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The Impact of Synthetic Biology in Chemical Engineering – Educational Issues

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Abstract

This paper describes the development of synthetic biology as a distinct entity from current industrial biotechnology and the implications for a future based on its concepts. The role of the engineering design cycle, in synthetic biology is established and the difficulties in making and exact analogy between the two emphasised. It is suggested that process engineers can offer experience in the application of synthetic biology to the manufacture of products which should influence the approach of the synthetic biologist. The style of teaching for synthetic biology appears to offer a new approach at undergraduate level and the challenges to the education of process engineers in this technology are raised. Possible routes to the development of synthetic biology teaching are suggested.

Key Words

Synthetic biology; chemical engineering; education

1. Introduction

In a recent paper (Hall and Howe, 2010) it was argued that a new paradigm for chemical engineering might be imminent based on a move from a reliance on fossil sources for basic chemicals to reliance on bio-based raw materials which would be renewable and thus sustainable. In tandem with this change was the prospect of a combination of engineering principles and biology, under the name synthetic biology, which would synthesise biological systems with entirely novel functions beyond current biotechnology. Given the potential impact of these changes this paper takes these concepts and investigates their significance for process engineering and the education of the next generation of chemical engineers.

2. What is Synthetic Biology?

Engineering and biology have gone hand-in-hand for a long time: developing from early food fermentations, particularly brewing and baking, through to modern industrial biotechnology using whole organisms or enzyme extracts to produce products such as antibiotics and functional food components. These activities have also brought about a good understanding of the physiology, growth characteristics and genetics of the organisms involved, such as *Penicillium* spp, *Aspergillus* spp, *Saccharomyces cerevisiae* and *Escherichia coli* which could be manipulated for greater expression of natural or recombinant products. However, the genetic manipulation of these organisms in current biotechnology is considered to be *ad hoc* or serendipitous at best whereas synthetic biology offers the promise of specific design for purpose (European Commission, 2005).

Although it has grown from the engineering/biology axis other fundamental advances in a third sphere have enabled synthetic biology to become nearer to reality. These developments have been in the fusion of mathematics, computer modelling and information storage, retrieval and communication which have enabled complex biological systems to be mapped, quantified and masses of data transmitted as necessary. Table 1 gives a list of the contributing disciplines and their individual roles in synthetic biology. As a result of the potential control which can be achieved there are great claims for synthetic biology in fulfilling the promises which conventional biotechnology has not delivered to date. Table 2 gives a list of the broad areas of activity with specific applications within these areas. The list is pretty all-encompassing with no area of current commercial activity (and by extension process engineering) omitted. Immediate goals are the next generation of biofuels which are capable of driving the high-fuel usage sectors of heavy haulage, railways and aviation where current biofuels are not sufficiently energy-rich. Another area of immediate impact could be in the production of drugs and pharmaceuticals such as the production of the antimalarial drug (artemisinin) precursor, artemisinic acid in engineered yeast (Ro *et al.*, 2006). This

offers an alternative route to its extraction from the medicinal plant, where limited availability is reflected in price, and a shift from plant to microbial production would give a reliable and affordable supply (Zeng *et al.,* 2008). This project was supported by the Bill and Melinda Gates Foundation, addresses a massive health issue and, being near to fruition and thus attracts the headlines for synthetic biology. However, other potential applications of SB as listed in Table 2 may come to the fore such as the current emphasis on the production of biofuels.

Synthetic biology is also of great public interest because it deals in the fundamentals of life with concomitant ethical, security and safety issues. The successful sequencing of the human genome (International Human Genome Sequencing Consortium, 2001, Venter *et al.,* 2001) gave synthetic biology another media boost but also raised, in the eyes of some observers, the spectre of, "Frankenstein", organisms with malign uses or, at the very least, the threat of accidental release into the environment. Thus, this eye-catching and newsworthy disciple has been the subject of debate far removed from academia (Specter, 2009) which, in turn, has brought about calls for regulation by bodies other than the active synthetic biology community itself. Alongside the scientific discovery goes great commercial potential and fears for a profit-driven monopoly of multinational companies who can afford to fund the initial research and the sources of biomass on which they will be founded (Action Group for Erosion, Technology and Concentration, 2010). The replacement of natural sources of bio-active compounds (such as for antimalarial compound artemisinin mentioned above) could also deprive developing countries of revenue (Balmer and Martin, 2008).

