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Position paper
on the priorities of the European industry in the field of synthetic biology

November, 2009, Frank Notka, GENEART

Background information

EMERGENCE is an EC-funded coordination action committed to provide the instrumentality for the synthetic biology community to identify itself and to establish networks. Central goals are the identification of crucial topics for the development of synthetic biology, to mature these topics and make them "actionable", and to agree on best practices/strategies for these topics. The mission further includes the provision of flagship projects to visualize crucial concepts on bioinformatics infrastructure and standardizations for promoters, and different aspects of education.

One crucial step for a sustainable development of this emerging scientific discipline relays on the proper management of the industry/academic interface. Adoption by industry depends on three main factors: (i) that the concepts and tools developed by synthetic biology research programs help to address major bottlenecks in industrial R&D, that (ii) key players in industrial R&D are familiarized, trained and convinced by the opportunities and achievements of synthetic biology, and that (iii) a competitive environment is created for start-up companies in this field. After three years of examination and discussions with various experts form industrial and academic background, this report summarizes our findings and provides our perception of the status and the role of the European industry in the field of synthetic biology.

Introduction

One attribute of existing natural biological systems is a design by evolution to survive in specific ecological niches rather than to fulfill specific human requests, although, this strategy has been applied by humans to direct parameter value for the development of valuable features and behaviors by breeding for centuries. Synthetic biology now aims at creation of value in the opposite direction. Instead of a top-down approach, which is still driven by random modification of genetic information, the design and production of synthetic genes and genomes following a bottom-up engineering principle is by far more precise, although the effectiveness and predictability is dependent on a number of parameter, which can be regarded the synthetic biology's most relevant questions. While the precise production of genetic information is state of the art service provided by the gene synthesis industry, the way of using this commodity to produce a particular biological behavior is far from being commonly applicable. From an economical perspective the industry involved in synthetic biology can therefore be divided into two categories: On the one side there is a strong enabling technology-focused provider group consisting of gene synthesis firms in the first place, but also including technology supplier for wet-lab (e.g. sequencing, analyses) but also software (e.g. programming, simulations) applications. This group of industries has already established a market, merely because their services are not a consequence of the emergence of synthetic biology, rather the opposite is true, but they will face new challenges and a profound changing of economics associated with the synthetic biology developing. This group of enabling technology providers can be expanded by a distinct class of firms, which build their business on the demand of the new development, providing new services and technologies, e.g. in the course of expanding the

genetic code or integrating nano-technology or microfluidics, or exploit synthetic biology to advance processes previously based on genetic engineering. The other category comprises the potential user of synthetic biology, mainly large multinational biotech and pharma companies and represents members from the environment, energy, medical or biotechnology fields, accordingly. For this group the challenges are even more severe and a change from established processes, based on documented concrete and manageable project environments, to complex, unstructured and legally vague processes requires tremendous efforts in providing solutions or at least guidance on legal, operational, infrastructural and regulatory issues, among others. These companies often need collaborations with smaller but more flexible and innovative biotechs providing the essential expertise. The large projects in synthetic biology will therefore most likely include members of all categories in combination with academic players. For a commercially successful development, sustainable business models, in a broadly acceptable environment regarding legal, societal, ethical and safety issues, have to be found.

Currently, the research and development activity in the field is dominated by fundamental academic research, which is for some application fields heavily funded by private entities. However, as synthetic biology techniques mature and successful proof of principle projects are being presented, their development will become increasingly driven by commercial interests and the demand to implement applications and solve problems in industry. In turn, the involvement of industry in developing a strategy for synthetic biology will ensure that research becomes progressively more directed as it becomes more applied. This will promote a faster and more focussed translation of research into commercial applications.

Given that the techniques involved are to a great extent at the pre-commercial stage, significant funding from private as well as from public sources, e.g. central Governments, is likely to be required. It is essential that a robust partnership between academia and industry is initiated and maintained and the public sector should take an interest to ensure that projects of high national economic importance receive priority. This should include developing and applying new technologies to existing industry, e.g. the biotech industry, as well as supporting new and existing SMEs.

