Cambridge Consultants

BUILDING THE BUSINESS OF BIODESIGN: THE SYNTHETIC BIOLOGY INDUSTRY IS READY TO CHANGE GEAR

WORKSHOP REPORT 2018

A workshop hosted by Cambridge Consultants

Synthetic biology remains nascent, yet full of promise. The idea of using rational engineering approaches to design biology has the potential to solve some of humanity's biggest challenges, such as securing food supplies or developing new cancer drugs. The last 20 years have seen massive technical progress and increasing global interest in what synthetic biology might achieve. However, this has not yet been translated into significant business growth. Synthetic biology products and services need to become a major part of economic activity if they are to truly deliver on their promise.

To understand why this is the case, and what can be done about it, Cambridge Consultants recently hosted a thought-leadership workshop for senior leaders and influencers in the synthetic biology industry. The remit of the workshop was to define the issues stopping synthetic biology achieving wide commercial success and identify the opportunities to resolve these issues over a relatively short five-year time frame, that is by 2023.

Workshop participants represented a range of stakeholders, including end-users, product developers, tools developers and researchers. Participants came from a range of organisations including multinational companies, small-and-medium enterprises, early-stage technology investors and academia, representing industries from pharmaceuticals to materials.

The participants identified numerous opportunities for driving commercial success in synthetic biology and moving towards true biodesign. This report summarises the collective views and captures key points in the discussion that took place. We believe it offers timely and unique insight into how synthetic biology must evolve to be successful, as seen through the eyes of industry leaders.

We are grateful to our attendees for investing significant time and effort to participate and share their insights. The workshop was held under the Chatham House Rule to promote open discussion; quotes in the report are not attributed. We are also indebted to our guest speaker, Professor Tony Purnell, Head of Technology at British Cycling and former Team Principal at Red Bull Racing Formula One Team who gave a stimulating talk on building successful technical teams to start the workshop.

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INTRODUCTION

Synthetic biology has emerged from traditional biotechnology and molecular biology approaches over the last two decades. This emergence is driven by considerable technological progress, which is now supporting growth in commercial activity. The ability to use rational engineering approaches to design biological systems that carry out required functions has enabled the field to mature towards a bona fide engineering discipline. It is poised to deliver new and game-changing products and disrupt a wide range of industries, from food and medicine to new energy sources and materials.

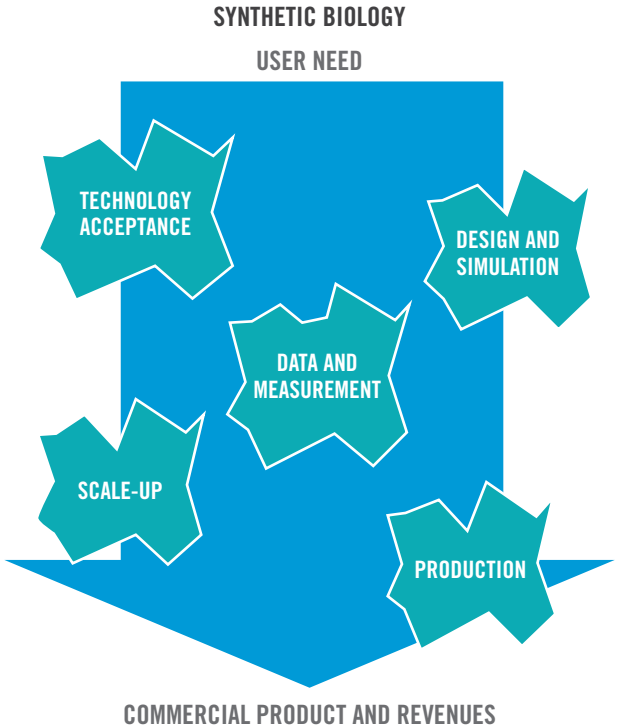
Nevertheless, despite its potential to tackle many of the problems facing the world today, synthetic biology remains some distance away from fulfilling its promise. The field of synthetic biology is still to become the fully-fledged engineering discipline it is aiming towards. It has not yet completely evolved into biodesign, whereby engineers can consistently create desirable, competitive biology-based processes and systems. Such consistency would drive significant economic and business activity as user needs could be met and novel products and services could be developed in many markets. Why is this not yet happening? What is missing? What needs to be done?

To answer these questions, Cambridge Consultants convened a workshop with leading-edge experts in the field of synthetic biology. The participants represented a broad range of interests from the US and Europe, including big industry, SMEs, academics and investors. The range of sectors represented was also broad, including pharmaceuticals, consumer products and industrial chemicals. Following a full day of lively and intense discussion, the participants defined the main challenges facing the field, before developing a set of tangible and actionable solutions to the current challenges over the next five years – all with a view to helping transform synthetic biology into biodesign.

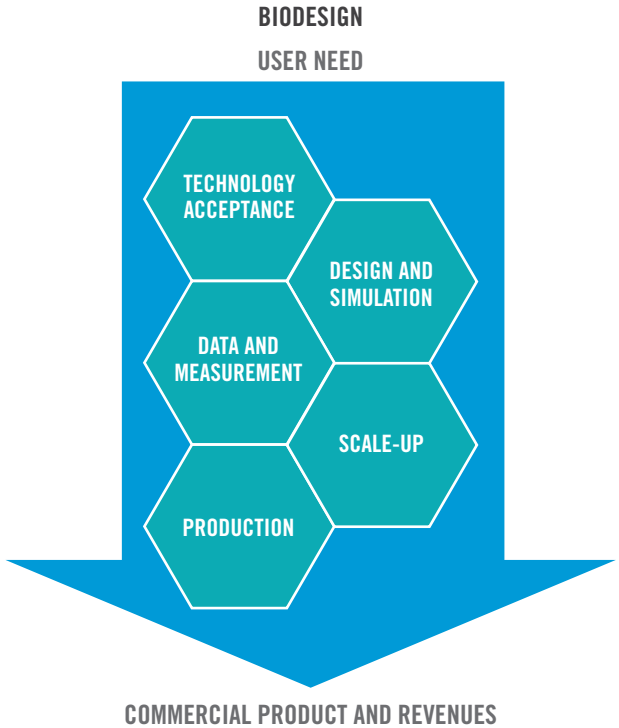
The insights and ideas generated during the workshop are summarised in this report. As expected, when assembling thought leaders to consider a complex problem, the views were many and diverse. But everyone unanimously agreed that the significant advances in technology in recent years mean that synthetic biology is now superbly positioned to provide much-needed innovation across all industries.

