SIXTH FRAMEWORK PROGRAMME

SYNBIOLOGY

An Analysis of Synthetic Biology Research in Europe and North America

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EXECUTIVE SUMMARY

This document provides a literature and statistical review of the Synthetic Biology sector in Europe and North America. It is provided as Deliverable Number 3 of project FP6-2003-NEST-B4 Project 015357 – SYNBIOLOGY.

There are many different practical approaches to Synthetic Biology that emanate from different disciplines, which can all claim to represent Synthetic Biology research and engineering. Thus, a definition is required that classifies Synthetic Biology research in the context of existing technology and already existing and accepted terminology.

Any definition of Synthetic Biology has clearly to reflect how Synthetic Biology differs from classical simple genetic engineering. This difference is illustrated by the increase in complexity of functional genetic arrangements.

All Synthetic Biology applications aim at the design of artificially modified living systems, such as specialized cells for biosensing and biobased and highly controlled synthesis, or for high yield production of (xeno-)biological molecules for *in vivo* or *in vitro* use. In integrating all analysed investigations and experiences carried out for this Report the term Synthetic Biology - in its central meaning - is mainly aimed on functional bioconstructions and is application-oriented.

Synthetic Biology is not primarily a discovery science, as it builds on our current understanding while simplifying some of the complex interactions characteristic of natural biology. Thus, it is intentional design based engineering of systems based on biological functions and rules aimed at obtaining new functions which are not present in nature.

Therefore our working definition is as follows: *Synthetic Biology is the engineering of biological components and systems that do not exist in nature and the re-engineering of existing biological elements; it is determined on the intentional design of artificial biological systems, rather than on the understanding of natural biology.*

This Report also investigates upon participants in the Synthetic Biology field, by including the preliminary results of a statistical analysis of individuals, organizations and activities being undertaken in the Synthetic Biology field. In total over 200 individuals have been identified and more than 100 different national sources of funding by public and private organisations.

This Report is provided by the consortium led by Sociedade Portuguesa de Inovação (SPI). The consortium members are ATG:Biosynthetics, the Center for Economic Research and Environmental Strategy (CERES) and the University of Maryland Baltimore County (UMBC). The main author of the report is Dr. Hubert Bernauer of ATG:Biosynthetics. The analysis in the report will be updated throughout the project and the final results will be published in the upcoming "Final Report on Analysis of the Synthetic Biology Sector" (June 2006).

1. INTRODUCTION

1.1. Note on Report

This Report provides a literature and statistical review of the Synthetic Biology sector in Europe and North America. It is provided as Deliverable Number 3 for the project FP6-2003-NEST-B4 Project 015357 – SYNBIOLOGY.

The project is funded by the European Commission Framework Programme (NEST – New and Emerging Science and Technology).

The Report draws heavily on the current research and publications in the field. It is provided by the Consortium as a whole, with Dr. Hubert. Bernauer (ATG:Biosynthetics) as the main author.

The Report is structured as follows. Section 1 provides an overview of the objectives of the work in the Synthetic Biology sector and a discussion of life processes. Section 2 provides a detailed review of Synthetic Biology research, including discussing the type of research that can be termed Synthetic Biology, both via a "top down" and "bottom up" approach. Section 3 provides the results of a statistical analysis into the individuals, organizations and publications in the field. The project has developed a method to identify individuals, organizations and publications in the various sectors that make up Synthetic Biology research. This method is being continuously updated and forms the basis of a comprehensive database of Synthetic Biology research that will be a major output from the project as well as a support for a survey to be carried out under the following step of the project – a survey of European and North American leading participants in the Synthetic Biology research, industry, and funding communities.

1.2. General Objectives

Natural biological systems consume energy during the processing of materials and information. Unfortunately, our ability to use biology as a technology is limited by our understanding. Integrating molecular biology with interdisciplinary advancements from systems science including engineering, mathematics, and physics is rapidly increasing our understanding and knowledge. This work offers valuable quantitative insights into naturally occurring information processing activities.

Synthetic Biology combines knowledge from many disciplines for *de novo* design and construct of new biofunctional systems to build novel proteins, genetic circuits and metabolic networks. The fields of activities are wide spread, and include those shown in Box 1.

Box 1: Activities in Synthetic Biology

Activities in the field of Synthetic Biology include:

- biochemical or genetic network design
- energy sources, parts fabrication
- characterization
- assembly
- network analysis
- biomaterials
- biomimetics
- computation using biological components
- design principles of systems and networks
- device physics
- directed evolution and evolutionary optimization strategies
- information processing and control theory
- microfluidics
- molecular machines
- modeling of synthetic systems
- noise in systems and components
- organism engineering
- programmable organisms or systems
- protein engineering
- quantitative measurement techniques
- reporters
- sensors and actuators
- single molecule manipulation and/or measurement methods

See footnotes [1] [2] [3] [4] [5]

Synthetic Biology is a new technology with a cultural dimension which is resulting in scientific, technological, economic and political impacts [1]. It explores the potential for providing future solutions based on the availability of the close to unlimited prospects of engineering and deployment of bioprocesses.

1.3. Life Processes

Since new results from the field of Synthetic Biology fundamentally break the limits of conventional molecular biology by focussing on systematic aspects of regulation, more theoretical definitions of Synthetic Biology should be discussed.

The first stage to define Synthetic Biology consists of determining its position of integration in the more general context of biology. The next step is to determine how Synthetic Biology may be differentiated from the other fields and classified to set its boundaries. Thus, to find an

acceptable definition of Synthetic Biology it is necessary to find an acceptable definition of what "Life" is. Key features common to all living beings that contribute to the process of finding a minimum definition of life are:

(1) Self creating

(2) Self assembling and organizing

(3) Self sustaining by

   a. Self replicating

   b. Informational Processing

   c. Steady energy consumption and flow

Life is far from being thermodynamic balance. It is highly logically structured and, therefore, consists of information and a suitable matter in which information can be fixed, processed and evolve additional functionalities. In addition, a steady flow of energy is necessary in order to maintain structural integrity and mobility. The energy sources that life is able to utilize are nearly as heterogeneous as life itself.