Gene synthesis business

Status and perspectives - Although the gene synthesis business has evolved way before the synthetic biology development gathered momentum (more than a decade ago), synthetic biology's implications on price, capacity and delivery times are evident. Gene synthesis is a demand driven business and hence the reduction of production costs in combination with a steadily adjusted market price has led to a still ongoing expansion of the market. This in turn has been employed to increase the productivity and by increasing the fidelity and robustness of synthesis technology to reduce the production times. The actual technology is sufficient to serve the synthetic genes market of today. The average customer requested sequence is restricted to gene-length constructs (mean of 1 kb), with few exemptions of longer constructs resembling virus genomes or multi gene cluster. However, as illustrated by recent advances in artificial genome synthesis by the Craig Venter group, synthetic DNA manufacturers will have to prepare for an increasing pressure to reduce costs and turnaround times dramatically in the context of growing synthetic biology improvements. With easier, faster and cheaper access to synthetic DNA, applications in synthetic biology will also increase and the overall market, including enabling technology, integrated systems and products will expand. A 2009 BBC research report states that the market volume will increase to $2.4 billion by 2013 (Bergin, J.

Synthetic Biology: Emerging global markets; BCC research), provided that gene synthesis and assembly costs can in reality be cut dramatically. While gene synthesis process technologies are rapidly advancing by applying miniaturization, parallelization and automation principles, the assembly of readily fabricable fragments for the production of genetic metabolic networks or even genomes is at the moment practically a manual process. Although, the potential of assembling genomes using recombination technologies in yeast has been acknowledged (Gibson, 2008, Science, 319, 1215-1220) and technological progress is evident (Shao, 2009, NAR 37, e16). Looking at the commonly applied gene synthesis processes, which still rely on oligonucleotide synthesis and conventional amplification and cloning methods, the room for innovation is immense. The major cost drivers in gene synthesis are oligonucleotide supply, sequencing and assembly labor. Each of this cost categories is addressed by research and development pathways, which are often pursued independently from the gene synthesis business (e.g. next generation sequencing, oligo on-chip synthesis for array-applications) or have to be supported by public funding because there is only a small commercial relevance in today's market but a high potential anticipated (e.g. progress in automated assembly, standardization of regulatory parts). The technical advances of independent application fields (genome typing/sequencing, expression profiling, etc.) which result in a rapid development of economics (low price, large information capacity) like sequencing and oligonucleotide production can readily be aspirated by gene synthesis developers. Costs can in addition be reduced by streamlining processes, either by automating standard processes or by introducing intelligent solutions to avoid costly production steps, e.g. by implementing proofreading methods to reduce the number of sequence runs necessary for the identification of positive products. Already today it is possible to synthesize a complete *E. coli* genome within one month by one commercial entity. However, the assembly of all the DNA fragments into one piece would need several months of basically manual work. The technical challenge of DNA assembly has therefore some value – at the moment. However, with the described potential of improvement it is only a matter of time until gene synthesis based on extreme reduced prices and very comfortable turnaround times is replacing any genetic engineering and conventional cloning activity, and opens the door for "mass production" of large-size fragments, as already demanded by synthetic biologists. This of course also implies a severe loss of value for the provided DNA material compared to the embodied information. Since the value of the design of the circuit and the entrapped information depends on the achievements/potential regarding the aspired application - usually commercial products - there will be further pressure on fast delivery and low prices in order to facilitate rapid development of these new values.

Impact of regulation - Further decrease in price will be directed by advanced automation, improving scales and additional savings including material and notably labor associated with essential non-production activities. Accordingly, there will be an impact of any regulatory burden in practice and vice versa the market need will shape the regulation of gene synthesis supply. The recent discussion about best-practice protocols and voluntary code-of-conducts defining screening standards and the development of federal guidelines for biosecurity are based on the actual market size for gene synthesis services. Both regulatory frameworks (industrial and governmental) include screening of customers and of sequences, and one central issue is the involvement of human experts for decisions of critical matters. The proposed practices are feasibly and economically acceptable with the current number of orders to be processed. Within the light of the described increase in demand and capacity however, the human factor within this process becomes excessively valuable, and expensive. Firms might have an advantage if they can abandon the screening activities to reduce costs. One way would be to neglect or ignore regulations, another way would be to avoid screening labor by establishing regional production sites with

unrestricted delivery approval, leading to a decentralized landscape of gene synthesis provider, although regulation will not be the only parameter. Therefore, the implications of introducing screening obligations or regulation have to be carefully examined, and it can be suspected that screening regulation will adapt to the developing market.

