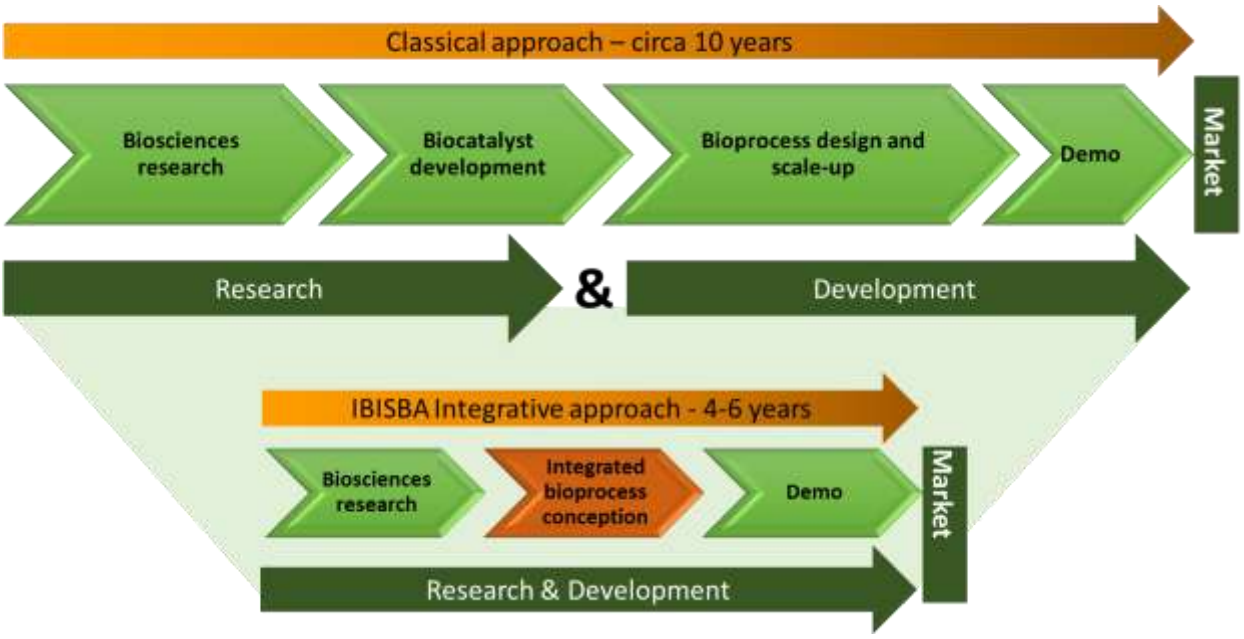
Meeting the challenges of industrial biotechnology in the age of synthetic biology

Description of a proposed European research infrastructure dedicated to integrative industrial biotechnology[1]



[1] A European Research Infrastructure for Integrative Industrial Biotechnology has been proposed to the ESFRI committee by a European consortium coordinated by Dr. Michael J. O'Donohue (michael.odonohue@insa-toulouse.fr; LISBP, Toulouse, France). This white paper was co-authored by the members of the consortium.

Executive summary

The context

The bio-economy transition is a unique opportunity for Europe to develop more sustainable processes and address grand challenges, such as climate change and food security. Moreover, this shift is a chance to create new jobs, regain competitiveness and maintain industrial leadership in many high added-value market sectors.

The problems

According to specialists, industrial biotechnology will be a cornerstone of the bio-economy, with synthetic biology providing impetus and considerable innovation. However, for industrial biotechnology to fully realize its potential, a number of hurdles need to be surmounted in order to reduce time to the market of products. One of the first identifiable hurdles is the current difficulty to keep up with the flow of big data, notably when it involves the detailed functional validation of bioparts. Presently this is happening at snail pace compared to the speed at which putative parts are being identified. Beyond this it is clear that knowledge flow is suboptimal. This translates into the fact that it is not easy to implement cutting-edge scientific knowledge at the latter stages of process/product development and inversely it is equally difficult to translate industrial know-how and process constraints into the ideation and early TRL phases of bioprocess design, including the engineering of enzymes and/or microbial systems. Reproducibility and scalability of biotechnological tools and processes are also persistent problems, as is the high level of technological fragmentation in the European arena. This latter problem is compounded by the rarity of initiatives aimed at greater mutualisation and interoperability. This is very damaging when one considers that R&D in industrial biotechnology is currently considered by both public and private stakeholders to be highly resource-intensive.