However, technological progress must now be followed by a breakthrough in the fundamental approach to building synthetic biology as a business. A concerted effort is required to join all the necessary parts together, by improving predictability, by building an integrated, efficient and competitive supply chain and by enhancing the accessibility of the industry, both commercially and to the general public. To borrow a metaphor from another engineering discipline: synthetic biology is ready to change gear.

SYNTHETIC BIOLOGY V BIODESIGN



Synthetic biology today has many of the parts but they are not yet coherently organised and able to work together



Biodesign brings the parts together so desirable products can be developed cost-effectively

METHODOLOGY

The aim of the workshop was to answer the key question:

What are the tools and technologies we need to develop in the next five years to make biodesign a commercially successful approach that drives significant business activity?

This question frames what Cambridge Consultants believes are the core issues for synthetic biology today. Firstly, it asks about business activity and commercial success: how do we build on the strong technical progress to create revenues, economic activity, growth and jobs globally? Secondly, it gives a time frame of five years: how do we achieve this aim relatively quickly so industry can capitalise on the current excitement and interest in synthetic biology?

To answer this question the workshop used the methodology shown below.

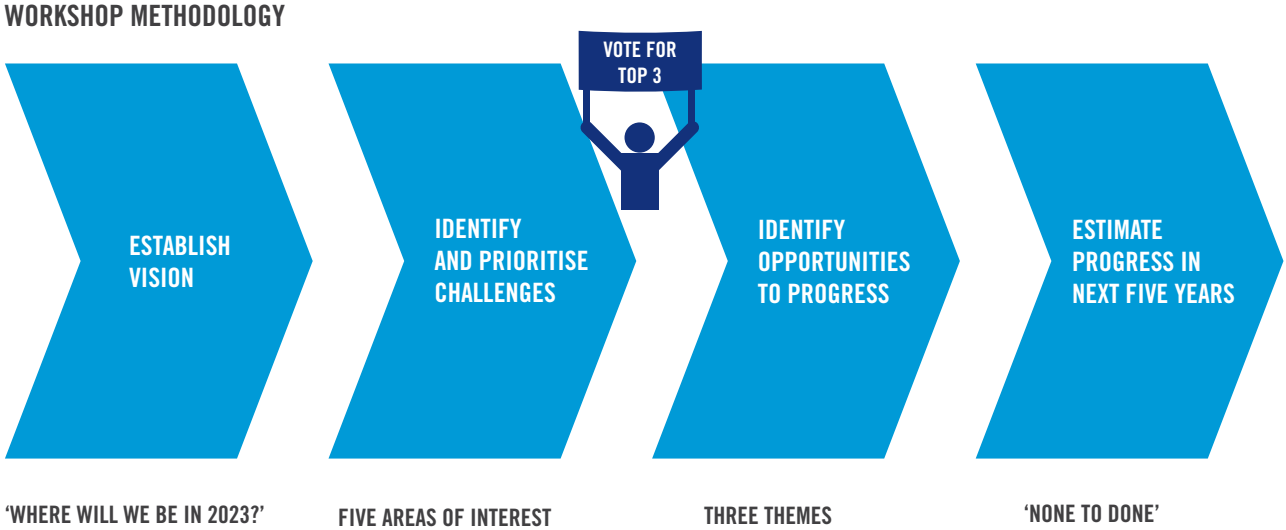
As a first step, the participants were set the task of defining a vision for the next five years, i.e. up to 2023. What needs to be achieved? Where does the field need to be in 2023? What does significant business activity look like five years from now?

Following on from the vision discussions, the participants were asked to define the key challenges related to the vision statements. What is stopping us? What are the main gaps between the current state and where we want to be in 2023? The participants then voted to select the top three challenges and engaged in an in-depth discussion regarding what solutions will be required to reach the 2023 vision.

Finally, the participants estimated the likely progress towards the vision now that the solutions had been articulated, to gain a better judgement for how much progress might realistically be made in the next five years.

As shown opposite, the challenges debate was organised around five areas of interest: manipulating biology, managing information, barriers to user adoption, IP and regulatory and creating commercial value. Similarly, the opportunities debate was organised around three themes: technical progress, business progress and organisational progress. These prompts were chosen to encourage broad thinking during the workshop across all aspects of successful business creation.

WORKSHOP METHODOLOGY



The workshop followed a four-stage process. Firstly, we established an agreed vision for the next five years. We then identified the key challenges to realising this vision. This was done by considering five areas of interest to drive broad thinking. We then selected the three with the biggest impact if solved. With the vision and challenges defined, we then moved to identifying specific actions and tools required to address these challenges considering three themes. Finally, given these specific actions, we estimated how much progress is likely to be achieved in the next five years towards the original vision.

AREAS AND THEMES

IDENTIFY AND PRIORITISE CHALLENGES

MANIPULATING BIOLOGY:	what are the issues around working with and engineering biological systems?
MANAGING INFORMATION:	what are the issues around gathering, storing, analysing and sharing data?
BARRIERS TO USER ADOPTION:	what is stopping users wanting synthetic biology products?
IP AND REGULATORY:	what are the issues around legal frameworks that hinder commercialisation?
CREATING COMMERCIAL VALUE:	what is stopping synthetic biology products being profitable?

IDENTIFY OPPORTUNITIES TO PROGRESS

TECHNICAL PROGRESS:	how do we improve our engineering and scientific capabilities?
BUSINESS PROGRESS:	how do we improve our business models and legal frameworks?
ORGANISATIONAL PROGRESS:	how do we improve our communications and interactions?