It is the exclusive ability of life to cover all these functions (through realisation of DNA-encoded structural information) that enable life to exist even in the most extreme habitats [1] [2] [3].

However, it seems that there was a single event that led DNA to be the chosen compound to store biological information. The development of DNA as a means to store information might have been driven by history. It may have descended from RNA molecules, the so-called prebiotic life phase [2] [3] [4] [5]. It is presumed to have taken place in protected microenvironments of ice/water boundary layers in arctic oceans where RNA molecules provided tri-functionality: biocatalytic, structural and coding sequence information storage [6]. This could be the most critical argument for the self initiation of life to be only possible with RNA. Therefore, life from any other carbon source would only be initiated artificially (e.g. RNA based proto-life) but never self creating.

Based on the discussion about artificial life, in order to differentiate the top-down approach by theoretical assumptions it is necessary to understand what the key features of biological life are, and to settle on a definition for Synthetic Biology.

In this context, we should consider more features of existing biological life in order to arrive at a definition:

1. The only biological life that can be experienced today is carbon based, which is different from silicon based artificial life created by humans in computational sciences as it is ionic not electronic.

2. The self creating initiation of the process of life is not documented.

3. The history of molecular evolution is documented in existing natural DNA-sequences which can be read by molecular-biological or gene technological methodologies. The general and natural information storage (with a few exceptions in RNA viruses) in existing biological beings is DNA. Due to the theoretical sequence space (4N) which is close to infinite, theoretically functional coding and non-coding DNA sequence configurations exist, which were not invented by nature to be historic nor realized by natural evolutionary processes to serve biological functions during development of life on earth. These are still to be unravelled and await future discovery, realisation and application.

4. The universal genetic code is unique. The universal genetic code which is used in all living organisms on earth with only a few minor exceptional variations must have been created by a historical event. The code itself consists of 64 triplets, which code in a degenerated fashion into a fixed, determined scheme, but which are not necessarily allocated with functional necessity to the defined 20 amino acids. In addition, the molecular species of molecules and the numbers encoded as well as the number of different codons used are not necessarily the only convention that could be met for coding biochemical information into molecules.

Living systems need a permanent consumption and flow of energy to maintain structural, functional and informational integrity to survive. Life functions can be differentiated into different informational-crosstalking pathways as in Figure 1.

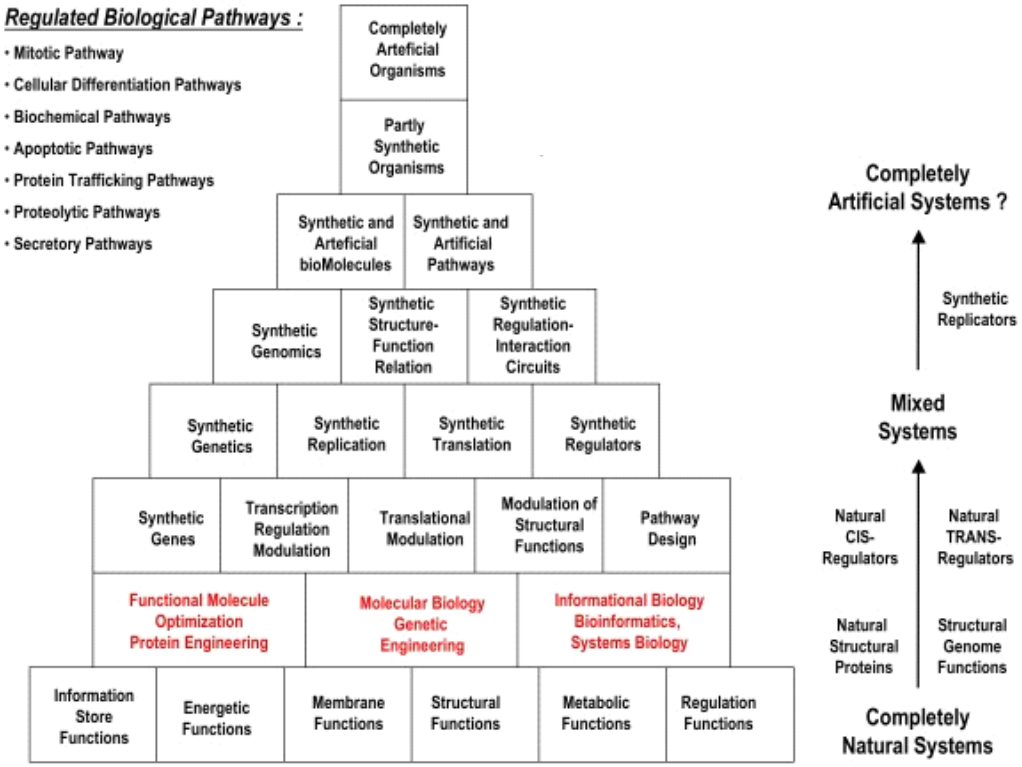

Figure 1: Synthetic Biology is a change of a paradigm: Analytic towards Synthetic, "Molecular Biology" towards "Modular Biology".

Figure 1 shows a shift in focus from the understanding of naturally occurring biological functions to using a minimalist approach to define and design them. This is provided in a more technical sense by integrating the modulation of regulatory function and improving functions on the basis of the knowledge provided by molecular biology. Biological functions can be subdivided into sets of different biological pathways, or networks of molecular interaction, where the exchange of regulatory information is aimed at the coordination of all the life processes for management of an organism in a holistic approach. The discrete pyramid shows on the bottom level the natural basic biological functions which can be differentiated from each other. These functions can be influenced by modulating the molecules using different technical methods, leading to different levels of Synthetic Biology towards artificial carbon based life.

Besides providing basic functions, the overall informational genetic content needed for survival depends on the environment to which the organism is genetically adapted. This results in logical systems of varying complexity with intrinsic information providing the key features.

Nevertheless, in a changing environment, life needs to be able to continually adapt and evolve. Artificial environments, like those of technical processes of biotransformation or bioproduction by microorganisms, are much less intricate than nature, thus reducing the complexity needed in regulatory function.

