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Review

Synthetic biology – the state of play

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ABSTRACT

Just over two years ago there was an article in Nature entitled "Five Hard Truths for Synthetic Biology". Since then, the field has moved on considerably. A number of economic commentators have shown that synthetic biology very significant industrial potential. This paper addresses key issues in relation to the state of play regarding synthetic biology. It first considers the current background to synthetic biology, whether it is a legitimate field and how it relates to foundational biological sciences. The fact that synthetic biology is a translational field is discussed and placed in the context of the industrial translation process. An important aspect of synthetic biology is platform technology, this topic is also discussed in some detail. Finally, examples of application areas are described.

It is now just over two years since the article 5 Hard Truths for Synthetic biology was published [1]. The article looked at some of the issues relating to synthetic biology at that time. As we will show, many things have changed in the interim period. Two years ago there was still considerable doubt about whether or not synthetic biology was likely to have significant industrial impact. It is now pretty clear that the case has been made and that synthetic biology will have very significant impact in a range of fields – leading to the development of new, major industries. The evidence for this statement can be found in a number of sources. For example the bcc report [2] which predicts that:

- The global value of the synthetic biology market reached $1.1 billion in 2010. It is expected to reach $1.6 billion in 2011 and it will further grow to $10.8 billion by 2016, increasing at a compound annual growth rate (CAGR) of 45.8.%.
- The global value of the enabled products segment reached $944.7 million in 2010. It is expected to reach $1.4 billion in 2011 and will further grow to nearly $9.5 billion by 2016 at a CAGR of 46.5%.
- The global value of the core products segment reached $109.4 million in 2010. It is expected to reach $126.8 million in 2011 and to grow to $698.8 million by 2016 at a CAGR of 40.7%.

There is, in some quarters, still doubt about the definition of synthetic biology. This is not a view held by the international synthetic biology community. (The community can be defined as people who attend the major international "SB X.0" [3] conferences and regularly organise teams for the International Genetically Engineered Machine Competition (iGEM) [4] – a prestigious student competition involving many of the world's leading universities.) The accepted definition is "synthetic biology aims to design and engineer biologically based parts, novel devices and systems – as well as redesigning existing, natural biological systems". Synthetic Biology is the application of systematic design – using engineering principles. In addition, whilst much has changed in synthetic biology over the last two or three years, much of the content of reports published at that time are still valid, e.g. the Tessy Report [5] and that of the UK's Royal Academy of Engineering [6].

1. The arguments against the synthetic biology approach

In simple terms synthetic biology aims to make the engineering of biological systems easier and more predictable. It also aims to allow accumulated knowledge on biological systems to be standardised to enable its utility in the synthetic biology design process. It is often argued that biological systems cannot be considered as engineers consider computer mother boards or other electronic devices, and, consequently, the concepts applied to these engineering disciplines are therefore not applicable in biology. This may be true at a simple practical level, but conceptually and strategically there

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are many areas of commonality. In fact synthetic biology is based on the engineering tenets of modularity, standardisation and characterisation [7,8]. The issue with context dependence in biological systems and the interaction between newly designed genetic circuits and the host organisms are, legitimate concerns. However, an important objective of synthetic biology is to constrain biological systems by controlling complexity through either the design of orthogonal genetic circuits that do not interact with the host system or by using biological processes like directed evolution to optimise the function of new designed circuits. As we begin to fully understand the function of single cells at a systems level through experimental and mathematical modelling, (which is the aim of systems biology), then our ability to predictably intervene in such systems will be significantly increased. It is important to note that similar situations exist in other fields of engineering. One example is semiconductors (e.g. transistors). Semiconductor physicists and engineers have worked for many years to constrain semiconductors to operate according to human designs.