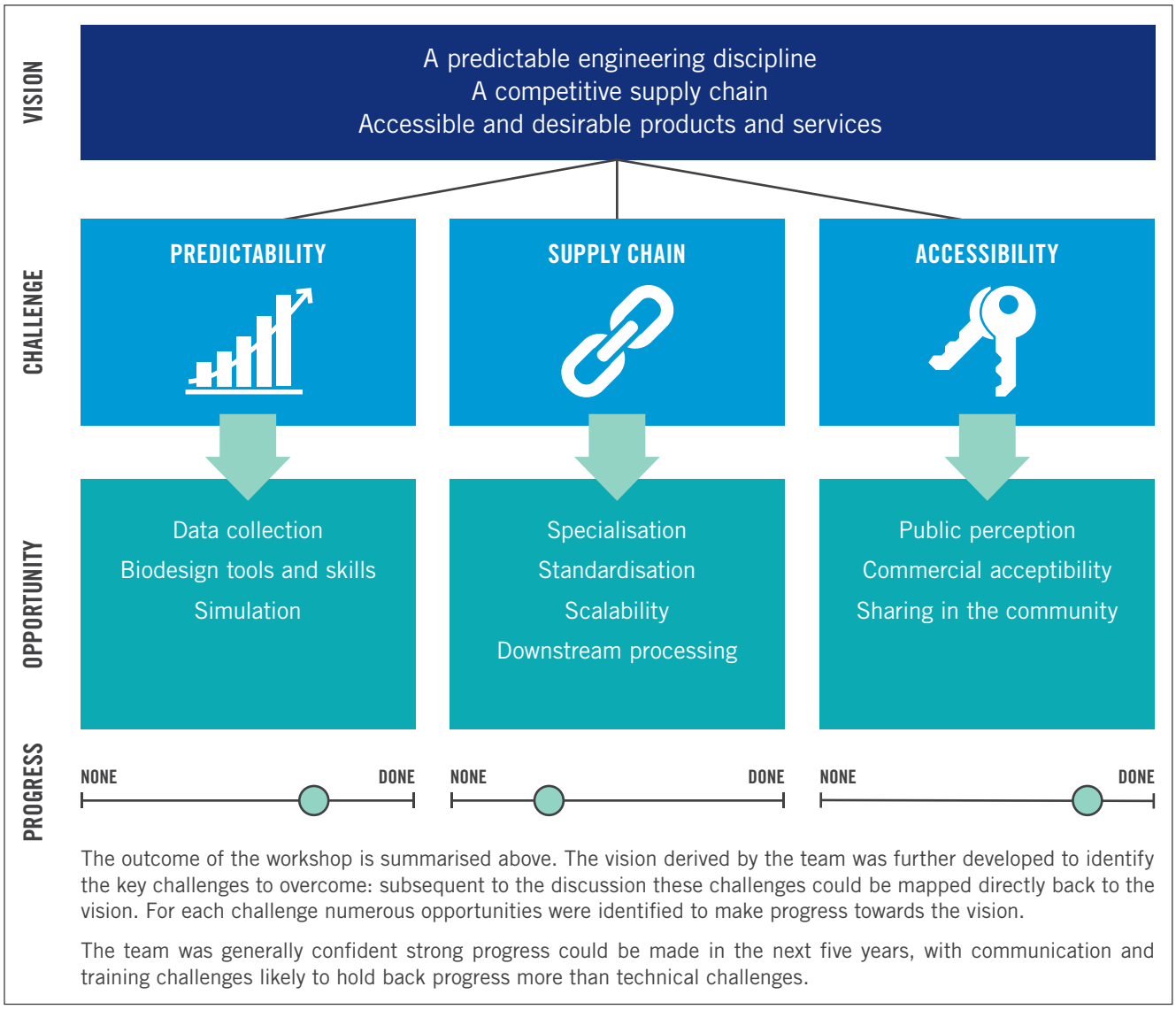
To promote a broad discussion amoungst the delegates, the challenges and opportunities were split into five areas and three themes respectively. Creating business activity requires insight and action across many fronts; by considering different aspects in turn we can be confident all aspects of the question have been considered.

VISION FOR 2023

The vision discussions converged on three overarching topics:

- **A predictable engineering discipline:**
  Synthetic biology will be established as an engineering discipline of biodesign with a high level of predictability. Effective standards will be in place to generate, collect, manage and communicate data across the industry
- **A competitive supply chain:**
  An integrated supply chain will exist that can take the complex requirements of biological systems and translate them into competitive products and services
- **Accessible and desirable products and services:**
  By 2023, synthetic biology products and services will be seen by all stakeholders (experts as well as non-experts) as an accessible and desirable solution to major challenges as well as to individual needs

This is encouraging as it demonstrates that a clear and consistent ambition for synthetic biology can be developed across multiple sectors, despite the seemingly disparate needs and market dynamics.



The outcome of the workshop is summarised above. The vision derived by the team was further developed to identify the key challenges to overcome: subsequent to the discussion these challenges could be mapped directly back to the vision. For each challenge numerous opportunities were identified to make progress towards the vision.

The team was generally confident strong progress could be made in the next five years, with communication and training challenges likely to hold back progress more than technical challenges.

CHALLENGES AND OPPORTUNITIES

PREDICTABILITY – *"BIOLOGY IS UNACCEPTABLY UNPREDICTABLE"*

THE CHALLENGE: It is not currently possible to engineer organisms and be confident that they will meet the requirements and predicted outputs from the initial design

As one participant put it; *"We are in a bad place from an engineering point of view when compared to other industries, such as the semiconductor industry"*. Both industries involve a set of design tools along with a variety of processes to transform raw materials into advanced devices and systems. However, synthetic biology has not yet reached the stage where those tools and processes are sufficiently well-defined and standardised that outputs can be predicted based on the inputs.

Nevertheless, the comparison with the semiconductor industry is useful for helping us understand what is needed to achieve better predictability.

Firstly, in semiconductor design and manufacturing, required and desired features can be defined at an early stage of the design process. For synthetic biology, this will only be possible if representative design-build-test cycles have been run enough times that the designers have sufficient confidence that their inputs will yield the expected output. For that confidence to be established, there needs to be consistent measurement during the design cycles, and the resulting data needs to be available to the designer.

Secondly, in semiconductor design, an engineering team can be assembled with sophisticated CAD and design skills. Advanced design tools are readily available to enable the design of products which meet specifications. Designers can use their expertise and tools to map out the functional requirements for features, verification processes and testing methodologies. For synthetic biology to achieve this level of sophistication, the current proliferation of tools needs to converge into a set of well-established and interoperable tools that can be reliably used by any biodesigner. In addition, the biodesigners themselves must have the requisite skills to use the tools available to them.

Finally, preliminary semiconductor designs are only turned into system-level specifications after simulation with modelling tools. Deliberately including features that can be tested to verify the accuracy of the modelling is part of the design process. Similarly, for biodesign, simulations and in silico computer modelling have an important role to play in turning design inputs into predictable outputs.

One of our participants asked, *"What does it take to turn the corner and predictably design biology?"* Predictable biology will only be possible if the synthetic biology field makes a step change in the areas of data collection, biodesign tools and skills and computer-based simulations.