The information which guarantees living functionality is necessarily bound to any suitable matter sufficient to maintain the key features. Only the elements of carbon and silicon, each with four valences, have so far shown the ability to serve as a suitable material basis for life in its basic definition and functionality.

Information for self replication in living systems is intrinsic – it is the central part [7]. In contrast to this, the information and blueprint for the structural design of technical machines is external and remote. For example, the construction and assembly of parts of machines requires the support of other different machines.

Computer algorithms and programs that process and maintain their informational heritage on the material basis of silicon, fulfil the criteria of the key features of life, and are termed "artificial life" It should be noted that in a more stringent definition, these programs are simulating life but do not actually live. This is due to the information being structural and the limited or missing congruency of matter.

The limitation on the capability of creating higher orders of life lies in the matter itself. Silicon, an element, having a crystalline structure is not able to resemble information in its own structure. Only carbon provides sufficient molecular diversity so that structural information and matter can exist in an intrinsic marriage which is self sufficient for forming life. Carbon has the greatest flexibility and highest number of possible combinatorial molecular self arrangements and a great variety of arrangements with hetero-atoms in forming hetero molecules at temperatures where the solvent water is in its liquid form [8].

However, what would the biological definition of carbon based life be if the information maintaining molecule, DNA, could be substituted with a different molecular species? The possibility of a totally artificial carbon based life without any resemblance to existing natural organisms arises from different assumptions.

2. REVIEW OF SYNTHETIC BIOLOGY RESEARCH

2.1. Introduction

One basic feature of all biological systems is to be biosynthetic. The anabolism serves each organisms' own characteristic repertoire and dose of naturally occurring substances necessary for survival in its habitat.

A crucial element for developing a definition of Synthetic Biology is the exact use of the terms "synthetic" and "artificial". Often these terms are used as substitutes for each other. This is not correct. In fact, to be described as synthetic, at least two distinguishable components are needed which can be combined artificially in a certain manner in order to form something new with extended functionality. However, creation of artificial life can also be degenerative – such as in the minimal cell approaches of Craig Venter, which are envisioned to become tools for use in Synthetic Biology applications [9]. The assembly of natural and artificial parts result in distinct possible synthesis products, for which the results are all artificial.

Synthesis of Natural + Natural = Artificial	Level 3	e.g. classical genetic engineering, cell fusio
Synthesis of Natural + Artificial = Artificial	Level 2	e.g. rational and evolutionary design of genes and their expression
Synthesis of Artificial + Artificial = Artificial	Level 1	e.g. artificial genes with artificial function in combination with artificial regulation

The term artificial simply means man-made and differing from naturally occurring structures or processes. Artificial biological components can be designed to have full functional compatibility within their respective biological systems. In technical terms, Synthetic Biology should be defined as distinct from previous technologies of molecular biology - from simple genetic engineering (bottom up) and from theoretical total artificial life in its extremes (top down). Therefore, in order to develop this into a more detailed description of Synthetic Biology, it is necessary to locate the correct transition borders.

The resulting product of a synthesis should be intentionally designed to have improved properties. Exploitation of synergistic effects of biologically active parts in fusion products often

play a role in considering how to plan biological synthetic systems. However the result of Synthetic Biology application consists in a new self-sustaining system of extended functionality. This means that the artificial system is functionally built in, replicating and co-proliferating within the host system, e.g. a new artificial pathway design in a host organism or an artificial "proto-living" particle [10] [11]. The synthesis products of these designed systems are artificial, and are intended for use or application.

Therefore, the expression artificial might be too strong and must be analysed in a more accurate and differentiating manner. While the expression synthetic has features between natural and totally artificial. Yet in scientific terms, Synthetic Biology should be defined distinct from previous technologies of molecular biology, from genetic engineering (bottom up) and from theoretical artificial life in its most extremes (top down).

2.2. Top Down "Synthetic Biology": Theory driven experiments towards the *de novo* creation of artificial life

Based on the theories of evolution derived from observations made in macro and microcosms of nature, experimental designs for creating carbon based artificial life are possible [12]. Recent projects in nanotechnology are aimed at emulating life processes and may provide the basis for creating real artificial carbon based life in the future.

Part of creating forms of primitive life artificially and to deploy these very simple forms of artificial life is called the proto-life approach [11] [13] [14]. A totally new type of living beings could be established that could not be regarded as a synthetic continuation of the natural historical process initiated by nature. Therefore the key features of being self creating and historic are a key feature for differentiating natural and synthetic biological life of natural origin from totally artificial life.

Artificial components of biological functionality can be theoretically integrated into totally artificial biological systems which show at least all basic features of living systems. Although this has yet to be shown, it would lead to the beginning of new evolutionary processes. If such systems can be designed to enter self sustaining cycles of evolution they might be termed "Artificial (carbon based) Life" in a scientific discipline which should be termed "Artificial Biology". If this could be achieved, the term Synthetic Biology, which at present synthesises biological compounds or organisms using artificial ones, could be extended to include the synthesis of artificial biological compounds using artificial ones.

This would be the most sophisticated approach for nanotechnology to emulate living systems by applying natural nanostructures from nanobionic knowledge and creating systems with a level of complexity that would possess features of living systems.

It is the goal of some bio-ambitioned nanotechnologists to increase the complexity of their systems towards those of living features, whereas biologists tend to focus on a reduction of the complexity of biological function towards the minimal cell [9] [15] [16].

A prerequisite is that at least one component of the synthesis precursors must fulfil the minimal criteria of a self maintaining life cycle under certain circumstances, and that the fusion product behaves in the same way. The opposite result of creating biobased nanoparticles is discussed in the in vitro Synthetic Biology section (Section 2.5 below). For instance, complex self organizing particles of diverse function that are not self replicating are at the frontier of bioambitioned nanotechnology and in vitro Synthetic Biology. Depending on the origin of the synthetic components used for (self) assembly, biomimetic chemistry is another overlapping field of activities.

If such artificial minimal organisms are employed in complex natural biological systems such as a human being, the synthesis of artificial with natural components would take place on a level higher than the molecular or cellular level.