As pointed out, the reduction of costs will be driven by an increasing demand of synthetic DNA and in addition the technical possibility to test a lot of produced genetic material. The value will shift from the material to the information (in design and function). Synthetic biology aims at standardizing this valuable information in order to make it predictable and reusable for additional applications. Now, considering the use of genetic building blocks in the sense of synthetic biology, at the same time being aware of the value of the information, it becomes obvious that regulation of IP will become a major milestone and success factor of synthetic biology.

Owning and sharing – IP in synthetic biology

In order for synthetic biology to move forward, a better environment – including research infrastructures, funding, education and very importantly intellectual property – needs to be developed. The complexity of the patent landscape has been acknowledged and is especially significant in the synthetic biology field, because it is dealing with a cumulative convergent set of technologies. There is a significant chance of patent thickets that hold back the ability to do research and to commercialize applications comparable to other technological areas, e.g. electronics. A lot of research has been attributed to clarify the way patenting should be organized in the field of synthetic biology, without being able to provide an acceptable general solution. To the contrary, opposite positions try to assure their proposition, both arguing with experiences from historical developments. There is a large group in the field to advocate openness and minimal patenting, but others indicate that, in some cases, having a strong intellectual property regime that can be controlled is the best way to protect openness.

With respect to openness, potential directions and problems in analogy to other open source concepts arise. The idea of non-restriction in an emerging field is, from experience, only transient. Regulations would necessarily arise while establishing a system. Hence, identification of patent-relevant parts would make sense from the very beginning, regardless of the ultimate process. A potentially negative progression is the tendency of network effects. A “lock-in” effect (accustoming to something used repeatedly) is to be expected for parts as well. To the degree that scientists exchange knowledge on parts, these (individual) lock-ins result in network effects and tend to lead to a collective lock-in. This means favoring previously/often used parts without the respective qualitative evaluation (winner-take-all trend). It is likely that “sets” of parts exist in synthetic biology, which are compatible and complement each other. The possibility of “tipping” and “winner-take-all” results then apply to these sets as well. Competitive situations occur between these sets where certain parameters like lifecycle costs (royalties), risk, transaction costs or investment costs have a direct effect on their success. Hereby the successful set may very well be proprietary. Another aspect of openness is that Open source is a term which is often misinterpreted. Open source relies on a very robust intellectual property system. Copy left and other types of licenses require a very efficient and effective intellectual property system to work. Open innovation is an important notion for industry and universities. One can, for example, look at strategic opportunities that “small” parts, with a low priority for companies, could become freely accessible (at least for R&D), while protecting complex systems.

With regard to a non-open solution it is essential to understand that besides patents there are many contractual restrains but also opportunities when dealing with complex technologies as anticipated within synthetic biology's concept of aggregating lots of standardized parts and devices. The world of patents is highly complex, especially for a discipline like synthetic biology which relies on multiple technologies. Moreover, there are a range of unresolved patent issues that are going to have a major impact in shaping the future of synthetic biology (e.g. patentability, how prior art is applied, non-obviousness, do patents really hold). Material transfer agreements are important to deal with the major concerns over ownership and access for material and information coming out of synthetic biology. There are unresolved questions, about how university tech transfer offices are developed and how they operate. Information and materials (e.g. parts) coming out of synthetic biology research are already being placed in registries or other types of database. There is concern about how these databases might operate. Copyright protects originality and expression. In synthetic biology, an increasing decoupling of design from manufacturers and processes might increase the likelihood of copyright issues. Trademarks like Biobricks have value. Its logo and its trademark are important quality control tools.
There are a number of other issues with IP in synthetic biology that need to be addressed. In the synthetic biology community, a mixture of cultures is likely to become an issue. The way a pharmaceutical company, a chemical industry, a university or a technology oriented company is seeing intellectual property rights and is approaching collaborations is different. Aligning the interests of all these players is difficult. It might turn out that more than only one solution are necessary to satisfy all the different players and scenarios, and that practical experience might be necessary to establish and evolve useful IP-management strategies.