Opportunity #1: Data collection

A key component of the drive towards biodesign will be the ability to collect and analyse high-quality data from biological and industrial processes. The current range of metrology instruments, sensors and devices were developed for applications such as analytical biochemistry, fermentation process monitoring and structural biology. As a result, collecting and comparing data from multiple systems is problematic, at both the hardware and software levels.

A useful analogy was provided during the keynote speech at the workshop, given by Professor Tony Purnell, Head of Technology at British Cycling and formerly Team Principal at Red Bull Racing Formula One Team. He made the point that motor racing has evolved in the past 25 years, from having only one useful measuring tool – the stopwatch – to the situation now where top racing cars have over a 100 channels of data flowing from instrumentation that relays the state of multiple components and systems. This includes everything from engine performance and brake temperature through to aerodynamic drag and the driver's heart rate. In synthetic biology, we often rely on simple measures such as temperature, dissolved oxygen and pH to assess the processes going on in a microbial or cell culture process. There is almost no mechanism for direct, real-time, in-line measurement of parameters such as cell physiology, product expression or carbon input concentration. Consequently, the paucity of data hinders the ability to create and test predictive models and simulations.

As a result, there is a real need to develop reliable, low-cost systems for analysing processes. The fact that *"Liquid Chromatography – Mass Spectrometry (LC-MS) systems cost more than $100K",* and that there are no standard software interfaces for diagnostic instruments, must be resolved. One possibility could be to develop software solutions to translate information from a range of sensors and instruments into a

standard output. It was noted that *"hardware developers are not threatened by software development"*, which means adoption of third-party software could be easier and quicker than changes in hardware standards.

A major discussion point was some participants feeling that we should focus on collecting more data; *"there are only a couple of places where data is being collected in sufficient volume"*, whereas others suggested that they have sufficient data, but lack the ability to analyse it to produce meaningful, actionable interpretations. The concern that *"we can measure a lot, but not understand it at all"* means that development of analytic software tools is paramount, especially where these can help in development of predictive models. It is possible that a machine learning / AI approach might help resolve the large data sets that can be collected into usable information.

Ultimately, it will require improvements in all the highlighted areas above if we are to be able to collect the breadth and multifactorial richness of data needed to model predictably and holistically.

Opportunity #2: Biodesign tools and skills

It is a well-known problem in synthetic biology that the combination of components into genetic circuits often leads to different results than those expected. To get around this predictability problem, synthetic biologists often opt for high-throughput, 'brute force' approaches, involving many trial-and-error experiments and potentially generating thousands of prototypes. This compromises the ability of the biologist to apply design principles to biology and it becomes cost-prohibitive to engineer a new pathway from scratch. Other, more traditional approaches cover a much smaller section of the design space, instead relying on what participants termed the *"artisanal"* abilities of the individual scientist.

What if biodesign tools were widely adopted that could circumvent the need for high-throughput approaches, while simultaneously incorporating the artisanal aspects of biological design? As noted by several participants, there is real need for a standardised set of biodesign tools that are used across the supply chain, with seamless interoperability, scalability and capability to support the development of bio-based products that meet specifications. These tools need to be adopted across the supply chain in a manner that is comparable to existing engineering design tools, while at the same time allowing the biodesigner to apply design thinking that harnesses the innovative power unique to biology. Indeed, it was noted that the current proliferation of competing tools, and the tendency towards tool customisation and protection, constitute barriers to wide adoption.

Another crucial element discussed during the workshop was the biodesigners themselves – as observed by one participant, *"people with the right skills are the most important assets"*. It was agreed that a major obstacle in understanding and modelling biological systems in the future may be the availability of the right skills. Some participants pointed out that biologists are generally readily available, but engineers with expertise in areas such as machine learning are a scarce resource. Others suggested that there are too few people with sufficiently deep expertise in microbial physiology and other relevant aspects of biology: *"biologists often have a narrow skill base"*. It is important to *"get biologists comfortable with modelling and automation and data analysis"*.

> *"People with the right skills are the most important assets"*

Nevertheless, while the *"biologist with coding skills"* may seem like a useful asset, it was recognised that *"depth versus*

holistic capability" is a difficult trade-off. Indeed, while some synthetic biology companies hire scientists who can code, others are keeping the skill sets separate. It was also mentioned that engineering skills are especially expensive to hire, and that the synthetic biology industry is competing with dominant players in other industries, including technology giants such as Google and Facebook, to acquire such skills. Biologists in the sector are certainly capable and generally excited about learning new skillsets, so this is likely to be a widely-adopted solution to overcome the skills gap. Academic training is also evolving to meet this requirement to equip graduates with a broad range of skills.

Opportunity #3: Simulation

Computer modelling is an essential part of the semiconductor, aviation and the automobile industries, which have long-used simulations for system integration and multifactor optimisation. The application of this technology would be of great benefit to the synthetic biology industry. Computer modelling of complex biological systems design has the potential to enable synthetic biology to predict cellular behaviour without resorting to hundreds of trial-and-error experiments. These multifactorial simulations could be used to predict cellular behaviour and improve development efficiency over time, using real-world data and measurements as described in the section on data collection. Automation of molecular biology workflows through robotics and liquid handling could be used to collect the data in a standardised way, to support simulations.

Furthermore, solutions are needed to enable better data analytics. One known problem is data completeness: the collected data sets may not contain measurements of the right parameters and this may lead to a non-measured parameter causing an experiment to be irreproducible in another laboratory. There is a consensus that tools are required which can provide a more fundamental understanding of what is happening within a biological system, for example inside a fermenter, that goes beyond visualisation and can provide robust predictions. The formation of partnerships and collaborations to transfer methods in machine learning, natural language interfaces and artificial intelligence from other industries are possible routes towards providing realistic solutions to these challenges.

Currently, software and operating systems for mapping multifactorial data to holistic models are not readily available for biological systems, and the available hardware is not being deployed in this manner. As these software platforms are developed they need to be standardised and interfaces need to be clearly defined.

SUPPLY CHAIN COMPETITIVENESS – *"MANUFACTURERS MUST RISE TO THE CHALLENGE"*

THE CHALLENGE: The synthetic biology supply chain is uncompetitive and not fit for purpose

A vital factor in transforming synthetic biology into a competitive biodesign industry is the presence of integrated, coherent and competitive supply chains that assemble commercially attractive products. It needs to be a commercially attractive option in comparison to the incumbent supply chains. The *"lack of confidence in biological approaches compared to chemical approaches"* requires changes that *"make it commercially worthwhile to transfer existing solutions in other industries to the synthetic biology industry".*

To create a competitive supply chain for the biodesign industry, several key areas were identified for improvement, including specialisation, standardisation, scalability and downstream processing.