The term "biology" combined with "synthetic" leading to Synthetic Biology in this definition should be used exclusively for creating artificial systems based on DNA as an information store. Other forms of artificial carbon based life should be discussed in the context of "evolutionary nanotechnology" or synthetic artificial biology [17]. This field of activities is the subject of the European PACE program with overlapping schemes with the NEST Synthetic Biology program.

2.3. Bottom Up "Synthetic Biology": classical Genetic Engineering approach

Any DNA sequence which is modified by human influence in any sequence variant that is not naturally occurring is artificial. In the first instance this is independent of any change of functional properties.

From the perspective of human intention, the creation of varieties of sequences can only make sense in order to change functionality, to analyse and unravel, or to create new functional features, such as reproducibility and/or robustness of function. For this, it is possible to differentiate three types of functionality – regulators of function, regulated function targeted for specific control by regulators and sensor function.

Changing the properties of regulators, sensors and targets by creating new combinations is a prerequisite for the design of new regulatory circuits with intrinsic new functions, for example on the level of systemic behaviour. Many different applications that have already been published are based on the generation of recombinant cells and organisms by genetic engineering and molecular cloning in combination with transformation or transfection experiments.

However, there is a question of locating the point at which simple recombinant DNA experiments end and Synthetic Biology begins. Firstly, most recombinant DNA experiments in the past were performed for the sole purpose of unravelling biological functions such as:

- The regulation of different levels of cellular function and regulatory cellular pathways and structure,
- Structure-function relations, such as affinity or adhesiveness, and
- Catalytic properties, such as kinetic behaviour, selectivity, specificity or qualitative features such as stability, pH, temperature or influence of chemicals or processivity of catalysis reactions.

DNA constructs engineered for this purpose are based on viral, phage or plasmid vectors, (non-) homologous recombinants, stable knock outs and other genetic systems which are fit for the purpose of functional analyses. These gene constructs are stable, but with the increase in knowledge of how the wild type function works, the value of these constructs has become obsolete in most cases. These experiments and resulting constructs cannot be regarded as Synthetic Biology.

Many successful heterologous expression experiments of genes for bioproduction are classical examples of organisms with designed artificial functionality, microorganisms, fungi, cell cultures, transgenic animals and plants [18]. In formal terms, the artificial combination of a homologous regulator controlling the expression of a heterologous gene results in a simple artificial design of at least two natural biological parts. From the perspective of the intention behind the application, these constructs are designed for the production of a single molecule species, mostly proteins. In differentiating these classical experiments from highly advanced Synthetic Biology applications the following question arises. Are the simple heterologous expressions of proteins or simple modifications of regulators sufficient to be regarded as Synthetic Biology applications? To define a means to classify different levels of Synthetic Biology applications, one has to consider the purpose for which application is intended.

Systems biology is the analysis of how sensor and regulating functions control natural pathways and how they interact through informational crosstalking at the systemic level. Based on the steadily increasing knowledge about systemic behaviour, Synthetic Biology having the opposite

intention, aims at designing artificial pathways for optimized regulation or extended catalytical capabilities towards technical solutions.

Functional processes in living beings are historic and from the evolutionary point of view are therefore not at an endpoint [19]. Research efforts unravelling molecular biological functions in recent decades have showed that they are not ultimately optimized in a technical sense, since functional efficiency and efficacy in living beings are very often a compromise of different competing requirements of functional life. No functional conflicts are expected by using technical systems in artificial environments such as fermenters.

Providing technical solutions to systemic regulatory information either needs optimization of single components according to requirement specification in rational technical designs for stringent functional regulatory behaviour or functional processing on the cellular level by optimization cycles for directed evolution on the genomic level, or both.

Technical solutions include deploying mathematical methods and models such as statistics and computational tools as simulation algorithms to create information for optimization.

Synthetic Biology applies solutions to biological systems in order to influence their function towards a desired technical optimization by generating artificial designs compatible with biological functions at the more complex level of molecular interactions.

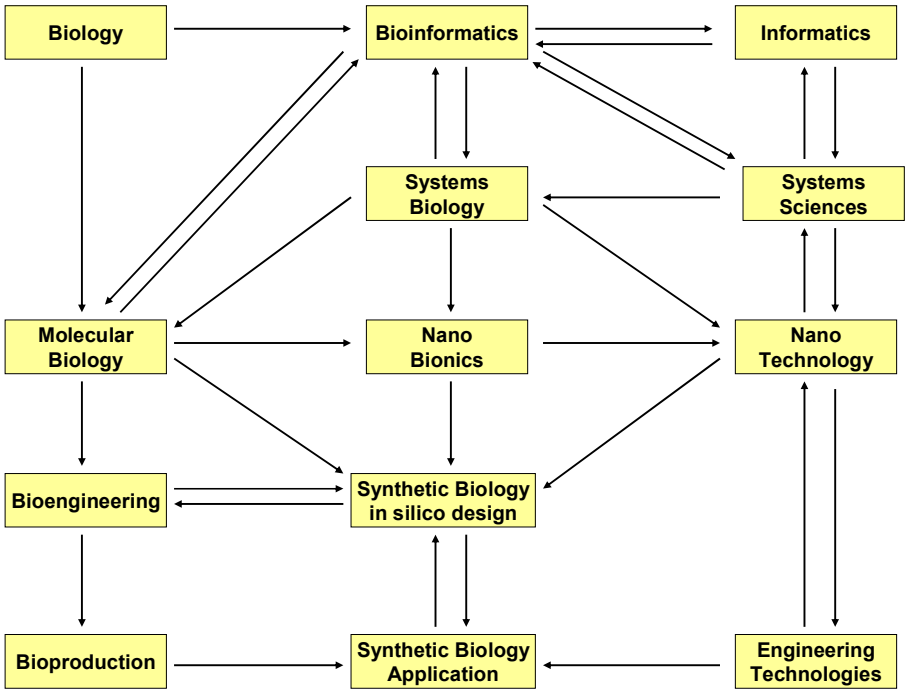

Figure 2: Synthetic Biology and its integration in related interdisciplinary fields of science and technology

2.4. In Vivo – Synthetic Biology: Practical engineering in vivo

2.4.1. From genetic manipulation to modulation to artificial systemic conditioning of biologic systems

Each natural molecular regulatory system, evolved by selection over long time periods, possesses a unique functionality [20]. The result of genomic evolution resembles a vast number of different components arranged in complex assemblies and interacting in only a partly understood fashion.

