S&T REVIEWS

Synthetic Biology & the BWC

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In preparation for the forthcoming Seventh Review Conference of the Biological and Toxin Weapons Convention (BWC), the Harvard Sussex Program has produced a series of papers considering developments in science and technology of relevance to the Convention. This paper assesses developments in synthetic biology.

What is Synthetic Biology?

Synthetic biology is an emerging field combining biology with engineering but lacks a coherent and agreed definition. For some commentators, synthetic biology reflects an "explosion in our ability to genetically engineer increasingly complex systems"[1] through a bottom-up approach; for others, the term synthetic biology does not have any meaning at all, or should be understood as actually referring to synthetic biotechnology. Synthetic biology is perhaps best understood in relation to its aims, which are described by the OECD as being "to design and build new biological parts and systems or to modify existing ones to carry out novel tasks".[2]

What are the potential applications?

Synthetic biology has been lauded as a technology-based response to a range of societal challenges. For example, the US Department of Energy has stated that the successful application of synthetic biology will replace a third of U.S. transport fuel usage by 2030 and increase ethanol production capacity 12-fold to 60 billion gallons by 2030.[3]

Synthetic biology has *potential applications* in a number of areas, including:

Synthetic biology aims to design and build new biological parts and systems or to modify existing ones.

There are a number of potential applications in the fields of health, energy, environment and food.

However it remains complex and costly with limited concrete commercial applications developments to date.

Synthetic biology has implications for Articles I, III, IV, VI, VII and X of the BWC.

- **Health** including enhanced drug production and delivery;
- **Energy** including the development of new pathways for producing fuel;
- **Environment** including engineered dispersants and environmentally friendly materials;
- **Food and Agriculture** including engineered or optimised crops; and
- **New materials** including systems to produce proteins of industrial interest, for example silks.[4]

Whilst there has been some progress particularly in relation to energy and health applications, the promise of synthetic biology in many areas has yet to come to fruition. Progress thus far has been hampered by the complex, costly and time-consuming nature of research and development.

Overview of activities up to 2006

By 2006, the field of synthetic biology was beginning to take off. For example, publications incorporating the term synthetic biology started to rise in number from 2004 onwards, as shown in Figure 1 overleaf.[5]

1 Editorial (2009) "Synthetic Biology: What's in a name?", Nature Biotechnology 27(12), 1071 – 1073.

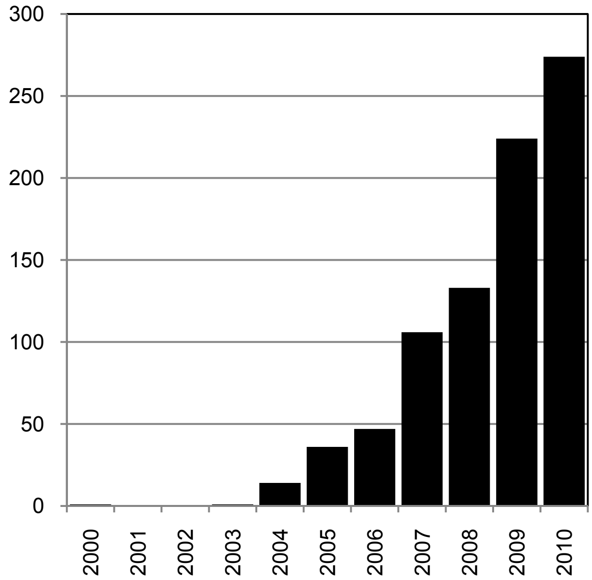
2 Secretary-General of the OECD (2010) "Synthesis Report", Symposium on Opportunities and Challenges in the Emerging Field of Synthetic Biology, OECD & the Royal Society.

3 Suppan. S (2007) "Patents: Taken for Granted in Plans for a Global Biofuels Market", Institute for Agriculture and Trade Policy, October 2007.

4 The Royal Society (2008) "Synthetic Biology", Scientific discussion meeting held on 2-3 July 2008, Summary report August 2008.

5 Bibliometric data was obtained from ISI Web of Science, the world's leading citation database with multidisciplinary coverage of over 10,000 high-impact journals in the sciences, social sciences, and arts and humanities, from 76 countries.