Another major critique to the engineering of biology using synthetic biology approaches is in the nature of living cells. Cells are constrained volumes of highly concentrated chemical entities. Both macromolecules and small molecules freely diffuse and/or are actively distributed within a complex three-dimensional matrix that constitutes the cell. The self-assembly of cellular components and stochastic behaviour of living systems provide significant challenges for synthetic biologists. However, living cells utilise many regulatory elements in their decision-making processes – using, for example, genetic switches and logic like inverters, toggle switches, pulse generators and biphasic switches [9]. They also use sensors like small molecule inducers to activate transcription of specific genes or environmental sensors like light also to active gene networks or cell-cell communications systems that signal between cells again resulting in a transcriptional response. Cells are thus exquisitely evolved to sense and adapt to their living environments and have genetic circuits that encode these functions, which synthetic biologists are now adapting for different applications. One aim of synthetic biology is define these genetic modules as functional devices, which can be used in a design process to create more complex responses or functions. This has been defined as harnessing 'natures toolbox' [10], which with the expanding metagenome is an exciting prospect for synthetic biologists. An estimate from existing genome information suggests ~5 to 6 million open reading frames (including redundancy) not including genetic regulator elements, and it is likely that this number will increase. It is also interesting to consider naturally occurring DNA encoded functional modules like bacterial operonswhere biological context and complexity have been already encoded within the DNA sequence through evolution. The challenge here is to correctly interface such modules, which again requires a systematic and cyclical approach.

Another argument against the design of biological systems is robustness. As cells are highly adapted and exist to replicate, evolve and/or perform specific functions, for example in multicellular organisms, they have mechanisms which protect them from the addition of genetic material that would perturb their viability. For example, bacteria utilise the host restriction modification system where foreign DNA (e.g. form bacteriophage or viruses) is rapidly degraded by bacterial encoded enzymes. Moreover, molecular biologists have long discovered the random accumulation of mutations in certain cloned plasmids, the products of which are toxic to the cell during the cloning process and thus are mutated by the host cell. For synthetic biologists these pose significant challenges in that the robustness and functionality of designed synthetic biological circuits could be compromised over time by the natural host system. Thus one aim of synthetic biology is to define host cells that are tolerant to synthetic biology designs either by minimising their natural systems or by defining areas of the host genome or even insulated cellular compartments which would incorporate new genetic material with minimal host effects. These areas could be thought of as 'islands of robustness' and although the designed functions of the new synthetic biology circuits will have a causative effect on the hosts tolerance, the use of natural biological mechanisms to direct rapid evolution and/or selection will enable the establishment of more robust systems. This also extends to the metabolism of the host system, as any complex synthetic biology circuit e.g. multi-step biosynthetic pathway will create a burden on the hosts metabolic processes. This metabolic loading will also induce stress responses that will again impinge upon the robustness of the newly designed circuits. Here synthetic biology solutions will include the rewiring of the hosts transcriptional networks to select optimised hosts for the particular biosynthetic pathways combined with dynamic metabolic flux modelling to optimise the regulatory elements of the newly design pathway. As synthetic biology involves a systematic engineering approach, what is learned from these procedures will be fully characterised and therefore available to other researchers. As we learn more about rewiring host cells for synthetic biology design, including dynamic regulatory models of such processes, we will ultimately be able to carry out in silico design with a more predictable outcome when implemented in vivo.

So what is the situation regarding synthetic biology today? The first point to make is that many groups around the world are now taking a professional engineering approach to synthetic biology. This is important because one key endpoint of synthetic biology is industrialisation. (This is not the only endpoint; synthetic biology will also have a significant impact on the fundamental understanding of biological systems, particularly in relation to systems biology.)

2. Synthetic biology industry and foundational science

Even though there is a clear definition of synthetic biology which most people in the field accept, there is still quite a high degree of misunderstanding about the true nature of the field. A clear distinction must be made between various fields in life science (which, in the context of synthetic biology, can be considered to be foundational science) and synthetic biology itself. A helpful example is the distinction between physics and engineering – where physics, in this context, is foundational science for engineering. Referring to Fig. 1, the right side of the diagram shows the main fields of pure and applied science which contribute (in a foundational sense) to synthetic biology. The left side of the diagram illustrates what comprises synthetic biology and how it relates to industrialisation. Referring to this side of the figure, three inputs to synthetic biology are defined: the academic base, Bio-knowledge and foundational science. The academic base refers to two things, (a) the basic infrastructure of research-led universities, and (b) teaching and educational programmes relating to synthetic biology. There are now a number of leading universities that are teaching specialist courses in synthetic biology. If the assumption that synthetic biology will be the source of a range of new industries and new approaches for existing industry is correct, then a specially trained workforce will be required to meet these needs. This problem has already been identified, which is why there are now a number of university courses in the area of synthetic biology.