In order to unravel biological functions, genetic engineering experiments in the past were performed by changing regulatory parameters that depend on or effect the DNA itself (CIS), or on protein whose function is to bind DNA (TRANS), even over long genomic distances [21] [22, 23] [24]. Other regulatory efficient molecular locations which were subjected to molecular analyses are modification signals on biomolecules like DNA as well as regulated proteins. Regulation of gene activity as an intrinsic function of RNA molecules [25] is effective mostly on the level of translation. Silencing Riboswitches that control the gene expression on/off state upon conditional stimuli are also suitable for the generation and tailoring of regulation networks [26] [27]. Regulation also takes place at the level of the stability of biomolecules like RNA and proteins, where the degradation rate of regulators is of enormous importance [28].

Applications that simply need a change in one regulatory parameter should be regarded as second order and can be termed as classic, preliminary or preparatory technologies for Synthetic Biology. However, this raises the issue of what are Synthetic Biology approaches of the first order?

For the definition of a Synthetic Biology construct with artificial components integrated in/with natural or artificial cells, the artificial arrangement and molecular context of components is more specific than simple modification of an artificial regulating or regulated component. Regulating arrangements with minimum complexity are constructions with more than one interacting trans-regulator controlling a minimum of one genetic function, for example complex artificial regulatory schemes for highly regulated synthesis [29, 30] [31]. Systems like this might for example be those with the purpose of exact dosage of biopharmaceuticals *in vivo* dependent from various parameters being integrated like in medical applications.

For all subcellular artificial genetic parts which can be combined with natural or other artificial biological components, there are at least two interacting parts necessary to fulfil the criteria of creating systemic regulatory elements like simple circuits. Arrangements of increased complexity, e.g. artificial arrangements of more than one regulator for one or more genes dependent on at least one sensor part, should be termed first order Synthetic Biology systems.

From the perspective of complexity, different assemblies can be designed such as highly signal integrating assemblies with many regulators responding on a complex signal pattern with only one output signal, in contrast to complex arrangements of artificial genes with simple regulation patterns, or combinations of both.

Different applications can be designed, with complex stringently controlling regulatory schemes for the synthesis of enzymes with different specificities, for molecular modelling of small molecules to be synthesised in a bioproduction cell reactor for use of the products *in vitro* or *in vivo*.

In addition to be basically functional on the molecular level of biochemical pathways, Synthetic Biology applications can have an effect on more complex biological functions such as programmed pattern formation of multicellular systems, organs or organisms [32]. These developments are directed towards the design of artificial developmental regulators [33]. Synthetic Biology in future applications might be targeted at influencing organism complexity on all different levels, such as artificial viral systems, proto-life cells, minimal cells, normal bacterial and archaebacterial cells, unicellular eukaryotic or multicellular eukaryotic cells, tissues, mixed tissues, organs, and complex organisms. The resulting Synthetic Biology based systems can be deployed *in vivo* in more complex biological systems, for example in humans for designated applications such as drug delivery, removing cellular debris *in vivo* (Alzheimer, dissolving coaguli), generating programmed stem cells for stem cell therapy, tissue engineering or applications in regenerative medicine.

Synthetic Biology applications which intentionally influence the organismic complexity of targeted cellular communities might also aim at the creation of transgenic animals or plants with new desired properties, including synthetic organs for regenerative medicine or desired features for tissue engineering.

2.4.2. Programmable biological systems or organisms

Synthetic Biology involves a change of paradigm – it is a move away from analytic towards synthetic, and from "Molecular Biology" towards "Modular Biology" [19, 34, 35]. Strong efforts are being made towards designing artificial biological regulatory components showing technical features. One intention is to generate limited sets of biologically compatible regulatory switches composed of only a few parts sufficient for designing complex patterns of function to create varieties of different regulatory circuits [36] [31] [37-39] [40]. Their functional characteristics are intended to be optimized and defined, and the behaviour of such regulatory switches is intended to be predictable [41-43].

2.4.3. Parts fabrication, characterization and assembly

In order to provide a highly predictable expression of single components in gene assemblies in the correct amounts, different regulators are needed to those in natural expression. These aim at either regulating complex schemes of networks integrating many signals to form different circuits and sensors or at simply providing improved productivity for the purpose of a highly optimized product yield.

Different operating modes are possible. Existing natural biological pathways can be influenced or new pathways, including complex ones, can be designed by use of more than one regulating gene. This creates an artificial pathway which is controlled by different combinations of natural or artificial regulators [44]. The result can be a regulated design of crosstalking pathways in a pathway regulatory circuit modelling for the conditional control of the synthesis of proteins in the perfect dosage, for example mediated through prokaryotic as well as eukarotic cells such as stem cells in medical applications [45] [32, 46].

Isolated natural elements often show unpredictable behaviour and do not behave according to critical performance criteria such as robustness, reproducibility, ratios of signal strength relative to basal noise and noise propagation in networks, functional characteristics, and speed of action [47-49] [50] [51] [52] [53].

Recent research in Synthetic Biology aims at finding artificially designed biological regulatory function with technical characteristics which are combinable in a modular sense. This is the subject of intensive research under the leadership of MIT following "The BioBricks strategy" (http://parts.mit.edu).

2.4.4. Engineering of regulated catalytic and structural function

DNA synthesis is the most basic enabling technology for future Synthetic Biology applications [54-56]. The technology of *de novo* DNA or gene synthesis has, since the first initial experiments by Khorana [57], been developed to generate a variety of different methods for the advanced synthesis of DNA molecules of many kilo bases. Projects are organized with the goal of synthesis of total genomes.