The pace of progress in certain aspects of synthetic biology has been rapid with the first synthetic organism, from the poliovirus genome (7,741 base pairs), taking two years of work (Cello *et al.*, 2002) whilst the genome of the bacteriophage ΦX-174 (5,386 base pairs) took just two weeks to assemble in the J Craig Venter Institute (Smith et al., 2003). However,

this latter achievement reflects the sustained effort of a large group of researchers underlining the challenging nature of the field. The first bacterium to be synthesised (also by the Venter Institute) was *Mycobacterium genitalium* with 589,000 base pairs (Gibson *et al.*, 2008). This opened up the concept of a minimal cell which could be the, "blank", canvas for engineering produced by removing genes which are not essential for life. The minimal cell would have the minimum number of components to support biological synthesis from inserted DNA material and be viable. *M genitalium* carries 485 genes, the smallest genome in laboratory organisms, and about one quarter (115 or more) could be removed with no effect on genome functionality in the laboratory although the organism would be unlikely to survive in the natural environment. More conventional microbial carriers (or, "chassis") for synthetic biology include E coli, yeasts, *Bacillus subtilis* and *Pseudomonas putida* reflecting the wide knowledge about these organisms built up over the years. Future developments could include cell-free applications where the non-specific elements of the living cell chassis are removed from the application.

With synthetic biology being based on the manipulation of genetic material there is the added issue of the Intellectual Property rights (IPR) for the new life forms created. The minimal cell based on *M genitalium* synthesised by the Venter research group (and dubbed *M laboratorium*) was the subject of a patent application although the concept of patenting life forms is being challenged. This application has at least opened up the debate over synthesised organisms and is likely to be the first of many such patent applications. The models for the development of the synthetic biology-based industry could follow a variety of routes and may learn lessons from evolution of the fast-changing computing and software industry (Henkel and Maurer, 2007).

3. Interaction of synthetic biology with chemical engineering

Table 1 includes the contribution of the engineering design cycle approach to the development of synthetic biology. The use of standard parts to build functional units/circuits in Electronic Engineering is a common analogy for SB where the standard parts are the basic biochemical elements which build modules to regulate, for example, gene behaviour and protein function (Purnick and Weiss, 2009) . Similarly, chemical engineers are well versed in taking concepts from the chemistry and biochemistry fields and converting them into industrial scale processes through the engineering design cycle and subsequent building and commissioning stages. Plant design also involves putting together a multitude of standard parts and unit operations into the most efficient system through an iterative process – recognising that a number of designs and process routes might be feasible practically but not from a commercial point of view. Learning the art of process design is at the very core of chemical engineering education being the culmination of the separate disciplines which make up the subject. Thus, process design is based on fundamental concepts such as heat and mass transfer, transport phenomena, reaction kinetics and modelling and fluid mechanics. The basic principles for the process in question are then broken down into the unit operations which comprise the complete process and described in block flow diagrams, process flow diagrams and piping and instrumentation diagrams. Other considerations include product throughput and quality; financial constraints and process criteria such as safety, flexibility and operational characteristics. All this knowledge can be applied to synthetic biology in the consideration of what route to take to production. The analogy between (chemical) engineering design and synthetic biology has been writ large in that the idea of taking discrete and standardised genetic units and putting them together to make an engineered organism is as direct or simple as in the physical world. The goal would be a world in which the genetic information is recognised and the separate constructs are put together by genomic sequencing which delivers the exact requirements of the process in mind. One approach to

the provision of these standard parts is the Biobricks Foundation which is a public-benefit organisation originating from workers at the Massachusetts Institute of Technology (MIT), Harvard and University of California, San Francisco. The declared aim of the foundation is to make freely available the fundamental components, or bioparts, needed to conduct synthetic biology and in doing so to introduce the mindset which underpins, for example, chemical engineering design (Biobricks Foundation, 2011).