The proposed solution

To solve some of the abovementioned problems, we propose to implement a pan-European research infrastructure for the development of new technologies and strategies for public and private researchers involved in the field of industrial biotechnology. The ambition is to create novel tools and adopt new R&D practices that will drive scientific knowledge further along the R&D pipeline, while developing approaches to better capture industrial process constraints in the earlier ideation and prototype building phases. To achieve this, a range of existing European facilities present in several member states will be interconnected using advanced ICT solutions and operated in a consistent manner, thus creating a R&D continuum covering project development from Technology Readiness Level (TRL) 2 to 6.

The ultimate goal

The overall aim of the proposed European research infrastructure is to provide the scientific and technical means to halve the average development phase (concept to market time) of bioprocesses (now approximately 10 years) by 2, thus matching the current performance of chemical processes. The achievement of this goal will (i) significantly reduce the financial burden and risk associated with industrial biotechnology, (ii) increase the number of products produced by industrial biotechnology and thereby (iii) increase the fitness of European industry to respond to changing global markets.

Introduction

The knowledge-based bio-economy (KBBE) is rightly hailed by the European Commission as a unique opportunity for Europe to increase the efficiency of its research, and thus reinforce scientific and industrial leadership and consequently create new jobs and increase competitiveness. Moreover, this change in economic paradigm represents an opportunity to reduce emissions of greenhouse gases and transition to a more sustainable society, using for example renewable resources and waste as raw materials for manufacturing of bulk and fine chemicals, nutraceuticals, pharmaceuticals, food and feed and energy.

A cornerstone of the bio-economy is industrial biotechnology, an area in which Europe has so far excelled, notably thanks to its thriving industrial chemistry sector and excellence in biotechnology of its academic research. However, for Europe to remain a world leader, measures need to be taken to fully reap the benefits of the bioscience revolution and thrust biotechnology towards full industrial maturity.

Harnessing the bioscience revolution and promoting open science

The bioscience revolution, epitomized by the omics sciences and big data, has already had a profound impact on industrial biotechnology, producing the underpinning knowledge necessary to tackle the design and redesign of biological systems (e.g. enzymes, metabolic circuits and whole microorganisms). Presently, synthetic biology is set to provide industrial biotechnology with a new generation of catalysts including new enzymes and engineered microorganisms that will open the way towards an unprecedented era of biomanufacturing applied to a large number of market sectors. However, for all of this to materialize, a number of vital challenges need to be addressed.

Aligning synthetic biology with industrial reality

Until recently, the availability of enzymes and microorganisms relied on the exploitation of natural biodiversity that has proved to be a rich source of enzymes and microorganisms, furnishing most of the workhorses of today's industrial biotechnology. However, recent advances in biosciences have provided a whole new array of scientific approaches (genomics and metagenomics) and high-throughput tools that are empowering scientists with the ability to push the exploration of biodiversity to hitherto unattained heights, using DNA-based technologies and intensive screening strategies to tap into the wealth of enzymes and other subcellular bioparts, such as gene promoters, regulators, transport proteins etc, even though much remains to be achieved in terms of high throughput characterization of newly discovered bioparts.

In the case of microorganisms, the omics boom and systems biology have provided the scientific foundations for synthetic biology, which is opening up opportunities to tackle the rational design or redesign of cellular factories using engineering principles. In this case the aim is to provide new and more robust microorganisms that are better adapted to the target application and that behave in a more predictable fashion under operating conditions. Finally, aforementioned advances in biosciences are also beginning to impact the understanding of microbial consortia. Consortia-scale metabolic modelling and engineering is the next goal.

Most of the work in biocatalyst (i.e. enzymes and microorganisms used to catalyze biotransformation) design and engineering is being performed by microbiologists, biochemists and computational biologists in the TRL range of 2 to 3. In terms of experimental targets, a lot of

effort is generally put on the improvement of stability and productivity, but the early integration of other industrial (e.g. those related to downstream separation and purification, or safety issues) and wider socioeconomic constraints is much rarer and so far no formal methodologies have been put into place to achieve this, although the idea of retrosynthesis in biology is an emerging concept that holds the potential to allow multicriteria optimization.