The section of the diagram that refers to Bio-knowledge relates to three areas: techniques and methodologies which can be applied to synthetic biology, background knowledge and naturally occurring systems.

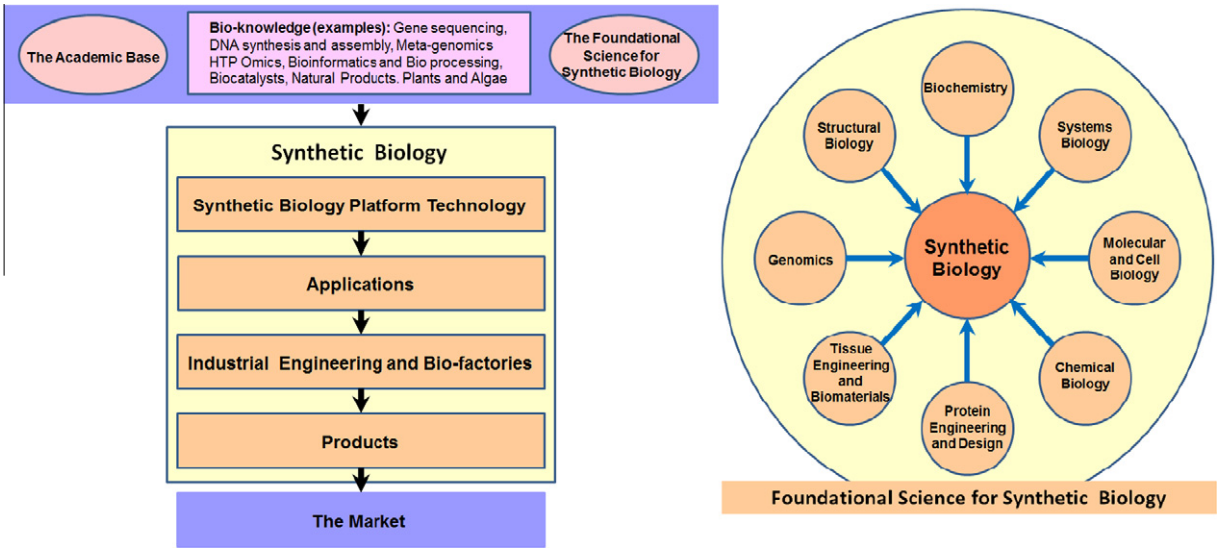

Fig. 1. Synthetic biology.

2.1. Techniques and methodologies

Many of the methods and techniques which are used in synthetic biology are derived from other fields – this applies to both the life sciences and physical sciences. For example, synthetic biology would not have been possible without fast gene sequencing and reliable DNA synthesis. Other examples are computer modelling and the application of computer aided design (CAD) techniques. (In many cases the methods derived from other fields are customised for synthetic biology.) There is, therefore, a technological base which has been constructed relatively rapidly by drawing on experience from other fields.

2.2. Background knowledge

This is a very interesting aspect of synthetic biology. There are at least two major areas under this heading. The first area is the application of knowledge from foundational science which is directly applicable to synthetic biology. An example of this is synthetic DNA introduced into a given host cell e.g. *E. Coli*. The hosts currently used in synthetic biology have been chosen because a great deal of knowledge has been accumulated about these types of cells which is directly applicable to synthetic biology. The second area relates to the concept of parts (or components), devices and systems. One example of this approach is where a thoroughly researched aspect of a biological system, which has been studied purely to understand the biology, is now seen as being part of a synthetic biology device (often with some modification). (The direct analogy here is the difference between pure and applied mathematics.)

2.3. Naturally occurring systems

This approach is based on the concept that there are naturally occurring biological entities which have interesting properties that can be applied to synthetic biology design. One example relates to reporters (or indicators). Green fluorescent protein (GFP) often forms part of a synthetic biology device to act as a visible indicator of when a particular event has occurred. GFP was originally found in naturally fluorescing jellyfish. Their biology was studied and the protein which caused the fluorescence identified and isolated.