However, the devil is in the detail for SB because the discrete standardised genetic units are not physical entities but biochemical units linked and controlled by biochemical regulation and hence prone to variation. Just as a physical chemical plant must be coaxed into an operational equilibrium so the genomic components of a synthesised organism must be brought together carefully to function correctly and there has been an evolution in the complexity and scale at which this can be done (Andrianantoandro *et al*., 2006, Canton *et al.*, 2008, Purnick and Weiss, 2009). In this respect the fuzzy aspects of chemical plant design could provide a good lesson to the synthetic biology discipline. Many chemical processes are difficult to control automatically because of nonlinearity, time-variable behaviour and poor/non-existent measurement of important parameters and human operator experience becomes crucial in these situations. Such processes include: catalytic cracking in petroleum refining, oil and gas separations, food processing, bio-reactors, crystallisation and in safety analysis. Fuzzy logic, and associated systems, can be applied to those processes where the complexity is such that the ability to be precise about behaviour diminishes and approximations must be made. Fuzzy logic allows such approximations through the development of knowledge-based systems (Emami, 2010). The emphasis put on empiricism in teaching SB (see section 4) and the rapid accumulation of practical knowledge in SB would suggest that a fuzzy logic approach to genetic manipulation would be a fair gift from the chemical engineering discipline.

A second, more practical, input from the chemical engineering fraternity to synthetic biology could be in defining the processability of engineered organisms and their products. Currently synthetic biology seems to be directed towards the genetic control of the organism for specific product expression but a substantial element in the cost of bio-products is their separation and purification – downstream processing (DSP). Here the chemical engineer could ask the question about processability and define the DSP characteristics required in the final design. This issue is being addressed in some instances, for example the use of *E coli* to produce biofuels which are expressed externally and, being immiscible with the aqueous fermentation broth, can be separated off easily. Where products are expressed and water soluble it may be possible to select for ease of DSP, for example, by developing organisms which require a minimal/simple fermentation medium which can be easily removed in the early/high volume stages of DSP. The minimal cell, with much genetic material removed yet viable in a simple growth medium, would be a good model for this approach. Where products are expressed as internal inclusion bodies they must be separated from the cell contents. Ways to achieve this separation would be helped by simple cell biochemistry and susceptibility to cell disruption paving the way for separation of the cell contents and the inclusion body.

4. Education in synthetic biology

The time taken to teach all the required aspects of chemical engineering has lead to the modern degree with a curriculum as described in Table 3 (Hall and Howe, 2010). Other aspects of a university degree have always been prominent in chemical engineering education such as problem solving and the modern chemical engineer with good mathematical ability

and literacy, combined with the ability to communicate with those from a range of disciplines, has much to offer the development of a synthetic biology discipline.

However, bringing together as it does biology and engineering, synthetic biology is considered by some to be interdisciplinary and as such it falls into the uneasy territory between the two separate disciplines. It is notable that the leading lights in synthetic biology, whether from engineering or a biology background, have embraced the other discipline and recognising the contribution it makes to their own expertise. Such magnanimity towards an alien discipline appears to be an essential for synthetic biology to flourish. This might suggest that an undergraduate course in synthetic biology would be difficult to construct and it would be better given at postgraduate level once students have a sound grounding in their favoured discipline and are mature enough in outlook to take on, "the new". Additionally, given the synthetic biology is still in its infancy it seems appropriate that teaching is taking place at the postgraduate Masters level with a joint intake of biologists and engineers. Such courses could then lead students into PhD studies in the discipline. However, as with any emerging discipline, there is an almost instant demand that synthetic biology be taught at the undergraduate level in its own right and that its important characteristics are taught to closely aligned courses such as chemical engineering.

As with the research activity, the teaching of synthetic biology has been concentrated in the USA and the EU (with the UK to the fore) although centres in Japan, China and India are also springing up (RAE, 2009). Imperial College, London in the UK was the first European university to offer synthetic biology at undergraduate and postgraduate levels and at the undergraduate level this comprises a final year module offered to biologists/biochemists and bioengineers. In the USA, several universities (MIT, Harvard, Princeton, Stanford and the University of California, for example) are developing full synthetic biology undergraduate courses and many others offer components which could be the foundation of synthetic

biology studies. The concept of discipline hopping has been introduced in recent years for academic staff to allow them to get a taste of other subject areas and to understand the working culture of another discipline and this could be applied equally well to undergraduates, but probably outside the confines of their core timetable (RAE, 2009). In this context, the iGEM (International Genetically Engineered Machine competition) held at MIT in the Summer holidays has been very successful in raising the profile of synthetic biology. Undergraduate multidisciplinary teams from universities across the world have to design and build a functioning biological device for a range of practical applications in competition and, in doing, so develop new thinking and experiences beyond the conventional classroom. The number of student groups and countries taking part has increased year on year (RAE, 2009) and is a clear demonstration that teaching an interdisciplinary subject can demand unorthodox approaches.