Opportunity #1: Specialisation

A supply chain is founded on an ecosystem of different organisations performing different stages of the product development and manufacture process, and seamlessly passing material and data from one to another. This is demonstrated in more mature industries such as the automotive industry, where multiple companies produce components, which are assembled into sub-systems, which are in turn assembled into finished products. Each of the companies in the supply chain has a focus and specialisation, which allows each to improve throughput and product quality while reducing cost.

> *"We want to assemble products, not make all the components ourselves"*

In contrast, in synthetic biology we have a few larger companies having to integrate vertically and perform all functions, ranging from construct design through the downstream processing at production scale. Companies at the consumer end of this value chain would like to break away from this model. *"We want to assemble products, not make all the components ourselves"* was the stated desire of one participant. This would in turn depend on a shared understanding of the biodesign

product development process and agreed standards and manufacturing methods.

One aspect of this is the idea of Contract Manufacturing Organisations (CMOs) having a larger role to play in synthetic biology and industrial biotech. If a discovery organisation could design and develop a product to an agreed-upon standard at lab scale, and produce supporting data necessary for the next step, then it would be feasible for a CMO to take on this product and perform scale-up process development, before in turn passing it on to the next step in the supply chain. Without an appropriate ecosystem of specialised companies in place, this is very difficult and results in bespoke solutions being developed for every product, which increases cost, lowers throughput, and is a threat to quality.

Specialist companies could develop deep expertise in the scale-up of products at the end of the supply chain, from pre-production to production scale. By applying these skills and facilities across multiple products for several customers, they can manage their risk; they are not reliant on a single product being successful to gain their reward. This would enable synthetic biology companies to focus on the process of designing exciting new products through biodesign, thereby becoming true specialists and concentrating on their strengths. Other companies could become in-depth specialists in downstream processing, whether specifically focussing on synthetic biology products or being specialists in processes to convert intermediates into the final products.

Due to the fragmented nature of today's synthetic biology field, it will be challenging to build an efficient and integrated supply chain, while maintaining the speed to market and creating value for each member of the chain. As a result, it may be necessary to *"manage expectations of the value chain members"* in the short term, while these supply chains are being formed.

Opportunity #2: Standardisation

Standardisation has been central to the success of many industries. In the automotive industry, first tier suppliers supply parts to many different car manufacturers through long-term partnerships, guided by clear industry standards (e.g. issued by ISO) to ensure functional safety throughout design and manufacturing.

Significant effort has been made towards standardisation of biological parts and systems, for example the well-known and oft-cited Biobricks. Organisations such as BSI and NIST are active in developing standards for synthetic biology in the areas of data transfer and measurement.

However, the synthetic biology industry is still a long way away from the required level of standardisation to support effective business activities. This was particularly emphasised during the workshop, where standardisation was highlighted as a key enabler across all aspects of the synthetic biology field, and an absolute requirement for the field to transform into a true biodesign engineering discipline. From the recording and analysis of raw data at the R&D stage, through execution of automated workflows in custom hardware, to design transfer, data management and curation, commercial manufacture and regulatory approvals; standardisation is fundamental to success. Nevertheless, standardisation has proven a difficult nut to crack. There is no unified set of standards or as one participant put it, *"there is currently no operating system for synthetic biology."*

As touched on previously, the proliferation of tools is seen to counteract the drive towards standardisation. There is no agreement on which are the best standard tools to use in which situation. At a basic level of implementation, cross-communication between different pieces of equipment in the laboratory is difficult, a situation that has created an opportunity for Laboratory Information Management Systems (LIMS) tools providers. However, accurate implementation of protocols often relies on the individual scientist's capability to execute a protocol, a situation made worse by unintuitive and complex user interfaces, ambiguous and incomplete protocols and a lack of incentive to standardise workflows. This situation was viewed as potentially addressable by imposing standards, with some participants even suggesting that *"we should reset GLP (good laboratory practice) to include standardisation".*

> *"There is currently no operating system for synthetic biology"*

Another issue is how scientific data is recorded and annotated. If systems such as LIMS are not standardised and easy to implement and use, scientists resort to recording data in multiple places and without the requisite consistency and error-checking. There are many different LIMS platforms, with different software applications and bespoke data management standards, which leads to even more variation. The view that *"LIMS only work when there is one workflow and any LIMS needs a lot of customisation"* means that current solutions are not flexible enough for the more complex workflows required by a synthetic biology laboratory.

There is a clear need for improved modularity, flexibility and integration in tools for collecting and storing data to support standardisation. The current situation, where *"everything*

is siloed", means that data may never be integrated, data loses its context or negative results are excluded. Laboratory automation is often cited as a potential solution to these issues, however automating the manual processes of the lab scientist is not that simple. Even a workflow that is well-defined, documented and produces good outcomes may currently be problematic to reproduce on a computer or using robotics. Improving the ability of automation hardware and software systems to execute static and dynamic workflow components might alleviate this problem and lead to increased adoption in synthetic biology laboratories.

The lack of standardisation also affects how results are communicated once they have been generated, recorded and analysed. It was noted during the workshop that the lack of clear and unambiguous standards for communicating data results in large variability in how data from different sources are merged and shared. There is also a widespread problem of data being locked in *"organisational silos"*. It was suggested that one potential solution to these problems is a standardised, universal common language for biodesign. This might take the form of a technical standard, issued by a group such as the International Organization for Standardization (ISO) and thus developed using existing mechanisms and processes. Such a standard would unambiguously define types of data, what data is needed in what circumstance, how data is tagged and presented and – critically – how data quality is maintained.

Going beyond laboratory data management, standardisation was also highlighted as the key to successfully interfacing the many constituent parts and stakeholders of the biodesign industry and supply chains. From the setting of design parameters by non-experts, to transfer of laboratory protocols by scientists, to commercial scale production by CMOs, to public relations and marketing, the ability to exchange relevant information concisely and consistently will be crucial for building trust in the field of biodesign.