Figure 1: Publications by year containing the term 'synthetic biology' as recorded in ISI Web of Science.[6]



Major funding followed a similar timeline and trajectory, with significant funding for synthetic biology beginning in the past decade. The European Commission, for example, launched the Pathfinder initiative on synthetic biology in December 2003, likewise a significant US funding initiative began in 2005.[7] A search of the World Intellectual Property Organisation[8] for the term 'synthetic biology' revealed no results prior to 2006. It is important to note however, that patent data only reflects one aspect of commercial activity, and there is a tendency towards open access.

Whilst these trends suggest that synthetic biology was in its infancy over the course of the first BWC intersessional process (2003-2006), there were a number of developments. Prominent examples include:

- The construction of the first synthetic virus in 2002, "solely by following instructions from a written sequence";[9]
- the construction of the bacteriophage phiX174 from scratch "in just two weeks" in 2003;[10] and
- The reconstruction of the 1918 influenza virus in 2005.

These experiments drew media and policy attention and raised concerns about the potential misuse of synthetic biology. However, the headlines understated the complexity and sophistication of these projects. The 2002 construction of polio virus was contingent upon highly specialised knowledge and equipment. Similarly, the two-week claim in relation to the work in phiX174, whilst technically correct, masked that it was the result of work that began years earlier.[11]

Developments since 2006

Since 2006 synthetic biology has received considerable amounts of funding. Reports from 2010 indicate the US spent around $430 million on research related to synthetic biology since 2005 whilst the Netherlands, United Kingdom, and Germany spent approximately $160 million during the same period.[12] In addition to funding, there has been a continued increase in the number of publications, many of which have been trans-nationally co-authored and originate from research institutes primarily in three clusters located in North America, Europe and South East Asia. This clustering and the transnational nature of collaborations are illustrated in Figure 2 overleaf. Countries in which papers have been authored over the last decade are shaded, instances of authorship that have occurred between 2006-2010 are represented by nodes – the size of which is proportional to the number of instances - and international co-authorship is shown by the connecting lines.[13]

6 Searches were conducted as "topic search" (which thus covers title, keyword and abstract) in the ISI Web of Science using only the term "synthetic biology". It is not a definitive assessment of synthetic biology related publications, but provides an illustrative snapshot.

7 Synthetic Biology Project (2010) "Trends in Synthetic Biology Research Funding in the United States and Europe", Research Brief 1, June 2010.

8 The World Intellectual Property Office (WIPO) is a specialised UN agency, providing, *inter alia*, a searchable patent database (Patentscope®) which encompasses patent filing data from 184 countries, including the US, European and Japanese Patent Offices, containing over 7.7million patent documents. Front page searches were conducted which cover the front page data fields of patent documents, thus identifying the focus of the patent as contained within the abstract and title, rather than secondary data embedded in the document, e.g. background.