3. Synthetic biology and platform technology

Referring again to Fig. 1, the three components (the academic base, Bio-knowledge and foundational science) are all inputs to the field of synthetic biology. The details of platform technology are covered in the next section, but the term refers to a suite of tools and methods which can be applied across a range of fields. Hence, the platform technology can be applied to a spectrum of application areas. This is primarily a translational process which relates to industrial applications. For this process to be effective, there will be a need to develop new methods of industrial engineering and to modify existing methods. One important example of this is the development of programmable bio-factories – where the cell is considered as a manufacturing unit. For this to be achieved, the host cells used for applications will need to be optimised for particular applications. This may involve developing new strains of existing cells for industrial purposes (e.g. yeast or *E. Coli*) or, in the future, to develop so called minimal cells. Conceptually, in simple terms, a programmable bio-factory can be thought of as being roughly equivalent to a computer controlled machine. The DNA, modified by the synthetic biology design process, is the "software" that drives the host (i.e. the bio-factory) to produce a human-defined product. Here, the DNA comprises a number of components (BioParts) which are interfaced (the DNA of synthetic biology device). When this DNA is introduced into the host it produces the "device". In the industrial context, this process will result in a product [11,12].

Synthetic biology can be thought of as comprising two components: (a) the development of platform technology, and (b) application projects across a range of fields – both with potential impact on systems biology. These will now be considered in turn.

3.1. Platform technology

The term platform technology refers to a suite of tools and methods which can be applied across a range of fields. To understand why this is important it is necessary to consider one of the tenants of synthetic biology, modularity. Here, in common with other fields of engineering, the strategy is that standard systems can be produced from standard devices, which, in turn, are produced from standards parts (or components). In synthetic biology an important element of this process is the development of fully

characterised parts, which sit in a Registry of Parts. Broadly speaking, at present, a part comprises a sequence of DNA, which has certain characteristics. When such a sequence is placed in a host the cell responds by producing the pre-defined function (e.g. the production of a protein to sense a chemical). This process effectively is the translation of the encoded information within the designed DNA sequence. As stated above, the robustness and predictability of the synthetic biology design poses significant challenges. Part of the systematic design approach is to define the behaviour of synthetic biology parts within a particular host such that it is repeatable. This is the process of Characterisation [13]. Hence, associated with the Part's performance are two sets of information – the characterisation data (which defines the Part's behaviour within the host cell) and the data about the experimental and other conditions (the metadata). Both sets of information relate to a particular Part (BioPart) and are stored in a Registry. Currently, a Registry may contain physical sections of DNA; however, in the future (and in some instances this is already the case) the DNA Part sequence will simply be stored electronically. Hence, the Registry comprises a Database.

Currently, there are problems with existing Registries of Parts. For example, in the Registry used for iGEM many of the parts are not fully characterised. Because of these problems, a number of research groups working on characterisation are now working on professional registries of parts – which are fully characterised in the context of the hosts in which they are to be used. The objective is to achieve a situation where a single part [i.e. specific type] can be produced and stored in multiple locations. (This concept has direct equivalence to a particular transistor type being produced by multiple manufacturers.)

The definition and production of standard parts, devices and systems relies on the tools and procedures which comprise the Platform Technology. In terms of parts and devices, this comprises three principal sections: host cells, part characterisation and DNA assembly.

3.1.1. Host cells

As previously stated, the operation of a particular biological part must be seen in the context of a given host. Hence, in synthetic biology the process of device or system design is done in the context of a particular host cell (also know as chassis in synthetic biology). This means having, as far as possible, detailed knowledge of the host cells. For this reason, currently there are a number of cell types that are widely used in synthetic biology – e.g. *Escherichia coli, Saccharomyces cerevisiae and Bacillus subtilis.* Detailed information and data are stored in the Registry and used in relation to a particular part. Specifically, growth characteristics, single cell behaviour versus population cell behaviour, metabolic loading and essential gene analyses will be key aspects of host cell characterisation in synthetic biology.