How, then, should standards be created and implemented? It was recognised during the workshop that the process of standardisation must be treated sensitively, as the imposition of restrictive standards may lead to undue restraints on the emerging industry, leading to innovators being excluded from entering the market place. Conversely, standards may offer an opportunity for early adopters to entrench their market position. Consensus on standards definition was highlighted as an important aspect, to ensure that there would not be multiple variants of standards from different bodies. Standardisation within software was agreed to be a useful place to start, as *"once the language is standardised, the quality of the content increases"*. The standardisation would then emerge naturally and provide an incentive to standardise components across all levels.

One advantage that the synthetic biology industry has over other industries in agreeing on and establishing standards is that it is a highly collaborative field, where the players *"are prepared to talk to each other"* unlike other more entrenched and closed industries.

Opportunity #3: Scalability

Scalability is a major challenge for synthetic biology. Whereas the aim, in the words of one of the workshop participants, is to be able to *"take a molecule from a whiteboard to production scale of greater than one tonne reliably within one year"* the reality is that bridging the gap between laboratory scale and production scale is a major bottleneck.

Currently, *"CMOs have not risen to the challenge"* of taking a 250ml volume at lab-scale to 50,000 litres at a commercial scale. It was discussed that contract manufacturers may not be physically or organisationally set up today easily to manage the diverse and complex requirements of synthetic biology. This leads to extensive one-off customisation and can require prohibitive up-front capital expenditures that are not fully de-risked. The CMO struggles to balance the risk and reward, particularly with high-volume low-margin products where small changes in feedstock cost or product price have a big impact on profits.

To add to this, the commercial volumes required by start-ups with novel products may not justify investment in the equipment required to set up a dedicated plant. There is, in the words of one of the participants, a clear opportunity for *"CMOs that can output a range of synthetic biology products using one set of assets"*.

To achieve this range of products while maximising their use of plant and capital, CMOs could become more agile

and capable of adjusting their manufacturing processes to accommodate many different types of variability. There is variability in the cell type, from mammalian cells to *E. coli* or *Clostridia*, and there is even more variability stemming from the unpredictability of biological systems and individual pathways, or from novel genetic circuits. The requirement for flexibility to allow for customisation will need to be balanced against the need to standardise to ensure efficient transfer from low-volume R&D batches to commercial scale.

> *"CMOs that can output a range of synthetic biology products using one set of assets"*

Key to managing this variability will be simulations of fermenters at different scales, given known initial conditions. To that effect, scale-down simulators are now being used to generate insights into differences in transcriptional and metabolic response within cells in large-scale fermenters. These insights can be translated into models and applied to predict scale-up performance. As more and more multifactorial data is collected on such systems, the predictive power of simulations should increase.

Our lack of understanding of how to switch from lab-scale to production-scale may also be caused by not being able to measure enough parameters to build a true understanding, and having limited experimental bandwidth to validate simulations. One potential solution is simply to use large numbers of low-volume fermenters, which could be called a form of 'horizontal' scaling. We know well how the process works at a small, lab scale. 400 small-scale fermenters carrying one litre each could be used, instead of one production-scale fermenter which can carry 400 litres. Creating demand for small-scale fermenters could make the economics of lower-cost fermenters to be used in this way feasible, for example WAVE bioreactors. This was discussed at length during the workshop, with some suggesting that the costs of such a horizontal process might be a limiting factor.

It was observed by participants that there is a general lack of confidence among CMOs regarding biological approaches versus chemical approaches. There is limited assurance that every member of the chain will receive value and an acceptable speed to market. Uncertainties also exist in the access to finance for emerging companies. Some venture capitalists feel that the *"good science"* from synthetic biology companies leads to very expensive scale-up and uncertain outcomes. This is unlike safer investments in the pharmaceutical industry, which also has expensive and difficult scale-ups, but has more predictable outcomes in terms of value creation due to the high value of the product. Many synthetic biology companies have therefore either avoided or missed out on early-stage venture capital funding.

This need for flexibility and straightforward customisation implies a much closer relationship between development and scale-up teams. There is already a trend for CMOs to become Contract Development and Manufacturing Organisations (CDMOs), driven in part by the increasing prevalence of biologic drugs in the pharmaceutical industry with complex manufacturing processes. Synthetic biology can capitalise on this trend for integration of development and optimisation of manufacture.

In summary, improvements in the predictability of biology will lead to an increased ability to properly de-risk the scale-up process and successfully transfer lab scale cultures to commercial production scale. There is also an opportunity for more agile CMOs who can scale up rapidly across a diverse portfolio of products to manage their risk.

Opportunity #4: Downstream processing

To take a product to market, a biodesign company will have to engineer organisms and demonstrate feasibility on a lab-scale, scale up to production-scale and carry out downstream processing to manufacture the final biobased product. It was agreed among participants that while synthetic biology companies are often experts in engineering organisms and demonstrating them on a lab scale, proceeding all the way to a finished product remains a challenge.

The downstream processing part of the value chain *"absorbs up to 60-70% of the costs"* in manufacturing, due to the need to customise processes on a case-by-case basis. Other challenges in downstream processing include purification, as the presence of impurities can cause problems for customers, or in meeting customer requirements further down the supply chain.

There must be a more holistic non-siloed approach to resolve this. Biodesigners can take the limitations of downstream processing into account and design products that require simpler processes. For example, customising more selective enzymes in the organism. R&D teams need to focus on by-products and impurities at lab scale and during pre-production, so that issues are found well before full production, where changes are very costly. The R&D teams need to be equipped appropriately to do this, with both knowledge of downstream processing limitations and instrumentation to characterise by-products.

There also must be a seamless integrated transfer between large-scale upstream production and subsequent downstream processing, using both chemistry and biology techniques. Existing chemical processes and technologies are well developed, or a biological equivalent may not exist, meaning that retaining chemistry in the supply chain may be the best approach. Allowing flexibility to adopt hybrid chemical/biological approaches is an opportunity to attain higher efficiencies, lower costs or to enable novel products to reach the market.

ACCESSIBILITY – *"DEMAND IS HELD BACK BY NON-EXPERT PERCEPTIONS"*

THE CHALLENGE: Communicating the potential of biodesign to solve problems in a way a non-expert can understand

During the workshop, it was observed that *"perceptions of users and commentators are very far from those in the synthetic biology industry"*. This has a fundamental impact on the field, as it means that biodesign is not seen by non-experts within other industries as an accessible and available path to creating products that are acceptable to end users. The lack of information sharing within the synthetic biology community was also seen to reduce accessibility. It was generally agreed that for biodesign to become an engineering discipline on a par with, for example, electronics or mechanical engineering, it will be necessary to improve accessibility within the field itself, as well as the acceptability to the general public and among commercial buyers.

