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CO	Confidential, only for members of the consortium (including the Commission Services)	

Exploratory Workshop on:
Industrial Opportunities in the Emerging Field of Synthetic Biology

June 25, 2008, Airport Munich, Germany

Background information

EMERGENCE is a coordination action committed to provide the means for the community to identify itself and network with each other. 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. As a first step towards sensing the general perception of and expectations from Synthetic Biology amongst the European industry, an exploratory workshop has been organized by Geneart, who is one of the industrial partners dedicated to promote this important task of training industrial players and developing a strategy for an integration process.

Frame work

The main objectives of the workshop, held on June 25th 2008 in Munich, were (i) to introduce Synthetic Biology and defining the industrial expectations, priorities and concerns, (ii) to discuss topics regarding regulation, collaboration, and business challenges and (iii) to link the actual development of Synthetic Biology in Europe with major projects, funding and network options. The workshop addressed participants from a broad range of life science disciplines covering chemistry, pharma, energy, environmental and Bio-technology as potential users of Synthetic Biology concepts. Introductory talks on different aspects, intended to inform about concepts, challenges, opportunities and visions of Synthetic Biology, were followed by an open discussion focusing on the industrial assessment of the practicability.

Introduction

An introduction to EMERGENCE's view of Synthetic Biology was given by Sven Panke with the aim to provide a definition and a comprehensive basis for discussion. Synthetic Biology has many different aspects and hence a number of heterogeneous definitions are phrased in the society. A condensed broadly acceptable definition covering many implications is "The rational implementation of novel living systems". Novel stands for (substantially) different from existing systems either through a novel combination of existing items or by implementation of fundamentally novel items. Living is condensed to self replicating. System is defined as the ambition to manipulate on a substantial scale. Rational translates as following an engineering agenda.

What is the difference to existing systems and why do we need novel systems?

One characteristic of existing biological systems is a design by evolution to survive in specific ecological niches rather than to fulfill specific human requests (such as manufacturing chemicals, biofuels, or biopharmaceuticals, or treating diseases), which typically leads to poor biotechnological performance. Consequently, adapting an existing system can be the equivalent of tuning a VW beetle to become a Formula 1 race car and bears enormous economical and ecological potential. In addition, re-building an existing system and then building novel, functioning systems is the ultimate proof of understanding and mastership.

How can we build novel systems?

Major impacts on Synthetic Biology came from a better understanding of evolution and environmental processes on the one side and advances in design and assembling technologies on the other side. The composition of the system can be developed best in a standardized sequence of well defined categories. First there is knowledge - recruitment is not finished, but we have a huge potential to exploit, followed by a series of building blocks of increasing complexity: (i) Sub-parts - functional modules that can be freely combined (e.g. zinc fingers, transcription factor recognition sites). (ii) Parts – regulatory and functional DNA-sequences like protein coding sequences (orf), promoters, ribosome binding sites, etc. (iii) Devices – combination of parts (e.g. promoter // coding gene // terminator = inverter to switch e.g. from low signal to high signal) and (iv) Systems – designed organism with new properties (e.g. photographic *E. coli*; artemisinin production). Finally, novel systems require a suitable container that supports proper function, the chassis – a universal vehicle for the implementation of new properties that requires insulation and separation (compare to radio with spatial, thermal or electrical separation). One possible way to a universal chassis is the definition and realization of a minimal genome with reduced complexity resulting in improved orthogonality. A minimal genome as basis would allow for rationally re-constitute more complex organisms and would support additional options, e.g. to expand the chemistry of live (rewrite genome, redefine codons, expand genetic code).

What are the requirements for the implementation of novel living systems?

Most importantly, we need and realize already a shift of the focus in biotechnology from PARTS to SYSTEMS on every level. These levels include technology (e.g. for assembling) and design (e.g. abstraction), with tasks related to standardization mainly on the parts but also on characterization or quality, on modularity to enable combination of parts and devices and on orthogonality for the successful implementation of systems.

An Introduction to the major technical and philosophical substance of Synthetic Biology (presented by Luis Serrano)

What we encounter/promote in Synthetic Biology is the transition from science to engineering: “Scientists discovers that which exist, engineers create that which does not exist”. However, this transition is associated with risks originating from the nature of the different discipline. Compared to the established engineering disciplines, handling living organisms implies certain unpredictable behaviors: Mutations, evolution, chemical diffusion, cross talk, cell growth/death, which challenge the central ideas of standardization and engineering from the scratch, and renders the deliveries of Synthetic Biology questionable.