9 Cello, J & others (2002) "Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template", Science, 297(5583), 1016-8.

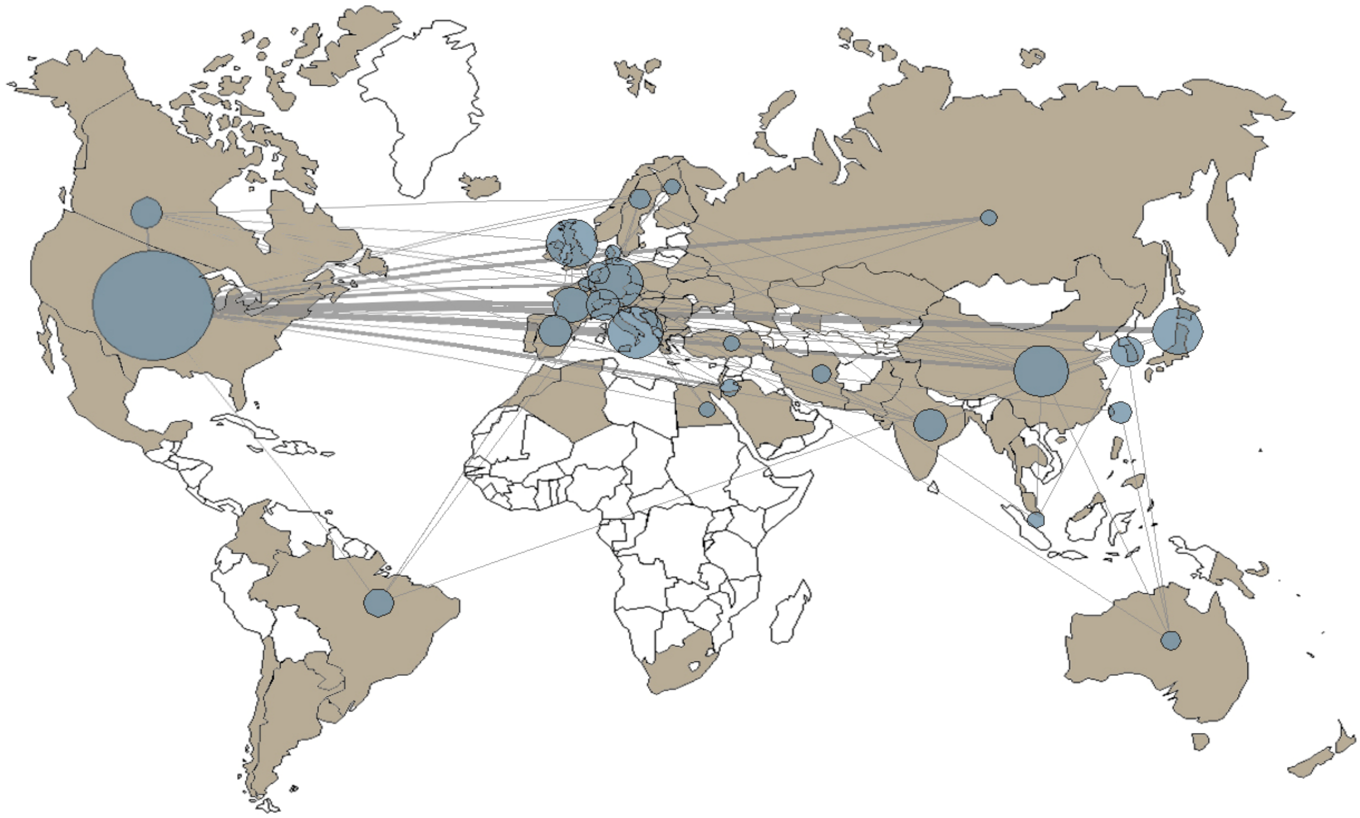
10 Smith, HO & others (2003) "Generating a synthetic genome by whole genome assembly: phi (variant)X174 bacteriophage from synthetic oligonucleotides", Proceedings of the National Academy of Sciences, 100(26), 15440-15445.

11 See for example: Dispatches (2003) "Scientists build virus in just 2 weeks", The Guardian (London), 20th November; and Ouagrham-Gormley, SB & Vogel KM (2010) "The Social Context Shaping Bioweapons (Non)proliferation", Biosecurity and Bioterrorism, 8(1), 9-24.

12 Synthetic Biology Project (2010) "Trends in Synthetic Biology Research Funding in the United States and Europe", Research Brief 1, June 2010.

13 Data is sourced from ISI Web of Science which covers 10,000 high impact journals from 76 countries.

Figure 2: Global distribution and patterns of collaborations of publications on synthetic biology. (Source: ISI Web of Science)



A small number of synthetic biology applications have also started to emerge. For example, in a collaboration between NGOs, scientists and industry, synthetic biology techniques were used to produce an anti-malarial drug (Artemisinin) in yeast.[14] A number of companies have also used synthetic biology in the production of fuel through inter alia, bacterial or algae-based production methods.[15] Furthermore, since 2006 explicit references to synthetic biology can be found on the front page of patent applications.