Opportunity #1: Public perception

Participants suggested that one way to improve the public perception of synthetic biology is to visibly and directly address otherwise intractable issues. It was repeatedly emphasised that for synthetic biology products to be successful commercially, accessibility needs to be improved and the benefits clearly communicated, particularly to non-experts.

By developing narratives describing benefits that are easy to articulate with clarity, such as the production of antibody-based therapeutics using recombinant DNA technology, the field can be seen to receive *"permission"* from the public. The development of products and services which have major impacts on people's lives have the potential to generate strong public acceptance, which may balance out lingering negative connotations associated with Genetic Modification (GM) technology, for example, the potential for biodesign to create non-polluting bioplastics. The field must create *"a new standard for GM that consumers can understand"*, replacing the unfavourable undertones associated with terms such as GM and 'gene hacking', while remaining sensitive to legitimate concerns around safety and dual use.

Adoption of new products and services emerging from synthetic biology will be dependent on public opinion, which in turn may hold sway over political and regulatory authorities. Public acceptance of synthetic biology and biodesign is paramount, regardless of strong scientific evidence of product safety. The need for products that win public acceptance and meet real needs is particularly important, focusing on *"putting more effort into product definition"* and *"manipulating biology with the end use case in mind, not just generating diversity"*. It will be critical for the field to engage in *"advocacy to create pull-through"*, to generate strong demand for products based on unequivocal benefits.

Several workshop participants emphasised the need for the synthetic biology industry to have more *"winners"* and *"success stories"* to aid in the public communication of the benefits of synthetic biology. It is worth noting, however, that there was a split between participants in the workshop on this matter, with some participants instead focusing on the need for the synthetic biology community to *"stop putting ourselves down"*. However, it was agreed the products themselves are a necessary part of any success story, with easy-to-communicate benefits. It was felt that to improve access, synthetic biology should focus on truly disruptive new products, rather than chase existing products where it may be difficult to demonstrate value – there is *"no point tinkering around the edges"*.

> *"...manipulating biology with the end use case in mind, not just generating diversity"*

It was suggested that tackling an iconic 'grand challenge' might be a positive way to demonstrate the value of synthetic biology and biodesign to the public. A grand challenge might be an opportunity to promote an open-source approach and to align with industry, regulatory bodies and government initiatives. One participant observed that *"there has been a lot of success around the edges of the XPRIZE[1]"*. The XPRIZE initiative offers a cash prize for solving a particular, big,

[1] https://www.xprize.org/

difficult problem and the expenditure this encourages leads to rapid innovation around the problem. Often the work it inspires greatly exceeds the value of the prize itself; the prize is a catalyst to innovation.

Several participants suggested that the reduction of plastic waste might be a suitable similar grand challenge for biodesign. Biodesign could be used to tackle this in many ways, from better management of waste streams to creating novel materials to replace plastic. This challenge would be ambitious, have global impact and could inspire biodesigners around the world.

Opportunity #2: Commercial acceptability

For commercial customers and partners – who may or may not have any previous experience with synthetic biology – acceptability is dependent on a clear business case. The current lack of a long-standing track record for synthetic biology means that investors face significant uncertainty in relation to cost estimates and the timelines involved in commercialising a novel product derived from synthetic biology.

Synthetic biology will also need to establish itself as an attractive technology platform for commercial customers comparable to existing approaches. Incumbent businesses and customers have established processes and locked-in technology, and they will need to be convinced of the advantage of synthetic biology over their existing technologies. Acceptability issues may also arise because of mismatched stakeholder needs, as one participant put it; *"the customer may be a brand guy who is only interested in cost/benefit, whereas the language of synthetic biology is technical"*. Conversely, if the benefits are clearly communicated and needs are met, it was argued that commercial customers do not necessarily need to understand the details of how the biological platform works.

Another perceived disincentive for commercial uptake is the current regulatory requirements for demonstrating product safety. It was observed by a workshop participant that the time taken for regulatory processes to be updated is not keeping pace with the development of the industry, and that this process is becoming ever slower. The consensus among participants was that *"regulation influencing business decisions is a good thing, but it must be unambiguous and intentional"*. One suggested route towards solving this issue was the development of tools for *"predicting and proving safety upfront"*, which would allow companies to educate regulators about the risk level, while simultaneously de-risking processes throughout the supply chain and providing better justifications for investment.

Opportunity #3: Sharing in the biodesign community

Data accessibility was a keenly discussed topic during the workshop and seen to be essential for the future success of biodesign as an established engineering discipline.

Data sharing, including metadata to give the complete context, was emphasised as crucial for progress: *"we need to make it beneficial to the individual to share data and results, including negative ones"*, so that 'bugs' can be solved, blind alleys are not revisited, and allowing scientists to build on the data and insights generated by their peers. However, there are several limiting factors to data sharing, including confidentiality and ownership issues, intellectual property concerns and regulatory restrictions.

How can valuable scientific data be shared without compromising competitive edges? Currently, tools and processes may be central to what makes a synthetic biology company competitive, and as such they may be the subject of several layers of protection: *"one person's tool is another person's business"*. At the heart of those tools and processes is experimental data, which is therefore treated as a protected asset, which in turn leads to a general lack of openness in the scientific community. In the words of one workshop participant: *"we need to establish business models that enable and encourage data sharing and open source"*.

As with many other aspects of synthetic biology and biodesign, standardisation is seen to play an important role in data accessibility. For instance, a database that can hold all types of data generated by synthetic biology could be created to enable all users to access and understand not only the data itself, but also how it was generated and its general context. The role of creating such specialist data could be in the hands of aggregators, people who take the responsibility of collecting and curating the data so that all users have access to it.