Who will benefit from Synthetic Biology?

Application fields of Synthetic Biology cover a broad spectrum of life science areas. Biomedical applications include tumor killing bacteria, medicine producing bacteria and stem cell reprogramming. Prominent applications in the environmental field engage the development of detectors, e.g. TNT- or arsenic-detectors or the degradation of waste products. Alternative energy ressources like biofuels or biosynthesis pathways e.g. the production of Artemisinin, represent Synthetic Biology developments with high public perceptions and industrial intersts. In the field of systems biology the focus is on measurement and manipulation tools. Finally, recent examples demonstrate the advances in logics towardso oscillators, memory, and computation.

What are the technological needs for a functional design?

The requirements for a functional Synthetic Biology environment include (i) intelligent databases and repositories, (ii) simulation and engineering software and (iii) molecular tools for protein and RNA design and the design of gene circuits. The design tools will have to be adjusted to allow the manipulation of protein properties, protein-protein interactions as well as protein-DNA interactions. For any structuring of proteins for specific functions a good structure (high resolution) and high homologies are absolutely essential. In the line of an increased availability of biological information these requirements can be achieved within conceivable time lines. The future in protein design within Synthetic Biology will have a strong focus on applications regarding backbone moves, loop modeling and docking. The requirements are already implemented but for a comprehensive usage of existing systems we will have to elaborate the levels of information (data bank) → design (modeling program) → testing (simulation program).

General discussion

Following short case study presentations by Sven Panke and Martin Fussenegger depicting limitations in orthogonality and resulting implications for Synthetic Biology development, and an example of a successfully designed biological airborne broadcasting system, respectively, different industry-relevant topics were discussed.

Strategies, tools and systems

In view of potentially useful organisms the question came up, if *E. coli* is special or preferred or if the process should be used for all model/production systems? It was mentioned that, from the practical point of view *E. coli* is a very robust and broadly used system and therefore should be of special interest. In addition, in order to bundle resources we should concentrate on few carefully selected, relevant organisms right now, implement the tools, processes etc., and gain experience. It might turn out that we do not need other organisms than the initially selected ones. Regarding the matter of minimal genomes, size and knowledge/acquaintance are key factors for an advanced development. Efforts to other minimal genomes therefore focus on small genome and established organisms, e.g. Pseudomonas, Yeast, Mycoplasma genitalis, or Mesoplasma florum.

Regarding the process of standardization it was stated that there are overlaps with standardization in established disciplines like Systems Biology. However, Synthetic Biology is one step behind Systems Biology in terms of analysis.

Another issue that has been discussed was how to best generate at a political level and how to best address funding organizations. We should work out more precisely relevant applications (e.g. oscillator) and work on a clear nomenclature and definition of formats,

since these are success factors for Synthetic Biology. The importance of knowledge has been mentioned in the context of different aspects, and the consensus has been that the current knowledge is sufficient to start engineering.

Registry of parts: MIT vs. European Registry: is the further development similar?

The major view amongst the participants is the development of centralized, interconnected facilities, which implies the implementation of an European Registry of Biological Standard.

What should it look like? A European Registry would have the opportunity to learn from and to avoid shortcomings of the established network and has in addition the mission to provide all means to be attractive for the participation of industrial members. It should be accurate and well maintained, contain, update and provide trustworthy data, quality controlled, with novel analyze measurements, DNA-Sequence and functions. It would greatly benefit from a comprehensive literature-connection, including information on IP-relevant issues.

Biobrick Warehouse: Do we need a data base only or do we need real parts in a freezer?

A physical registry will probably evaporate within the next years, due to decreasing gene synthesis costs and easy access to not only parts but also devices and increasingly complete systems. The main focus should be on the establishment and maintenance of an information system that is based on (i) a mandatory set of standards, (ii) established quality control tools and rules, (iii) a set of mathematical parameter for design purposes standardized SPOs to quantitatively assess and exactly describe the BiobBricks, thus creating new standards comparable to DIN (German Industry Norm) and (iv) the mentioned literature data base featuring automated data retrieval tools.