Innovation and use of synthetic biology

Industrial and environmental biotechnology was described as the third wave of biotechnology innovation (following healthcare and agriculture). This increasing attention brought to innovation in industrial biotechnology is partly due to the major challenges that this century is starting to raise: How do we reduce our dependence on petroleum? How do we decrease pollution? How can we improve manufacturing processes so we generate less hazardous waste and use less energy? How can these processes serve the developing world as well as they do the developed world? Synthetic biology is conceived or has been pushed into the role as being able to help shape their answer. There is a long list of potential applications and accordingly also interests from various industrial fields but the challenges and concerns are as various and thus commitments are biased.

Synthetic biology, biotechnology and the chemical industry

There is an increasing use of biotechnology in the chemical industry for various reasons. First, biotechnology improves the chemical industry's sustainability, and offers the qualities of recyclability, stability, and biodegradability of bio-based products as well as increased safety and sustainability of the production process itself. Biotechnology in the chemical industry is today mainly about metabolic engineering. However, "traditional" metabolic engineering is raising some important challenges because of the complexity of metabolic pathways. Metabolic engineering hardly tackles the issue of complexity, but synthetic biology may be able to address it. For example, minimal chassis strains might allow evading the issue of interconnectivity and complexity of biological systems. It was argued that synthetic biology would allow reducing complex networks to small ones and rationalizing the design of the desired pathway. The pathway would thus be fitted into a chassis strain (not the conventional microorganisms as *E. coli*) that will be able to run this

particular pathway orthogonally avoiding extensive interactions with the remaining metabolism.
The production of the drug Artemisin by Amyris is the first example of the successful combination of synthetic biology techniques with traditional chemistry processes. Artemisin is now produced in a cheaper and faster way. In order for biotechnology to accomplish all its potential in the chemical industry, synthetic biology is expected to provide essential input by allowing more predictable and faster chemical development and by supporting the development of very complex production pathways and novel products.
However, some issues still impede a larger development of synthetic biology in the chemical sector. For example, the development of chassis strains is still at its infancy and there is also a lack of high quality parts registries. Access to material is not always straightforward, in part because of compartmentalized intellectual property structures. Another issue of concern is that the scalability of synthetic biology tools is yet to be tested. Currently, synthetic biology works on a very small scale but industry needs to produce large quantities of products, especially concerning biofuels. Questions regarding the integration of synthetic biology into a scaled-up setting, its role in the achievement of low cost, profitable end-products from an innovative front-end microbe, and many other need to be answered to assure the uptake of synthetic biology tools and techniques by the chemical industry.

Synthetic biology for bioremediation

Genetic engineering, and to a greater extend synthetic biology, can be used in many different ways to address the challenges of the environment, for i) mobilization purposes: for example, bacteria can be modified so that they can increase their ability to absorb metal, ii) detection through biosensors, iii) transformation: for example by setting up catalytic reactions allowing the conversion of industry waste in CO_2 or water, or iv) bioremediation or degradation. The latter point is raising difficult concerns, since great expectations were placed on genetic engineering for bioremediation purposes in the mid-1980s. However, many issues arise when putting modified bacteria in a contaminated environment. For example, bacteria developed in laboratories are not robust enough to survive in the environment, and their capacity for bioremediation developed in a laboratory was not readily transferable to the natural environment.
As in the case of the chemical industry, the complexity of biological systems has hampered their use in bioremediation, and engineering bacteria that are predictable when released in the environment has proved difficult. In this regard synthetic biology might prove to be able to help tackle complexity, particularly in a conceptual way by emphasizing the importance of engineering principles (such as standardization of parts or plasmids) blended with biology principles (such as the Darwinian evolution).