3.1.2. Part characterisation

In order to follow the principles of systematic design and modularisation, it is essential that the properties of parts and their functional behaviour are extremely well characterised [14]. In accurate part characterisation the objective is to ensure that the process becomes standard – so that the same characterisation data (the data) for a given part can be obtained at multiple, disparate locations when the experimental conditions (defined by the metadata) are reproduced. Accurate characterisation is designed to ensure that parts are compatible (if they are supposed to be compatible), once the interfacing and context dependency problems between parts are resolved. The context dependency of biological systems is a major issue in synthetic biology design and requires part characterisation to be carried out in many different contexts. Again, with a systematic and standardised approach, information on part-host compatibility will be learned such that a standard set of parts with defined functional behaviour within a given host can be established. It is important to note that significant control behaviour within synthetic biology circuit designs can be encoded using a small set of biological parts (e.g. promoters, ribosome binding sequences etc.)

3.1.3. DNA assembly

In synthetic biology design DNA assembly is a key technology since complex DNA-encoded designs will require the assembly of multiple DNA sequences. Moreover, optimisation of functional outcomes will require an ability to randomly reassemble DNA sequences to screen for optimal performance (e.g. the yield of a biosynthetic product). A number of ways have now been developed to achieve effective DNA assembly [15]. However, it should be pointed out that in many cases in synthetic biology commercial gene synthesis companies are used for this purpose – examples are Blue Heron, DNA 2.0 and GeneArt (now owned by Life Technologies). DNA assembly methods can be broken down into two main of categories: Part assembly (sequential and ordered) and Gene to Pathway (parallel-ordered and combinatorial, i.e. parallel assembly). In all cases the aim is to achieve assembly through robust, automated assembly methods. Details of specific assembly methods are beyond the scope of this article; however, two of the most commonly used methods are BioBricks (or standard assembly) and Gibson [16].

4. Synthetic biology is not Plug and Play

The design and construction of a biological device in synthetic biology comprises in conceptual terms, building a device from an assembly of standard parts. Such a statement often leads to misunderstandings in which the concept of building standard devices from standard parts is thought of as one of simply plugging standard parts together (i.e. so-called Plug and Play). This is a gross oversimplification of the process; it is not what happens in synthetic biology and, indeed, not what happens in many areas of engineering. Whilst it is true that many engineering devices and systems are built from standard parts and devices, the process of connection usually requires careful consideration. Interfacing is the process of ensuring that if, for example, two standard parts or devices in isolation behave in a well defined manner, that this will still be true when they are combined. Frequently, in engineering, the resolution of interfacing problems requires considerable time and effort – the same is true in synthetic biology. Nevertheless, the power of the approach rests in standardisation and the ability to routinely replicate a device or system using machinery (e.g. robots), this is the key to many industrial processes.

The systematic design approach for the construction a biological device or system will often require the application of the design cycle. This comprises a circle of activity, which consists of specification, design, modelling, construction and testing, and validation. Normally, there are several iterations of the design cycle before the biological device or system performs according to the specification. In synthetic biology there is an additional, important factor which is part of the process, namely, human practise (i.e. ethical, environmental and societal issues) which form part of responsible innovation and design.

5. Integration of the platform technology

The platform technology, which has been described so far – part characterisation, host cells, and DNA assembly are shown in Fig. 2. However, the missing piece, which completes the platform technology, is a web-based information system. SynBIS (synthetic