By artificial redesign, DNA sequences can be generated that are exclusively rational [58], directed by statistical approaches, or by the favourable combination of different approaches. Design of new biocatalysts through the redesign of DNA sequences has, for example, significantly impacted

medical diagnostics and therapeutics, as well as industrial biotechnology for pharmaceutical production of chemically interesting compounds [59] [60] .

Today a tremendous arsenal of molecular methods exist that can be used to achieve functional modulation of proteins by introducing mutations in nucleic acids, derived using information from different analytical methods such as X-ray diffraction structural analysis.

As a result of the degenerative mode of the genetic code, many nucleotide substitutions result in transitions and transversions that are silent when changing the protein level. Simple codon usage optimizations can generate such silent DNA mutations.

Other, non-silent DNA mutations change the protein sequence according to the rules of the translation process. These mutations cause amino acid substitutions in the protein sequence affecting protein structure and function. Mutations which substitute amino acids with significantly different chemical properties or structure can drastically affect both structure and function of the protein. However, amino acid substitutions with amino acids of similar chemical properties or structure can be undisruptive to protein function.

The most frequent mutations of this type have a negative effect on function or stability, but in rare cases these mutations can result in better functional properties that do not disrupt the protein structure [61]. Therefore it should be advantageous to be able to introduce desirable chemical and structural function artificially into protein sequences *in vivo*.

Synthetic Biology strives for artificial variation of protein sequence towards extended functionality by expanding the universal and natural genetic code, so allowing artificial xeno-amino acids, uniquely different from the 20 that naturally occur, to be built into the primary protein sequence. The result is an artificial extended genetic code which can be exploited for the directed introduction of new functionality into a desired sequence context [62] [63].

Investigations into molecular structures and processes have created the perception that naturally occurring proteins are mostly assembled by different functional protein domains. Functional protein domains are resembled by stretches of DNA which code for the corresponding functional protein domains. This can be exploited by molecular evolution experiments for domain shuffling at the DNA level, which results in recombined functional domains of different existing natural origin whilst maintaining the relative position of the domains [64] [65] [66] [67].

Statistical methods for sequence diversification such as molecular evolution technologies use different approaches for random mutagenesis, for example random chemical procedures (e.g. oligonucleotide chemistry), in order to assemble large populations of slightly variant genes of modulated function. Most advanced technologies use complex oligonucleotide populations synthesized on micro array surfaces, either by classical synthesis chemistry or photochemically by use of photolabile protecting groups for assembling sequence identical genes or also sequence

variant gene populations [68]. As in natural molecular phylogenetic systems of protein families, artificial descendents can be calculated and monitored. Other molecular-evolution approaches allow the creation of totally new arrangements of artificially diversified functional protein domains from natural or artificial sources. After iterative selection of advantageous protein variants in bioassays, the resulting products may be deployed in medical and pharmaceutical or technical processes or serve as components for further applications in bioengineering design.

The potential applications in the field of engineering for Synthetic Biology include the optimized production of xeno-biomolecules such as biologics, therapeutic proteins, antibodies, enzymes, small molecule fermentation products (like vitamins, drugs and biopolymers), fine chemicals, bulk chemicals or simple biobased commodities [69] [70] [71, 72] [73].

Enzymatic biotransformations of chemicals from artificial educts for the generation of artificial products is a subject of intensive study and is expected to have a future impact on sustainable or green chemistry, which is intended to substitute classical chemical production [69, 74] [75] [73].

The design of biological function is not limited to individual genes, their function and their arrangements for the construction of regulatory circuits and pathways [76]. On the level of whole genomes, there are ambitious projects which are aiming at the design of microorganisms specifically for use in industrial as well as for clinical applications [76, 77]. On the level of the genome, shuffling has shown desired results for the creation of new (xeno-) biochemical pathways of natural molecules or heterologous artificial expression [78] [74] [79, 80]. These genomic constructs are arranged in new combinations of natural and artificial genes, creating artificial regulons of intended natural and artificial function combinations, depending on the starting genomes used.

This all opens new perspectives on medical and pharmaceutical applications which are not fully foreseeable at present. With enabling technologies such as gene redesign by *de novo* gene synthesis and stem cellculture, manufacturing of drugs outside of cells, such as chemical synthesis, will be obsolete, to a certain extent, in the future.

2.5. In Vitro - Synthetic Biology: Biological Inspired/Ambitioned

Nanotechnology using Synthetic Biology products for *in vitro* applications

As discussed earlier, one of the central purposes of *in vivo* Synthetic biology is to provide efficient and highly regulated production of artificial molecules which are not accessible, or have only limited accessibility, through classical chemical synthesis and production.

Scientists claim that bio-ambitioned nanotechnology applications belong in the context of *in vitro* Synthetic Biology applications. Indeed these applications are at the boundary between the disciplines of nanotechnology, nanoelectronics and Synthetic Biology [81]. The field is also closely related to biological chemistry and biomimetic chemistry. Other Synthetic Biology technologies which are related including molecular modelling, enzyme engineering, biochemical pathway design and fermentation.

The term *in vitro* Synthetic Biology is strictly application oriented. Most approaches in this field are biomimetic applications. The field aims to use Synthetic Biology products as tools for the biofunctionalization of nanotechnology particles in order to create a variety of interesting nanotechnology products. The biofunctionalized nanoparticles created intentionally mimick biological functionality.

It seems reasonable to locate a border between the simple coating of nanoparticles for *in vitro* Synthetic Biology applications and the use of artificial DNA sequence motives and structures for the assembly of functional nanoparticles [82] [81] [83]. More complex assemblies with at least two biological functions interacting *in situ* with each other in order to result in a joint functionality can be regarded as real *in vitro* Synthetic Biology.

The term *in vitro* Synthetic Biology refers to the use of biofabricated building blocks, derived from higly cellular bioproduction systems designed by *in vivo* Synthetic Biology methodologies, for any application in any environment [84].