Keeping abreast of big bio-data

In the space of just a few years the cost of DNA sequencing has plummeted to the extent that single microbial genome can be fully elucidated for less than €300. These and other advances driven by miniaturization and automation provide the researcher with a wealth of putative biological parts (promoters, protein coding sequences etc), which are the nuts and bolts of synthetic biology. However, with an ever-growing reservoir of bioparts, it is increasingly evident that the new bottleneck is functional validation. Presently, in a database such as CAZy (www.cazy.org - a repository for sequences encoding putative carbohydrate-acting enzymes and related proteins), <10% of sequences have actually been characterized, which illustrates the gulf between DNA sequence determination and the experimental attribution of biological function. Moreover, even when bioparts are thoroughly characterized, there is no guarantee that the function of the biopart will be reproducible when transferred from one species to another, a fact that underlines the need for testing in multiple host systems (bacteria, yeast, fungi etc) and for suitable data repositories, such as the Registry of Standard Biological Parts (parts.igem.org/Main_Page) or the Inventory of Composable Elements public-registry.jbei.org/login

Producing reliable and shareable data

In the context of industrial biotechnology, complexity is ubiquitous, concerning both the biomass that forms the major feedstock of the sector as well as the bioparts that are the components of complex biocatalytic systems, such as microorganisms. In the case of biomass, this is highly complex composite material composed of a multitude of biomolecules that together constitute a considerable challenge for analytical biochemists. Likewise, the characterization of bioparts is complicated by the fact that these are sophisticated and often unpredictable components whose characterization is rather context-dependent and can involve quite elaborate analytical procedures. Clearly, the only way to tackle complexity in industrial biotechnology is to develop robust analytical procedures that can be shared with an extensive community of researchers who are properly trained in the use of these and who are interconnected in a dynamic process whose goal is to achieve maximum reproducibility and constitute a unified body of data.

Although a considerable amount of work has been performed in the area of protocol standardization, for example work achieved by the NREL (www.nrel.gov/biomass/analytical_procedures.html) in the USA that has standardized and disseminated protocols via its website, there is still a persistent problem of reproducibility, which significantly handicaps processes especially when it comes to scale-up. Regarding the characterization of bioparts, a similar diagnosis has been made by the authors of the ERASynBio vision paper[2]. They state that the use of registries, such as the Registry of Standard Biological Parts remains low, because of data

[2] www.erasynbio.eu/lw_resource/datapool/_items/item_58/erasynbiostrategicvision.pdf

quality control issues and that there is currently a strong risk of fragmentation. Although data quality is probably not an issue in the ICE database hosted by JBEI, it is clear that this service was not created specifically with product lifecycle management needs in mind. Therefore, it is urgent not only to devise robust protocols for dissemination to researchers, but more importantly, a consistent framework for the use of these and for the control of data quality. In this way, biopart characterization can be better standardized and adapted to provide appropriate data use in the development of bioprocesses, including descriptions of how various bioparts behave in different chassis organism environments and bioprocess conditions.

Among the most effective methods that can be adopted to improve the collection and dissemination of robust data, is efficient high quality personnel training for researchers and technical staff, and cutting edge education for students. In this respect, more cooperation among institutions active in the field of biotechnology is required to ensure that research personnel and students receive solid training using well-established standardized methods that can be reproduced in different laboratory environments. Additionally, researchers need to have greater access to analytical data and the means to rapidly judge its quality.

Tackling the specifics of the bioprocess challenge

New methodologies for process design

Industrial biotechnology is essentially about the deployment of biocatalysts (enzymes, microorganisms etc) within a process environment, the combination of which allows the industrial manufacture of goods. Therefore, like all process development work, bioprocess design involves activities that are familiar to the chemical engineer. These include the selection of unit operations (process synthesis), modelling, process flowsheeting and process integration. However, unlike conventional process design, where feedstocks and products are quite invariable, the design of bioprocesses needs to account for the greater variability of the feedstock (e.g. diversity of plant-based matter) and wider product diversity (from fuels to pharmaceuticals), and thus a larger spectrum of market sectors. Moreover, biological catalysts are quite different from conventional ones, making the design of bioprocesses a daunting task, much more challenging than the well-established chemical processes operated by the oil and gas industries. However, this added complexity also provides greater scope for creative thinking and new designs.