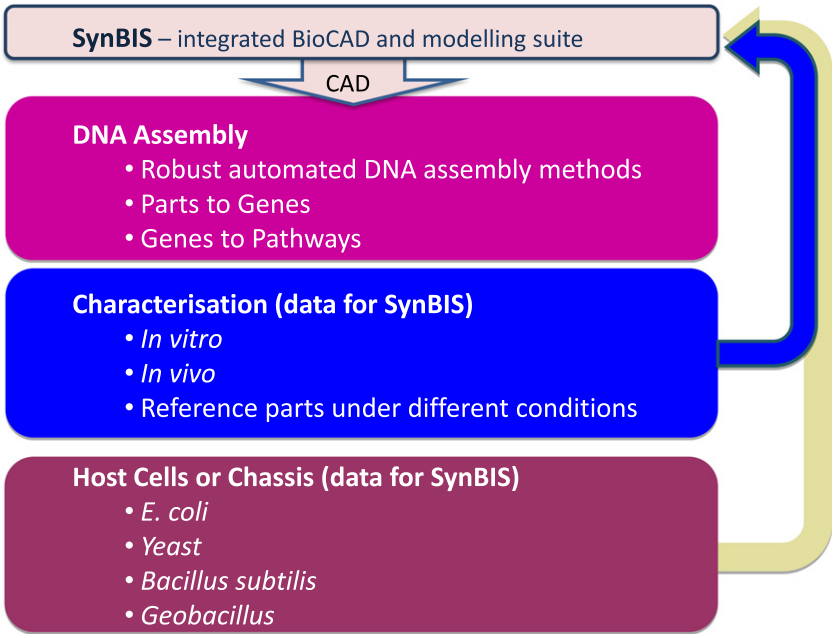

Fig. 2. Platform technology.

biology information system) is an example of such a system [17]. This has the ability to not only incorporate the characterisation, host cells and DNA assembly information, but, also, models and BioCAD tools. SynBIS (when fully completed) has a four layer architecture comprising a web-interface layer, a communication layer, a specialist software layer and an SQL database layer. SynBIS will allow open-source access by the synthetic biology community to a wide range of part data and models.

6. The emergence of BioCAD

The aim is that in the future synthetic biology devices and systems will be designed by designers working with high level computer code. (As synthetic biology circuits are encoded by DNA sequences, there are opportunities to make this process computational.) The term BioCAD or 'Biological Computer Aided Design' has emerged, which encapsulates these efforts. There is a pretty close analogy between this process and computer programming. In software-based design the designer usually works in a high level computer language, such as C++. The code at this level is then automatically translated into an interim level code, called assembler, and finally into machine code. A similar schema is being proposed for synthetic biology in relation to systematic design. Referring to Fig. 3, blockdiagram design is the equivalent to writing in high level computer code. There are already a number of academic and commercial packages which to apply to various blocks of the diagram (e.g. TinkerCell [18], Gene Designer [19], Clotho [20] and GenoCAD [21]). In the near future these and other software packages for synthetic biology design will be integrated into information environments such as SynBIS.

7. The need for standards in synthetic biology

As mentioned earlier, systematic design in synthetic biology uses the engineering principles of modularity, characterisation and standardisation. If synthetic biology devices and systems are to be accurately reproduced, they must be standardised. It is somewhat surprising that in molecular biology and biological sciences, in general, there are few standards. This also includes biotechnology, and although there are standard protocols (for example cloning, protein expression, DNA sequencing), there are no standards in terms of engineered biological function which can be documented and exchanged between researchers. In synthetic biology the development of standards is now underway. Currently there are three under development – SBOL, DICOM-SB and JBEI.

7.1. SBOL

SBOL (synthetic biology open language, [22]) is, essentially, a standard for the exchange of information, describing DNA components used in synthetic biology. In this context, the SBOL standard defines: (a) the vocabulary, a set of preferred terms and (b) the core data model, a common computational representation. The core of the standard currently comprises the following components, which are interconnected. The sample, the physical DNA, the Part, the sequence annotation, sequence feature, cell, vector and assembly format.

7.2. DICOM-SB

Research is being undertaken to develop a synthetic biology extension of the DICOM standard [23]. DICOM is a highly successful standard in biomedicine, which incorporates many features that are compatible with the requirements of synthetic biology (e.g. accurate image exchange). Another feature of DICOM is the ability to store and exchange data and metadata. In addition, web-based viewers can be incorporated. There are a number of areas of compatibility between DICOM-SB and SBOL.

7.3. JBEI

This work is part of that being undertaking at the Joint BioEnergy Institute [24] and involves their synthetic biology group. JBEI are developing a parts registry, together with BioCAD tools (this part of the work also involves incorporating tools from other sources). The assembly of parts from the registry using automation tools and high-throughput liquid handling robots is also a feature of the work.