Knowlegde gained from the study of bionics, the scientific discipline that is used to develop an understanding of biological function can be applied to technical processes. As discussed earlier, *in vivo* Synthetic Biology has the opposite intention - namely to apply technical knowledge to living systems. The discipline that develops an understanding of *in vitro* Synthetic Biology applications can be termed nanobionics [85]. It adopts molecular-biological understanding from living systems in order to apply the knowledge of biological function to technical processes on the nanoscale level. *In vitro* Synthetic Biology takes advantage of this technical knowledge and structural design of nanoscale building blocks in order to produce artificial components by bioproduction *in vivo* used for the creation of highly functional nanoscale assemblies *in vitro*. This field of *in vitro* Synthetic Biology activities will be analysed and exploited in the future for its potential to provide services to high impact biosynthetic target applications.

In general these applications are likely to be medical based with their components, biologically functionalized nanoparticles, being pharmaceutically produced. Therefore *in vitro* Synthetic Biology is likely to have a high impact and influence on human and animal health. Administered to living organisms such as humans, its effects could represent a new dimension of medicine. In particular, its application may lead to novel and functionally improved kinds of individualized

medicine, in the sense of being highly specific with improved efficacy and reduced side effects, therapeutic cell targeting and highly functional pharmacological drugs.

Other applications of *in vitro* Synthetic Biology aim at the use of highly specific nano-scale building blocks with extraordinary properties. Desirable properties for *in vitro* Synthetic Biology bio-ambitioned nanotechnology products are, for example, the self assembly of synthetic parts or monomers. The result of self assembly may be nanoscale semi- or highly powerful conducting wires for biocomputing, nano-sensors, and magnetic nano spools [86] [81]. This may include DNA-templated self assembly of protein arrays, such as "virus like particles" for biomedical applications or the generation of functional nanoparts [81, 83, 84, 87-89].

The self assembly of synthetic nano-parts can be supported by biomolecular motors, nanorobots or other actors [84]. In chemical terms, highly functional parts can serve for biomimetic function such as nanoparticle bound artificial light collecting photosystems or complex catalytic reaction cascades *in vitro* for synthesis of chemicals or functional building blocks [90] [87, 88] [91].

One example is the creation and provision of nanoparticles which imitate the photosystem of photosynthetic organisms to create power generating surfaces. Another example is nanoparticles for complex chemical biotransformation processes *in vitro*, where a more complex assembly of enzymes are bound on light exposed surfaces [92].

The final consideration of why bio-ambitioned nanotechnology, with the exception of biomimic chemistry, should be considered to be part of *in vitro* Synthetic Biology research is related to the bioproduction of xenobiochemicals and the fabrication of materials for the design of biomimetics [85]. For use in technical applications, *in vitro* Synthetic Biology provides, by way of artificial pathways, the desired artificial enzymes enabling, for example, stereo- and regioselectivity capabilities in structural design of building blocks. This can include artificial porphyrine base light harvesting and nanowires of desired functions [93].

Bio-ambitioned nanotechnology activities based on *in vitro* Synthetic Biology activities are organized and coordinated in different organizations world wide, including the European Nanotechnology Gateway and national organisations such as CeNtech (Germany - www.centech.de). More basic research oriented European projects are aimed at the basic understanding of biological life functions. They, by contrast, aim at alternative and artificial evolutionary systems in creating an "evolutionary nanotechnology" (see EU Project: PACE = Programmable Artificial Cell Evolution - http://134.147.93.66/bmcmyp/Data/PACE/Public) with logical and substantial elements learned from biological life and theories about life. This super loop of informational processing is the basis of rational design and simulation of evolutionary processes for creating a completely artificial carbon based life and different parallel cycles of evolution of artificial life which can be termed "Artificial Biology". It is clear that from

the top down perspective, *in vitro* Synthetic Biology is the marginal boundary layer of the beginning of a fusion of two different disciplines, whose merging will increase with time.

2.5.1. Designed Biosensors and Biosensoric Systems for in vivo and in vitro Application

Artificial biosensor systems can be designed as *in vivo* Synthetic Biology applications, where living cells serve as the biosensing entity. Alternatively they can be used in *in vitro* Synthetic Biology applications, where bioproduction and/or biofabrication of sensor-signalling and sensor-actuator parts that are assembled *in vitro* provide functional building blocks to biobased nanoparticles.

Biosensors intended to be active in intra-cellular environments are designed to specifically interact at an extra- or intracellular level with organic or inorganic molecules or to respond to an external physical influence such as light, heat or cold with generation of signals [94] [95] [96].

Upon detection of a specific interaction they respond by transmitting a signal which is communicated to the internal regulatory system, usually by secondary messengers. Signals of different biosensors in a network of cellular functions are integrated to an adaptive cellular response. Biosensors are predominantly located as specific protein receptors on the outer membrane, for instance a conserved modular design of an oxygen sensory/signalling network with species-specific output [96].

The immediate cellular environment depends on the type of organism. Unicellular and undifferentiated multicellular organisms are directly confronted with complex natural environments that frequently change. Biosensors of cells in higher organisms respond to fixed schemes of signals in defined internal environments of the organism containing molecules such as hormones, cytokines or chemokines, signals which are produced by other cells depending on the differentiation status of the corresponding tissue with the effect of intra- or intercellular communication. However other cells in complex organisms are differentiated by the biosensoric analysis of the environment such as the cells of the olfactory system.

Artificial biological sensor-signalling and actuating systems can be generated on three different levels [97] [98]. First, the specifications of natural receptors can be designed by molecular engineering. Phage display is a wide-spread technology for creating libraries of different peptides suitable for affinity based selection of specifically binding molecules to nearly any substrate or surface used for selection. Recently Aptamers, artificially designed RNA molecules, have been shown to have similar properties to proteins in specific structural detection of defined molecules with high affinity [99] [100] [101].

The most critical point is the generation of a signal and linking it to a signalling pathway while demonstrating correct regulating behaviour [102] [103]. This is the second level of artificial design. On reception of a signal, there can be interchange between signalling pathways, made possible by changing the response [104]. By artificial sensoric pathway design, for example, it should be possible to produce a GFP (green fluorescent protein) in any cellular system through the response of an artificial receptor system such as olfactor receptor on the surface of an E. coli cell [95] [35].