Synthetic biology and the food industry

The current scope of synthetic biology in the food industry is limited to incremental modifications in current processes or applications. Key contributions are likely to be made in the areas of health and nutrition, although there are further applications of synthetic biology. Particular areas of the food industry likely to profit from synthetic biology tools and techniques include i) metabolites, health products (e.g. vitamins) and processing aids in the manufacturing process of food and food derivatives, ii) preservatives, an area already largely based on genetic engineering, iii) flavours and fragrances, iv) biosensors, for example to replace human “nose” in the food industry with an artificial nose and v) food waste processing. A lot of money is invested in these fields, and again synthetic biology is seen as being able to facilitate, enhance and reduce the cost of production processes. Taking a synthetic biology approach will facilitate the design of compounds that

may be produced in a much more efficient way than by usual fermentation. The design of compounds from scratch beyond those found in nature will also be possible and will enable the food industry to enlarge its portfolio of products.
Biosensors are another example of efficiency gains that may be possible through synthetic biology. For example, employing a human nose to test aromas is expensive, and industry would profit from an automation of this role. Researchers are working on the development of an artificial nose composed of thousands of different microsensors. Each microsensor would be based on particular bacteria or enzyme systems that would allow detecting the concentration of one specific compound.
Challenges in developing these advances in the food industry are similar to those described for the chemical industry and bioremediation. Technology platform development is regarded crucial point for structuring the field. Intellectual property is also an issue: in complex systems there are worries about the protection of all the parts needed to construct that system. Work is still needed to overcome the many technical issues which still impede synthetic biology development into applications.

Synthetic biology in the health industry

Major pharmaceuticals companies are not yet involved in synthetic biology to any great extent although they already consider its sister field “systems biology” as crucial to tackle complex diseases. Synthetic and systems biology are especially tightly linked in the context of human biology and medicine. Synthetic biologists are confident that their work is of interest and importance to industry. However, for industry to make significant use of synthetic more proof of its utility in general and especially in health innovation is required. Some propositions were put forward to shape a more persuasive position for synthetic and systems biology. For example, from December 2000 to February 2008 the top 15 companies in the industry lost approximately US$850 billion in terms of stakeholder’s value, and current processes and approaches to generating pharmaceuticals are not considered to be sustainable for the future. What the pharmaceutical industry needs are new ways to innovate and systems and synthetic biology can be part of those.
Combining a holistic understanding of human physiology and developing novel therapies with synthetic biology’s innovative tools was proposed as a possible solution to current problems in health innovation in the pharmaceutical industry. These key developments in synthetic and systems biology will largely be driven by academia, but it is important that academia and industry start to work closely together. As a push, academia would have to be ready to demonstrate the applicability of its knowledge in an industrial and commercially relevant context. Indeed, industry is increasingly facing economic and regulatory hurdles which reduce its willingness to invest in blue-sky research. To bring to industry the benefits of synthetic and systems biology, it is crucial to put the different communities and stakeholders together to drive change. Better coordination is needed to generate a significant impact and mechanisms need to be found to get industry on board.

Conclusion

The involvement of industry into synthetic biology is in progress, although the degree of engagement depends on the industry field and business model. Moreover, one distinct industry branch, the enabling industry, is one of the foundational drivers of synthetic biology development. A progress as fast and comprehensive as expected for synthetic biology will not be possible without industry engagement. There will be a continuous pressure to provide synthetic DNA material as the value of the contained information starts to produce revenues. This pressure will in turn lead to an acceleration of DNA synthesis and assembly technology feeding this economical circle. Besides technical issues,

including standardization, scalability, safety and chassis development, which will be tackled with a sufficient supply of genetic material the most relevant concern that has to be addressed, is the employment of foreign innovation for ones own application. The challenge of synthetic biology is to define a most likely completely new and probably flexible regulation system of how to provide free or at least reasonably regulated access to all the individual contribution to a general parts catalogue. If synthetic biology turns out to keep its promises it will depend on continuous development and contributions. Therefore, it will rely on the participation of the different stakeholders from academia, industry, government and public and on a satisfactory allocation of the revenues.