The common feature of all of the work described here (under the heading of platform technology) is that it is being carried out

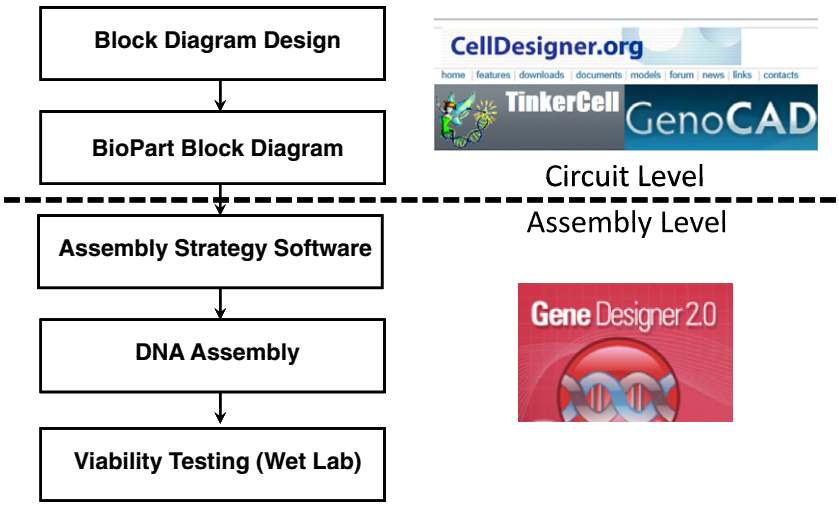

Fig. 3. BioCAD schema.

at a professional level –i.e. working towards a situation where synthetic biology parts, devices and systems are modular, fully characterised and standardised.

8. Application areas

As described in previous sections of this paper, the strategy in synthetic biology is to develop platform technology which can be applied across a wide range of areas. The areas of application need to be seen in the context of different timescales (short, 3–5 years, medium, 5–10 years. and long, longer than 10 years). What is important here is to differentiate between the development of the applications projects and the ability to establish new product pipelines within existing industries – as well as the development of new industries. In a number of cases the objective would be to break into the supply chain at an early stage. An example of this is biofuels. Here, it is already the case that the biofuels which are being produced today can be entered into the supply chain with relatively minor changes. In terms of longer term developments, it is likely that synthetic biology can help solve the reliance on petrochemicals. Whilst new, significant reserves of oil are being found on a regular basis, the problem is that the demand is rapidly increasing – for example the rapid development of demand in China and India. What is therefore required is the development of biologically based equivalents, e.g. bio plastics. Synthetic biology has an important role to play in terms of moving away from oil based feedstocks to biomass feedstocks. A great hope is that synthetic biology will lead to much more environmentally friendly products (where this is built into the design). More directly, there is the development of new sources of energy from different feedstocks, including waste.

The topic of applications will now be addressed more specifically.

8.1. The application of engineering principles

In this paper we have described how synthetic biology is based on engineering principles. Whilst the primary aim of the field is industrialisation – i.e. applications leading to products – the techniques and methodology which are being developed will have significant impact on the understanding of biological systems, particularly in the area of systems biology. Indeed the importance of engineering science to systems biology was clear recognised in the Inquiry into systems biology by the Academy of Medical Sciences and the Royal Academy of Engineering [UK] [25]. In this regard, the commonality of the two fields, in terms of basic methods, has been recognised in a number of books [26–28] –and [29] is an example of a paper which specifically addresses the issue of the application of engineering principles to synthetic biology.

8.2. Examples of applications

In terms of specific examples, biosensors are seen as an area where there are likely to be early returns from synthetic biology. These, of course, are biologically based sensors. Healthcare applications are an area of development. There are currently several examples of sensors which have been developed to detect pathogenic biofilms – two examples being the detection of urinary tract infection [30,31] and, alternatively, the detection of arsenic in drinking water. Synthetic biology based designs are also now being developed for the detection of parasites in water (e.g. a biosensor to detect Schistosoma). What is already clear is that because of the systematic modular design approach, a basic design can be modified for a range of applications. Biosensors can also be used as a tool for bioprocess design and optimisation. In any bio manufacturing process, a series of conditions can be varied in order to increase or decrease the yield of the desired product. These include temperature, pH, dissolved oxygen tension, and the availability of key nutrients (medium formulation). In many industries, bioprocess development is centred on a combinatorial exploration of these variables in order to determine which combination leads to the greatest yield of product. Biosensors can be used to aid process development and also to provide a greater understanding as to how process variables affect cellular metabolism in order to move towards rational process design in the future.