> *"We need to establish business models that enable and encourage data sharing and open source"*

There is also a general lack of clarity around the current state-of-the-art, resulting in Freedom to Operate (FTO) being notoriously hard to define, and there is not sufficient case law to set reliable precedents. The frequent question of *"am I allowed to do this?"* is often difficult to answer, as rules

around infringement differ between jurisdictions. This is also a consequence of the delay between patent applications and grants, which can extend to many years. The current state of play with regards to the patent protection surrounding gene-editing, in particular CRISPR/Cas9 and related technologies, has led to a situation where uncertainty is affecting decision-making around molecular biology strategies for construct design, cell-line editing for production and even investment decisions. The question can be posed *"will I get sued for this?"* and the only response is *"maybe".*

This concern is likely to escalate over the coming years, with more and more new applications being developed for gene-edited constructs and organisms and subsequent creation of valuable royalty streams. One strategy that might help to mitigate uncertainty around future freedom to operate could be the creation of patent pools, whereby rights holders place their IP protection into a common pool to simplify the licensing and royalty distribution arrangements for end-users and application developers. Such arrangements are common in other sectors, such as IT and telecoms, and could work well in synthetic biology which is a comparatively collegiate community.

In addition, global agreements and conventions may come into play, such as the Nagoya Protocol[2] which seeks to implement fair sharing of the benefits arising from access to genetic resources. This was an output of the 1992 Convention on Biological Diversity, and was adopted in 2010. The Nagoya Protocol has yet to be ratified in several countries, including the USA. There are many difficult and unanswered questions pertaining to how synthetic biology might be affected by the requirement to comply with the Nagoya protocol. For example, how does the protocol apply in the case of a rare plant from abroad which has been sequenced and the resulting sequences now being placed within a modified microbial organism? It was asked, *"what if we use sequences from an extinct plant?"* A further consequence may be that companies deliberately choose starting materials that are not subject to Nagoya, which could also hinder product development. More clarity is needed on the implications of these protocols, so that biodesign is stimulated, not stifled, by them.

This confusion serves to demonstrate a wider point around the gap between technology development and regulatory and policy development. The Nagoya Protocol doesn't have clear concepts that can provide guidance around the synthesis of constructs, let alone the idea of creating whole chromosomes

or genomes. Other regulatory regimes suffer from similar lags. For example, the release of genetically modified organisms into the environment, or for human consumption, is governed under different standards, by regulatory bodies with different philosophies, in different jurisdictions. This has been a real problem for products such as Friendly Aedes mosquitoes[3]. This latter case also leads on to the challenge of engaging both with regulators to navigate an ill-defined approval process, and working with local populations to secure buy-in and acceptance from the users who will be most directly affected.

A clear and unambiguous regulatory framework would therefore be very helpful, and could also be of benefit in other ways. One repeated desire was the ability to move safety testing of new products to as early a stage in the development process as possible. Clarity around the data that would prove environmental and health safety to the satisfaction of regulators would in turn allow the development of safety assessment tools and protocols that could be implemented in the discovery phase, and potentially made into high-throughput processes.

A final point on regulation was the observation that regulatory frameworks need to be both timely but also well-considered. "*It is very hard to get rid of a bad regulation once it is made*" was highlighted as a concern. The other implication is that changing regulations necessitate changes in production processes, which can be very expensive and time-consuming to implement.

[2] https://www.cbd.int/abs/

[3] http://www.oxitec.com/

CONCLUSIONS

How close is the synthetic biology field to reaching the 2023 vision of a biodesign engineering discipline? While workshop participants agreed that *"we need to change the fundamental approach"*, it was widely agreed that the technology aspects are well ahead of the overall cultural and organisational aspects. While some development is still needed to improve the technological tools from where we are today, participants broadly agreed that there are many reasons to be optimistic about the situation in five years' time. Where a breakthrough is greatly needed is in the overall systems approach and how the industry is integrated, *"we are just at the point of shifting from tools development to applications"*.

From a technology perspective, there is still a strong need for better tools and technologies that enable more powerful predictive models. It is only when a better system model is available that measurements become meaningful so that the correct system changes can be made and the outcome of those changes can be predicted. For this to be possible, the industry will need a greater number of *"biologists who are comfortable with engineering, and engineers who are comfortable with biology"*. The workforce for synthetic biology is evolving, with traditional scientist-at-the-bench molecular biology being replaced by automation through robotics. As a result, a particularly critical problem will be attracting and recruiting people with skills in machine learning and artificial intelligence, to interpret the large volumes of data and translate that data into valuable information. For synthetic biology to evolve and become more like other engineering discipline, it needs a step change in the ability of biodesigners and their tools to turn design inputs into predictable outputs. The participants were confident that the tools and technologies to do so will be in our hands by 2023, but their adoption and the change in culture needed to enact this step change seems less likely.

From a commercial perspective, it is time for a step change in how companies produce synthetic biology products. The industry needs to shift from a 'one company does it all' model to a network of specialised companies, contributing to an integrated, efficient and competitive supply chain. Not only does this approach build expertise and allow companies to focus on their strengths, but it also reduces development risk and thereby builds investor confidence.

Running right through this goal is the need for standardisation; as summarised by one of the participants: *"standards generate trust"*. Synthetic biology must become more standardised at many different levels, from R&D to manufacturing, with a set of viable, pragmatic standards that set attainable specifications and do not inhibit innovation at an early stage. Standardisation will also have an important role to play in enabling the synthetic biology industry to be able to transfer the benefits to commercial partners and other members in the supply chain, who are looking for ways to innovate in the manufacturing of products that answer customer needs. To achieve this, synthetic biology must be accessible to non-experts, with safety assurance and return on investment being the central factors for building convincing business cases that boost confidence in the field.

Finally, an increased focus on products, technologies and services with tangible benefits will enable the field to gain approval by the public and become a component of products that impact on people's everyday lives. The themes of community and communication will be key to realising the vision for synthetic biology to transform into the engineering discipline of biodesign. The community must work together to address the challenges of making biology and scale-up more predictable, through collaborations, and sharing tools and data in a commercially sensitive manner. It must work together to move from the technical language of synthetic biology to a language that all stakeholders – from the public, government and commercial buyers – can engage with and adopt easily. Above all, the biodesign community must be able to articulate the benefits and value proposition of synthetic biology clearly to these stakeholders. Biodesign then becomes accessible for all, moving away from outstanding technical scientific achievements reproducible only in a particular laboratory, to a commercially attractive, routine and robust way of making novel game-changing products.

Based on these discussions, Cambridge Consultants believes that synthetic biology is ready to change gear and over the next five years transition to true biodesign: predictable, competitive and accessible.

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About Cambridge Consultants

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With a team of more than 750 staff in the UK, the USA, Singapore and Japan, we have all the in-house skills needed to help you – from creating innovative concepts right the way through to taking your product into manufacturing. Most of our projects deliver prototype hardware or software and trials production batches. Equally, our technology consultants can help you to maximise your product portfolio and technology roadmap.

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