Development, Organization and Regulation

The realization of a project this complex might be more comprehensive and accordingly more expensive than expected (calculate at least €1 Mio. /year). One solution would be to start with something simple, e.g. to develop HTP / automated characterization and evaluation systems and regard the registry as focus point with different developments crystallizing around it.

Does the outcome of Synthetic Biology justify the big investments?

Different developments point to the fact that it will get cheaper, although no one will invest privately. Nevertheless, the development of Synthetic Biology can be considered a community task to some extent (e.g. construction of minimal strains will have long term benefit). In addition, a long term vision is also obvious in the BP / Berkley deal ($500 Mio.).

One recommendation has been to stop mixing up tactics and strategies. EMERGENCE is approaching the registry as tactical move, but what is needed are strategic approaches. A bottom up approach is very difficult (from the investors' site). The better way would be a strategic top down scenario: Push the buttons of politicians and investors. Strong scientific examples can have a strategic impact and we should also involve other types of Industries to a greater extent (green biotech, energy, etc.).

One of the problems associated with Synthetic Biology developments is that the first company trying to launch or approve a product based on Synthetic Biology, has to overcome the obstacles of authorities like the FDA. The FDA will block innovation by stringent regulation and a demand of established standards. Complex systems inhabit high

risks and utility has to be demonstrated. Therefore, suitable and accepted trouble shooting applications are the challenge.

IP and Industry involvement

Recommendation from the European Patent Office: Standardization.

Build a consortium in order to facilitate standardization; it is difficult to set up standards if there are already IPs existing. As a practical example the SNPs Consortium was mentioned that has something similar. The consortium promotes synergy by providing information (the non-profit Consortium identified and mapped 1.5 million SNPs, which have been made publicly available to researchers over the internet). A risk factor for an IP regulated process, in particular for the definition of standards is the activity of patent sharks: Disclosing of IP after it has been established as standard.

Explore how to set up an industrial consortium: Regulation.

Should a Registry be included? The mode a registry should be organized has been discussed controversially. On the one side, the working philosophy to be aspired is to provide a basis for unrestricted free working (in the sense of freedom-to-operate). This aim would favor a complete open source policy. On the other side, from a business point of view, a complete open source registry is not considered an applicable solution. Restrictions arise from the common business practice based on (cross-) licensing. One possible compromise is a diversification and classification of contributions to a registry, to institute different levels of innovation, e.g. to stipulate extra rules for the hot stuff. The quality of a more closed registry was pointed out, and the challenge is to find the right balance: With parts being made available without any restriction and others which may be accessible for R&D purposes only and require negotiations for commercial use. Regardless of how the registry would be regulated, an important demand is the organization of appropriate incentive regimentation.

Who should be addressed? An industrial consortium is hard to realize for big companies, since these questions merely address cooperate, business development and legal people, who should be integrated into the process. These people (merely from the law departments) should be involved to workout functional ways. We should start to establish a growing consortium and force others into the regulations.

Industry involvement: Acceptance.

There has been a broad consensus that the field would greatly benefit from the disclosure of successful developments and applications. Success stories would also have a huge impact on the acceptance of Synthetic Biology.

While for chemicals it is the right way to start now, probably also the right time, it has been regarded too early for the development of pharmaceutical products. Although, it seems not too early for generating tools for pharmaceutical development and it has been acknowledged that Synthetic Biology will change the way drugs are produced. However, the pharmaceutical industry is more interested and engaged in defined individual projects. The pharmaceutical system was established on small chemicals more than 50 years ago, and a change of attitude is considered a rather laborious task. Still, the prevailing opinion was better not to wait too long, i.e. Americans might be faster (or someone else might do it). It might help to argue in the direction of a more closed system and to support the restriction of disclosing key-technology.

Take-home messages:

- Gain more visibility by presenting successful and relevant applications
- Strategic top down approach recommended
- A clear bias in development
    - Procaryotic development much more advanced:
    - Metabolic pathways, Biofuels & fine chemicals, Biodetectors
- Big Pharma: Too early for our engagement
    - Prefer small cooperation strategies
    - Slow process due to extensive negotiations
- Redirect contacts
    - Address smaller companies
    - Include regulatory and IP manager
    - Involve other types of Industries
- Open Source policy
    - Clear tendency towards closed/semi-closed solutions
    - IP regulation a major issue