Presently, it is clear that bioprocess engineering, requires advanced models that will offer strong synthesis capabilities and new functions that will allow for an increased options in terms of processing pathways and products. Moreover, multiple chemistries need to be screened and selected, not only with respect to the individual products, but also with respect to their integration with other pathways. Similarly, bioprocess flowsheeting, using tools such as Aspen Process Tools (Aspen Technology or SuperPro Designer®), is also in need of new methods, since current models borrowed from the oil and gas industries are insufficient to support synthesis and *in silico* high-throughput analysis of bioconversion pathways, and regularly fall short of providing basic property and unit operation models. This means that it is often impossible to use modelling to address flowsheeting in a satisfactory manner. Moreover, bioprocess designs are often crude and result in misleading analysis, scale-up studies are inaccurate and lead to erroneous costing, the latter being rather negative for investor engagement.

R&D work on biorenewables has already produced strong evidence that there is tremendous scope for process integration and process innovation. Nevertheless, the systems background required to pursue the analysis is currently missing. Additionally, like all industrial processes, bioprocess design needs to take into account economics, industrial safety and increasingly environmental sustainability, the latter requiring particular attention with regard to energy and water consumption.

Rethinking process configurations and downstream processing

Generally, biological reaction rates are slower than chemical ones and are limited by mass transfer. Moreover, enzymes and microorganisms are often subject to product toxicity. For these reasons, novel arrangements of reactor compartments both within and outside the living cell are expected to make a difference. Similarly, new downstream processing approaches, such as the integration of reaction and product separation is a promising route that needs to be further developed in order to increase the performance of bioconversions that are currently deemed industrially unfeasible. Finally, apart from boosting reaction conversion rates and selectivity, novel equipment represents valuable intellectual property that will supply its inventors with a cutting-edge in the competitive world of industrial biotechnology.

New tools to face the scale-up challenge

Currently the scaling up of bioprocesses is probably one of the most troublesome phases in the R&D process. The reasons for this bottleneck are multiple and the result is often a considerable waste of resources and time. Briefly, scale-up requires the integration of industrial-scale engineering approaches and (sub)cellular-scale bioengineering, a process that is not yet formalized, especially because many of the correlations and relationships that have been described for chemical processes do not apply when using enzymes, microorganisms or microbial consortia. This problem is compounded weaknesses in current academic curricula. The result is that many scientists involved in the design of enzymes and microbial systems remain largely unaware of industrial constraints and process limitations and are in any case deprived of convenient methods to quickly evaluate the impact of their research. On the other hand, biologists are rarely engaged by chemical engineers in early dialogue aimed at stymying bottlenecks that prevent their knowledge from being translated into industrial processes. Moreover, the practical options to build readily-scalable biocatalyst technologies are currently throughput-limited, because initial scaleability trials are normally performed in bench scale fermenters (i.e. 1 to 20 L), which are incompatible with large numbers of parallel trials. Therefore, the need for high-throughput microbioreactors and microscale equipment to test downstream separation and purification protocols is clear, but these are not yet readily available to all research laboratories. Finally, the wide diversity of biocatalysts (e.g. enzymes, bacteria, yeast, fungi, microalgae etc) and the complexity of reaction mixtures associated with industrial biotechnology means that scale-up is often tricky, calling for the deployment of resource-intensive product isolation and purification methods, which generate quite diverse needs in terms of equipment and handling.

Addressing professional mindsets and societal challenges

The science-engineering divide

Logically industrial biotechnology requires strong synergy between biology, computer science and chemical engineering, a fact that is

emphasized by the advent of synthetic biology. However, educational trends do not globally reflect this fact, since biologists are not generally trained in both engineering and computer science, and chemical engineers rarely receive significant formal training in biology. This results in a well-known silo effect, where biologists are mostly responsible for the development of enzymes and microbial systems, while chemical engineers develop bioprocesses, moving these out of the laboratory and into industrially-relevant environments such as pilot plants. Therefore, while biologists usually have in-depth knowledge of the underpinning biological phenomena that determine the performance of enzymes and microbial systems in the simplified context of the laboratory, chemical engineers are well-versed in macro-phenomena that underlie some of the challenges inherent to the scale up of bioprocesses. Fortunately, some European universities have developed multidisciplinary undergraduate and graduate courses to address this issue, but much more needs to be achieved in order to ensure the continuum between biocatalyst and bioprocess development and to sustain the growth of the industrial biotechnology sector with a sufficiently large number of polyvalent professionals. Undoubtedly, there remains considerable scope for improvement, notably through the development of academic programs that are better adapted to the current realities of industrial biotechnology.