Progress however remains incremental rather than radical, and the engineering of biological systems with predictable behaviour continues to be a challenging problem. This challenge is exemplified by the Artemisinin project mentioned above. This 5-year, $20 million experiment spent “95% of its time trying to find and fix unintended interactions between parts”.[16]

It is difficult to predict the future potential impact of synthetic biology. Research is likely to be facilitated by reduced costs and increased speeds of DNA synthesis, and the commercial availability of bespoke biological materials (e.g. peptides and oligonucleotides). Already the next generation of life scientists is embracing synthetic biology tools and techniques, illustrated by the increased attendance at the *International Genetically Engineered Machine* (iGEM) competition.[17] If this emerging generation of scientists achieve the development of fully interoperable, standardised biological parts and simplify the process of putting bits together, as envisaged in the Biobricks registry, then synthetic biology might achieve its paradigm-shifting potential.

Synthetic biology, as well as trends in synthetic DNA manufacture and distribution should be monitored carefully over the coming decades. However, in the near future the potential for hostile use of synthetic biology is likely to be beyond the reaches of non-state actors and responses should be proportional to the reality of current scientific capabilities.

14 See for example: Dietrich, JA & others (2009) “A Novel Semi-biosynthetic Route for Artemisinin Production Using Engineered Substrate-Promiscuous $P450_{BM3}$”, ACS Chemical Biology, 4(4), 261-267.

15 See: The Royal Society (2008) “Sustainable biofuels: prospects and challenges” Policy document 01/08, January.

16 Henkel, J & Maurer, M (2010) “The economics of synthetic biology”, Molecular Systems Biology, 3(117), online publication.

17 iGEM website “About the International Genetically Engineered Machine competition (iGEM)”, http://ung.igem.org, accessed February 2011.

Relevance to the BWC

Article I	Article I states that all agents and toxins are covered, regardless of "origin or method of production". Accordingly, changes in the means of producing biological weapons are already explicitly covered by the Convention.
Article III	The potential to synthesise pathogens or their components from written DNA sequences makes control of electronic data and private sector DNA synthesis companies more important. Thus it may be useful to consider how the synthesis of DNA fragments and other biological parts can be most effectively regulated. However, the potential benefits of synthetic biology dictate that export controls must be proportional and should not hamper peaceful co-operation or collaborative research between scientists.
Article IV	Existing national legislation and regulations should cover the misapplication of synthetic biology. However, additional consideration of how these measures are enforced and promulgated to the scientific community, including the DNA synthesis industry, may be needed to ensure that the provisions of Article IV are being fully realised.
Article VI	Synthetic biology could support the development of validated bio forensic measures suitable for use to investigate biological incidents, for example to determine the sources of engineered pathogen strains.
Article VII	Although the current applications of synthetic biology remain limited, advances could increase the relevance of synthetic biology in the future: through, for example, enhancing the identification of drug candidates, as well as drug production and delivery.
Article X	There is evidence of international co-authorship in synthetic biology (Figure 2), which is important in the implementation of Article X. This will contribute to the application of science in addressing global needs. However, this is neither new nor unique to synthetic biology and reflects a broader trend of transnational research co-operation in the life sciences.

Synthetic biology is clearly relevant to the BWC. However, although the science has continued to evolve, there have been no entirely new developments in synthetic biology since the last Review Conference in 2006 that significantly affect the provisions of the Convention.

Even without major breakthroughs, such as the development of interoperable, standardised biological parts that can be easily assembled, synthetic biology has implications for the operation of the BWC, in particular in relation to Articles I, III, IV, VI, VII and X, as shown in the table on the left.

Recommendations

Trends in synthetic biology and the production of synthetic DNA fragments warrant further attention in future discussions of the BWC and some additional measures may be required. Such discussions must first recognise that assembling fragments and successfully applying synthetic biological techniques requires a special set of skills as well as equipment and second that synthetic biology has a number of potential positive applications in relation to the BWC including in enhancing abilities to investigate biological incidents and facilitating the delivery of assistance. In this regard, just as it would be inappropriate to dismiss the idea of synthetic biology being used for hostile purposes by state or non-state actors over the coming decades, it would be equally remiss to fixate on synthetic biology given the wide range and availability of natural biological agents and toxins.

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For more information about the project visit http://hsp.sussex.ac.uk/sandtreviews/

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