In the simplest case, a biosensor developed to detect the concentration of the desired product can be used as an in situ high throughput screen to maximise production. In one such example, Santos and Stephanopoulos identified conditions for the overproduction of L-tyrosine in *E. coli* using a biosensor circuit that converted the tyrosine into a coloured product called melanin. Conditions under which melanin accumulated in larger quantities can then be replicated in the absence of the circuit to accumulate tyrosine. In this way, both process conditions and genetic variants can be screened to find combinations which lead to overproduction of tyrosine [32].

Another strategy is to monitor metabolites which are correlated with productivity as an indirect measure of the best process conditions. This strategy has the advantage of being more generalisable as certain metabolites will be of interest in most systems. Metabolites

such as glucose, glutamine, ammonia, and lactate are important in many industrial production systems and their utilisation is already often monitored online using analytical chemistry techniques – e.g. [33]. Synthetic biology also allows the development of genetically encoded solutions for monitoring these key variables and also allows measurements of the intracellular concentrations, which for some applications is more informative. Recently, in vivo biosensors based on Förster Resonance Energy Transfer were used to monitor the concentrations of glucose and glutamine during the fed-batch cultivation of the industrially relevant protein production host Chinese Hamster Ovary cells. In this study, the authors were able to show a direct relationship between the fluorescence emission spectra of the cells and the metabolite concentration in a 96-well plate assay, suggesting the biosensors are appropriate for high throughput medium formulation studies in well plates [34].

Work is on-going on the development of biologically-based logic gates (e.g. AND and NAND gates) [35]. (These are the biological equivalents of their electronic counterparts, which form the basis of all digital devices – including computers.) Once multiple gate designs have been perfected they will have wide application in logical devices, e.g. in biosensors (for detection and the release of drugs, based on inbuilt logic). Ultimately, it should be possible to implant intracellular, human designed control devices that will override or replace the natural control and signalling mechanisms. An example of work in this area relates to in silico feedback in the control of a gene expression circuit [36].

As with electronic digital devices, the control of Bio-logical devices requires a clock. For this reason the area of controlled biological oscillators has been a topic of considerable interest in synthetic biology for a number of years. An early, well known, example is the Repressilator [37], which comprises three genes in a feedback loop – this is, effectively, a form of ring oscillator which uses green florescent protein (GFP) as its reporter. However, for oscillators to be really useful, in the context of human-designed biological devices, they must be controllable and stable in terms of frequency and amplitude, and have a high signal to noise ratio. Since the Repressilator there have been various attempts to achieve this objective; for example, by the use of Lotka-Volterra dynamics [38] and a tuneable synthetic gene oscillator [39] – and, more recently, be using a synchronised quorum clock approach [40]. A recent example of the use of biological oscillators in another area relates to their application to liquid crystal displays [41]. Again, in the area of biologically-based digital devices, the issue of rewritable digital storage in live cells has recently been addressed [42].

High value chemicals (e.g. surfactants and cosmetics) are another important application area, e.g. the metabolic reprogramming of the periwinkle plant [43]. In the pharmaceutical industry the development of new drugs, based on a much wider range of natural products, is being investigated – as well as the development of new methods for vaccine development and production [44]. The development of novel materials (e.g. synthetic versions of naturally occurring materials) is another application area for synthetic biology. Synthetic spider silk is one example [45].

9. Concluding remarks

- Synthetic biology is a new field which is based on the engineering principles of standardisation, modularisation and characterisation, coupled to systematic design (it is not a direct extension of genetic engineering).
- An important driver of synthetic biology, and indeed probably the key to its genesis, has been the development of increasingly low cost and reliable gene sequencing and synthesis methods which are becoming widely commercially available.
- Industrialisation is an important endpoint of synthetic biology (i.e. it is primarily a field of engineering).
- Whatever the relative economic growth figures for synthetic biology, from a variety of sources might be, its economic impact is generally predicted to be highly significant.

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