Putting science into society and alleviating public wariness

Although industrial biotechnology is already an integral part of day-to-day life, being widely used for example in the food and feed industry, it is mostly invisible to the public at large. However, the emergence of synthetic biology is strongly underlining the fact that industrial biotechnology is set to revolutionise manufacturing, thrusting the bio-economy to the forefront of public awareness. Accordingly, it is clear that the fast-track to a successful bio-economy will not only depend on the capacity of scientists and engineers to meet the technology challenges, but also on their ability to demonstrate that such technology is both useful to humankind and likely to lead to a more sustainable industrial future. To achieve this, public buy-in needs to be secured, ensuring future demand for the products of industrial biotechnology. A prerequisite for public buy-in is confidence in researchers working in the field of industrial biotechnology. For this, researchers need to raise their awareness of the underlying ethics and develop a clearer vision of how to best achieve sustainability, from environmental, legal and social standpoints. Moreover, researchers need to be better engaged with the public and other stakeholders, including industry, consumer associations, and policymakers.

Time to move forward

Creating the basis for the bio-economy transition

It is legitimate to consider the bio-economy as a new industrial revolution. Once implemented it is anticipated that the bio-economy will provide Europe with a new source of qualified employment, rejuvenated competitiveness and a new era of industrial leadership. Moreover, this shift represents an opportunity to address grand challenges such as global warming[3,4]. However, Europe is not alone and the bio-economy is a goal shared by many countries including economic giants, such as the USA and China. Therefore, for Europe to retain its leadership in this highly competitive international context, it is necessary to radically overhaul current practices.

History tells us that the first industrial revolution was brought about by a series of progressive

[3] Innovating for Sustainable Growth:A Bio-economy for Europe (European Commission 2012)
[4] The Bio-economy to 2030: Designing a policy agenda (OECD 2009)

changes that include the harnessing of new sources of power and resources, the development and deployment of new technologies, the growth of education and knowledge sharing, and the engagement of significant public and private investment. Many of these upheavals were made possible by structural changes that transferred financial and political initiative from the local level (towns and cities) to the national level, thus supplying critical financial mass and an appropriate level of coordination. Therefore, in the present context, it is possible to postulate that the ability of Europe to succeed in the bio-economy revolution, will to a large extent depend on its ability to draw together financial resources and political will in order to generate sufficient traction. In the field of research, this necessarily implies less fragmentation and more cooperation, notably regarding the purchase and operation of research infrastructures. Nevertheless, in the context of the European Union the creation of a single geographically-localized European research infrastructure in industrial biotechnology appears to be both unfeasible, undesirable and, in the light of experience that can be drawn from multinational enterprises, unnecessary. Instead, a distributed, multinational European infrastructure favouring strong collaboration between EU researchers and interconnected using the most recent developments in complex systems management is probably the most appropriate solution. An infrastructure of this type, with some form of central governance will provide the level of coordination necessary to generate added-value and provide the impetus to significantly accelerate the development of industrial bio-manufacturing processes. Moreover, accounting for the intrinsically applied aim of research in industrial biotechnology, a distributed pan-European research infrastructure will provide the ideal framework for a new form of collaboration between academia and industry, wherein national-based companies will continue to be able to easily identify their local academic R&D support network, while gaining access to a much wider and deeper set of scientific competencies and technical skills. Overall, this organisation will lead to increased academic excellence in this R&D field, faster and smoother innovation processes and ultimately improved services to European industry, including SMEs that do not currently have systematic access to the best of Europe.

