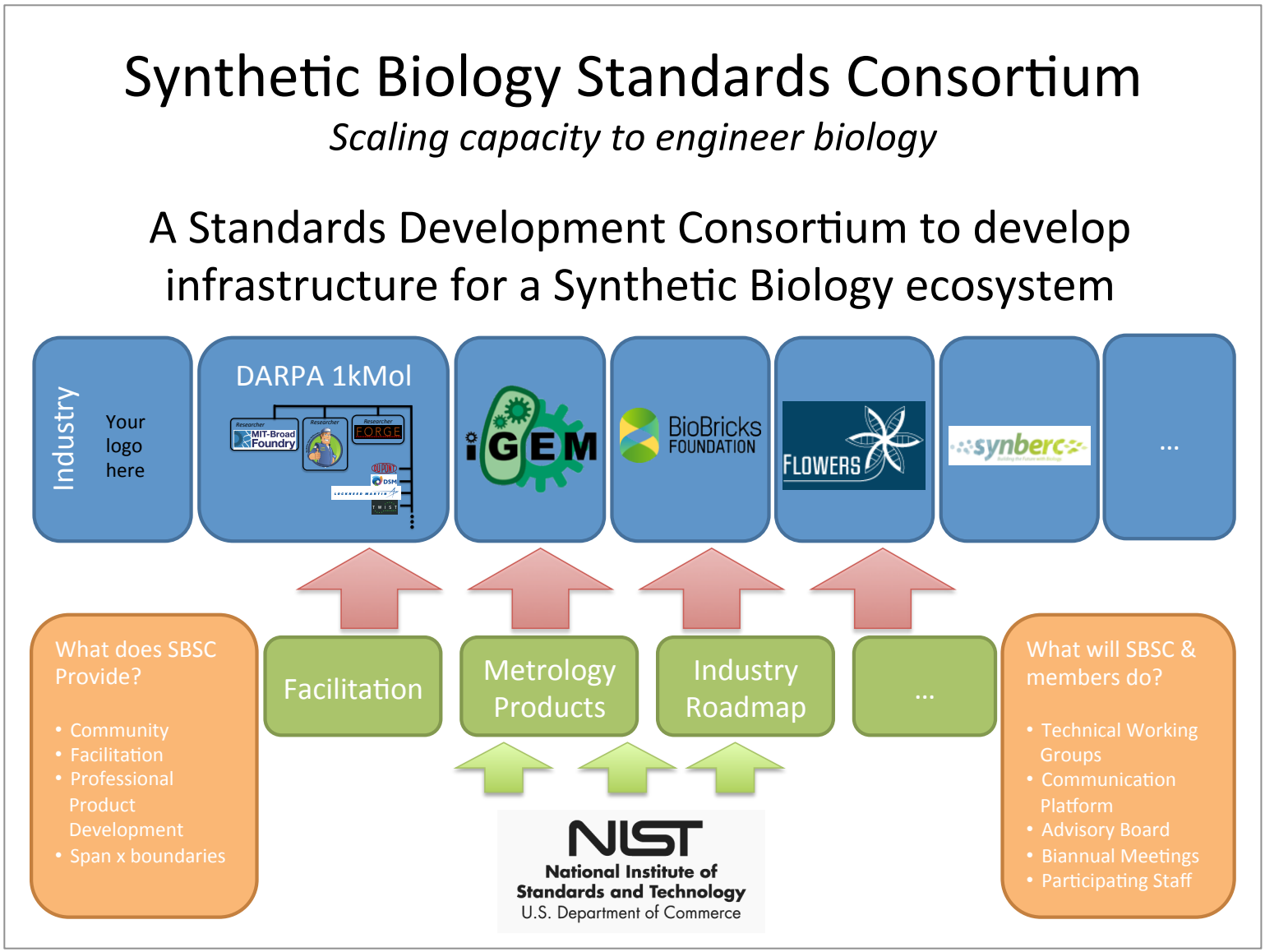


Figure 2. The concept for a Synthetic Biology Standards Consortium