Kuldell (2007) described the emergence of synthetic biology teaching to undergraduates at MIT and argued that the newness of the discipline militated against a traditional teaching approach because much of the framework and competencies required were still being developed. However, it did give the opportunity to develop student innovation and creativity, which in turn, would produce flexible thinkers able to grapple with the complex issues thrown up by the application of synthetic biology in the real world. Kuldell (2007) also argues that synthetic biology although being an amalgam of biology and engineering should not automatically be labelled, "interdisciplinary". Synthetic biology demands that its practitioners think and work differently to, "engineers", or, "biologists", confronted by the, "other", discipline. In this context, the sooner a student embraces synthetic biology with all its uncertainties and real world connotations the better and a full undergraduate course may be the way to achieve this and may appeal to the maverick soul who can appreciate the challenges inherent in the discipline. Dymond *et al.*, (2009) described undergraduate

teaching in synthetic biology at Johns Hopkins University from a geneticist's point of view. The Build-a-Genome course included introductory lectures on genetics then bioinformatics and also the economics and ethical issues associated with synthetic biology. Laboratory-based sessions were a central feature and included basic molecular biology techniques followed by synthetic gene assembly in yeast. The emphasis was on independent research, problem solving and creativity and where appropriate for students to follow up side projects on problems thrown up during the course of the practical work. The evolution of the Build-a-Genome course also highlighted the considerable staffing, practical and physical resources and financial support which are necessary to teach innovative material to undergraduates and the course was costed at US$30,000 for one semester for less than 20 students. A feature of both the MIT and Johns Hopkins teaching is the emphasis on undergraduates performing research-lead activities which could lead to commercial products and publishable work.

Given this background strategies for teaching synthetic biology to career chemical engineers could follow three routes:

> ***integration*** of synthetic biology concepts into existing courses in the final year (as done by Imperial College, London) but and only for high-level students?
>
> ***mixed*** teaching with interdisciplinary courses from non-engineering departments (akin to discipline hopping)
>
> ***dedicated*** synthetic biology undergraduate courses attracting engineering-orientated and biology-orientated students with a high degree of research-led activity.

All three approaches have their merits and their adoption could be dependent on the particular circumstances at any teaching institution.

An ***integrated*** approach would ensure that all chemical engineering students were aware of synthetic biology and those wishing to specialise in the discipline could do so in the later stages of an undergraduate course and particularly at the postgraduate level. The demands of a conventional chemical engineering course with its design and problem solving content would be a good grounding for such postgraduate study. ***Mixed*** teaching would allow engineers to discipline hop and the hands-on training such as through the iGEM and Build-a-Genome models can be fitted in around a conventional engineering course. The ***dedicated*** course offers the longest and most thorough teaching in synthetic biology, perhaps over four years, but would require careful marketing to attract the students who would embrace the unique challenges, both intellectual and practical, in mastering the biology/engineering disciplines. From the examples cited here a ***dedicated*** course does offer the chance for undergraduate students to be real stakeholders in innovation, to drive the subject forward and become critical thinkers and decision makers in the process. However, a ***dedicated*** course over a full undergraduate degree period of four years may lose the immediacy generated by the ***mixed*** approach where short bursts of intense practical activity support teaching in the student's favoured discipline.

5. Possible strategy for teaching synthetic biology to engineers

A further strategy for teaching synthetic biology to engineers is shown in Figure 1 which can be described as an ***integrated- mixed*** approach. Students following the integrated route will follow the basic chemical engineering course building up their expertise and interest in synthetic biology along the way with the option of a final year project in the subject. Students following the mixed route will receive the basic integrated course with the addition of out-of-session courses for a more intensive experience – enhanced by having the most challenging and exciting hands-on experience in the first instance. For engineering students the challenging aspects would be the practical skills of molecular biology and genome

synthesis whilst the informatics and communications should be taken up more easily. This approach will put an extra burden on the mixed route students but with the bonus of a thorough grounding in the discipline which could lead directly to PhD-level studies or employment in the sector. These combinations could also lead to a dedicated synthetic biology course with a strong engineering emphasis depending on the focus and expertise available at each academic institution. If the unique feature of synthetic biology is the hands-on, critical thinking and real-life scenarios experienced by undergraduate students there is no need, or indeed expectation, that all synthetic biology courses fit the same mould and perhaps no need for a **dedicated** course in the field. As with any established discipline a number of core competences will emerge and all synthetic biology courses will incorporate them but the individuality of teaching at any one institution must remain.

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