Designing a European research infrastructure to meet the needs of industrial biotechnology

The overarching ambition

In response to the various challenges facing industrial biotechnology, a large consortium of researchers representing numerous universities and research organisations in ten EU member states[5] recently came together to consider how strong European coordination of research infrastructures related to industrial biotechnology could provide a timely solution and accelerate the efficient transfer to industry of the results of biological systems engineering, including the fast-moving field of synthetic biology. The conclusion of this encounter is that a distributed research infrastructure composed of an appropriate array of facilities located in several member states and covering the different phases of R&D in industrial biotechnology will provide a solid basis for a new approach to industrial biotechnology. Specifically, this approach aims to better link the early and later stages of bioprocess development, translating process-level considerations, such as scale-up, downstream separation and processing, and

[5] EU-IBISBA a proposal for a European research infrastructure for Industry Biotechnology Innovation and Synthetic Biology Acceleration was submitted in March 2015 to the ESFRI committee. This proposal received political support from France, Finland, Spain and Italy and was additionally backed by commitment from institutions in Germany, Greece, The Netherlands, Poland and Belgium. Since submission, the EU-IBISBA proposal has received support from a major academic institution in the UK.

compliance with sustainability criteria into scientific and technical questions that can be introduced into the biocatalyst design phase, the idea being to create an R&D continuum and accelerate the overall maturation of bioprocesses towards industrial deployment.

The bricks of the future research infrastructure

In order to provide a comprehensive response to the various challenges that characterise the development of bioprocesses, a future European research infrastructure will need to be encompass a range of facilities, including those that are typically necessary to design and build enzymes and microbial systems, using the latest advances in the field of synthetic biology, and those that are used to move bioprocess development cross TRL2 to 6. These facilities include:

(i) A publicly accessible e-Bioparts archive containing high-quality, certified sequence-function data, protocols and other tools. The registry content will be built as an intrinsic part of the infrastructure using data generated by infrastructure activities and from those of the wider scientific community, applying carefully defined standards and innovative certification methods to ensure data quality and guarantee its applicability at the predevelopment phase of industrial processes.

(ii) *in silico* tools that will provide the means to perform CAD-based design of bioprocesses, including workflow modelling and biological retrosynthesis, process synthesis and modelling, and multi-criteria decision-making and multi-criteria post-analysis and a platform for high-throughput *in silico* screening and analysis empowered by tools with capabilities to target efficiency and scope the potential for process integration.

(iii) A range of devices and technologies based on the principle of miniaturisation and microfluidics allowing the high-throughput experimental operations for the discovery and characterisation of bioparts discovery, including DNA sequencing facilities, enzyme engineering and lab-on-chip biochemistry platforms.

(iv) High-throughput gene cloning, gene circuit construction and strain engineering facilities, once again relying massively on automated microfluidics-based devices.

(v) Micro-scale high-throughput equipment for early stage bioreactor development and suites of labscale bioreactors and photobioreactors for the cultivation of a wide range of microorganisms and for *in vitro* biocatalysis

(vi) Pilot scale facilities for bioconversion reactions and downstream separation and processing and facilities for pilot testing of integrated bioprocesses.

(vii) Experimental equipment for the processing and analysis of biobased materials providing the ability to procure well-characterised feedstock for bioconversion.

(viii) A platform for outreach and public engagement. This platform will provide researchers with decision-making and educational tools that will encompass ethics and social dimensions, and risk assessment. These will be designed to enhance researcher awareness and to secure buy-in by external stakeholders including the wider public.

The mortar of the future infrastructure

Individually, European member states possess all of the capacity that is necessary to build a world-class infrastructure in industrial biotechnology. Unfortunately, this capacity is distributed and managed in different ways. The result is that despite the considerable potential, the current array of facilities is unable to interact and provide a high level of service to the industrial biotechnology sector and experimental processes are duplicated and repeated over and over at various sites. However, with the recent rapid expansion of flexible ICT solutions it is now

possible to envisage the implementation of a systems architecture that provides efficient interconnection of geographically-dispersed, heterogeneously-equipped facilities, using emerging strategies to provide the basis for an innovation continuum, bridging bioscience research and bioprocess development. In this manner, it will be possible to move into a new era of innovation in industrial biotechnology, providing new opportunities for pan-European coordination and action, and a much higher level of service to European industry.

To benefit from advanced ICT solutions, the future research infrastructure will need to adopt standard operating procedures for R&D work practices and processes and use common formats for data exchange between system. However, the increasing ability of knowledge management frameworks to handle heterogeneous data sets will also be of help to avoid overburdening infrastructure operators and users. For efficient infrastructure operation, it is perfectly feasible to operate equipment duplicates using common software applications, thus harmonizing data acquisition for sharing and archiving purposes. Similarly, currently available user-friendly web-based portal technology can provide the infrastructure with the necessary seamless interface for infrastructure operators and clients alike. However, beyond the state of the art, the infrastructure will also require advanced data management tools to provide powerful indexing and searching functions that will account for the complexity of bioscience and process engineering data. Together these various e-solutions will provide the cement for the infrastructure and the means to execute complex processes, integrating industrial and market constraints into the ideation and early experimental phases of bioprocess development and facilitating the transfer of scientific data to the higher TRL (Technology Readiness Level) phases.

Building and nurturing precious human capacity

Although deployment of some of the most recent developments in ICT will provide a solution for infrastructure interoperability, the most important feature of infrastructure operation remains people. For this reason any attempts to create a continuum across the bioprocess development pathway must incorporate the human dimension and focus on bridging the biology-engineering gap. In this respect a pan-European effort built on the existing academic excellence and educational experience of member states will provide a solid platform for both internal staff training and the development of a variety of educational offers for early career stage professionals, including multi-site internships.

Managing IPR in an open science context

Experience shows that interconnectedness and openness are not easily reconcilable with IPR management, since patents confer exclusive rights to owners. Therefore, the future infrastructure needs to tackle these issues in a realistic, but pragmatic manner that will satisfy apparently conflicting interests. In this respect, the creation of central infrastructure governance and the implementation of an overarching management system to oversee process lifecycles will not only provide infrastructure partners with a forum for discussion and a structure for arbitration, but also a powerful means to eliminate silo-style scientific discovery. Importantly, this implies increased ability to perform early stage identification of emerging patent families and thus significant socioeconomic added-value, beneficial to all stakeholders, including individual inventors and patent owners.

Regarding the pan-European mission of the infrastructure, central management will offer unprecedented ability to conceive and launch complex projects involving individual facilities and possibly multiple private sector

stakeholders. This unique one-stop shop characteristic of the infrastructure will provide industrial stakeholders with a seamless, transparent way to interact with academic R&D providers, while offering the latter the guarantee of fair management of IPR and short-term financial returns on their efforts.

Engaging stakeholders and providing an interface for industry

The intrinsic nature of industrial biotechnology means that the engagement of industry stakeholders is a necessary part of the R&D process, even at an early stage. This is particularly important in the case of synthetic biology, a burgeoning technology that holds much promise for industry, but also poses a certain number of new challenges related to its 'innovation garage' dimension. The role of a future research infrastructure regarding industry will thus be both that of a service provider, furnishing excellence in R&D and access to a wide variety of state of the art equipment, especially for start-ups and small companies, and that of a networking hub, creating synergies and collaborations between Europe's SMEs and between SMEs and multinationals. Fortunately, successful examples of how research infrastructures can perform this dual function exist. Therefore, it proposed that a future research infrastructure dedicated to industrial biotechnology will incorporate a pan European public-private partnership, with industry supplying financial support for precompetitive R&D projects in return for a role in the governance structure. Accordingly, the research infrastructure's ability to offer access to young researchers will be reinforced and its alignment with European industrial initiatives, such as that of the PPP Bio-based Industries (http://biconsortium.eu/) will be optimized.

Concluding remarks

The 2016 update of the ESFRI roadmap is a key opportunity to confirm Europe's engagement to the bio-economy transition and reinforce implementation of its research policy. For this reason, a large consortium of institutes in ten member states have proposed to create a research infrastructure dedicated to integrative industrial biotechnology. According to the analysis of the consortium's partners, the time is ripe, notably because the need is clear, the basic building blocks are available and the means to link these together is emerging thanks to the development of powerful R&D-friendly product lifecycle management platforms that can deliver a variety of services and cohesion to distributed enterprises, such as a distributed research infrastructure. The creation of a research infrastructure in integrative industrial biotechnology will draw upon Europe's strengths and provide an adequate level of strategic coordination between partners and the basis for smart, shared investment in future facilities, and provide the ingredients for consolidated international leadership in industrial biotechnology.