The generation of a specific directed response to the signal by producing an effect on a dedicated actuator is the third level of artificial design which can be addressed by engineering according to sensor and actuator models.

The field of biosensing signalling and actuation can have an effect on different targeted technical biosensing systems (such as *in vitro* Synthetic Biology applications), where bioproduction and/or biofabrication provide building blocks of sensor-signalling parts (e.g. nanowires and sensor-actuator parts) assembled *in vitro* for providing a certain function for an application [105] [106].

2.6. In Silico - Synthetic Biology

Natural genetic rules, responsible for natural evolution, can be substituted by artificial design and can dramatically accelerate evolution of certain systems. Without use of computers and bioinformatics this would not have been possible. Classical bioinformatic software at the beginning of the era of genetic engineering was developed in parallel for sequence analysis, processing, and for analysis of data of molecular structures. Later algorithms were created simulating the resolution of the pattern of biological differentiation in space and time. There is now a large diverse volume of computer algorithms for the analysis of biomolecule sequence and structure related problems.

To define whether any specific software belongs to a Synthetic Biology enabling software category and which features define real *in silico* Synthetic Biology software, one has to consider the purpose for which the software is designed and programmed [107-109] [110-112] [113] [53].

Nucleic acid, protein structure and sequence related analyses for finding sequence motives were initially the basis of biofunctional computing. Increasingly improving algorithms enabled the design of single biomolecular components such as CIS-acting elements and regulatory and regulated proteins, as well as other functional cellular molecules like RNA and glycoproteins. Structural and sequence data, as well as related functional data were collected from experimental results over the last decades. These were stored in many different data bases predominantly available via the internet [109, 111, 113-115] [116]. This created data and information for the

rational design of biocatalysators and structural molecules that can be artificially modulated and designed by changing structural information, with respect to binding properties such as affinity constant (e.g. of small molecules) specificity or selectivity, and features such as stability against different physical, chemical and biological environmental influences [117].

Other algorithms have been developed for the simulation of directed evolution based processes [118] [119]. However, there is no recent review article available which covers the field. To design gene regulatory circuits, basic principles of systems and networks must be understood. Developing this understanding is the main task of systems biology - to learn by modelling of natural systems using computer data from the "omic" projects [120] [112] [121].

The recent development of systems biology software tools are clearly the basis for the analysis of predictive behaviour of natural biological regulatory systems according to the control theory [122] [123] [124] [125]. Systems biology software, in contrast to bioinformatic software described above, is not focussed on the analysis and design of single components of a regulatory system but on the analysis and description of the structure of interaction of all the components.

This is only possible *in silico* by computational studies of gene regulatory networks creating *in numero* molecular biology [126] [52] [53]. Virtual environments are created for computational simulation of cellular behaviour [110]. However most algorithms in biocomputing belong to the extensive field of enabling software of the second order. This raises the question of the location of the border between real *in silico* Synthetic Biology software and data bases of first order. Answering this is a challenge on which a variety of people are focussing their scientific attention [127] [128] [129].

In silico Synthetic Biology is clearly focussed on the design of artificial regulatory systems and circuits integrating biosensor-actuator machinery with signal transducing components and regulated function with predictive systemic behaviour and optimized technical features [130] [131] [48] [132] [49] [133]. It moves towards the simulation of predictive artificial molecular *in silico* evolution processes on the molecular and genomic level, and on the level of regulatory circuits of total pathways [49] [133] [134] [135] [136] [137] [138] [139] [140] [141].

In silico Synthetic Biology software packages should provide tools for the design of functional requirements of predefined regulatory circuit specifications and tools for the design of individual components. In addition, standard components of known characteristics should be made available by a related database. Moreover, integrated analysis tools for managing any experimental proof of conceptual designs and imaging software, graphically supporting the handling of the software, should be part of the package.

Research aimed at providing information about biological regulatory functional elements with technical characteristics which can be combined in a modular fashion and compatible

functionally has recently become the subject of intense development. Most advanced at present is the "Registry of Standard Biological Parts" under administration of MIT (http://parts.mit.edu).

A software package, named *BioJADE: A design and Simulation Tool for Synthetic Biological Systems,* for programming of algorithms for BioBrics, focussing on design, is available from by CSAIL (MIT Computer Science and artificial intelligence laboratory) [142]. A DNA "Open Source" concept (Andrew Hessel) is another approach for providing artificial functional genetic information to the Synthetic Biology community. This concept, if realized, will speed up the provision of DNA based development of therapeutics towards a new and more efficient evolutionary strategy of gain of functional information.

2.7. Summary

Synthetic Biology can be defined as the boundary layer between biological sciences and engineering sciences, in which technical approaches are employed to provide future applications.

All currently provided or intended Synthetic Biology applications focus on the design of artificially modified living systems, such as specialized cells for the biobased production of molecules for *in vivo* or *in vitro* use. The key features of Synthetic Biology are on different levels of living systems:

1. Deployment of living systems to engineer complex patterns containing components of artificial biologically compatible and functional assemblies which are sustainably maintained through continued life cycles.
2. Artificial assemblies of regulators in circuits with designed functions rather than simple single regulator modifications.
3. Deployment of functional assemblies of artificial pathways by modified artificially regulated genes of structural or catalytic function.
4. Production of artificial molecules as primary or secondary gene products
    (a) Macromolecules, e.g. RNAs or enzymes, for intracellular use as catalysts in an assembly of artificial enzymes or extracellular as molecular sensors, building blocks for complex subcellular assemblies of macromolecules, or other different functions.
    (b) Small molecules for use as biological drugs, building blocks for chemical synthesis, or for the purpose of nanotechnological engineering of more complex units for different applications.

Therefore, the first word "synthetic" in Synthetic Biology describes the synthesis of artificial and natural components forming a new artificial living system. Furthermore, as the techniques for system design, synthesis and optimization mature, we will witness a rapid growth in the capabilities of synthetic systems with a wide-range of applications made possible with the synthesis products of these artificial living systems.

Therefore the second intended core competence of Synthetic Biology is the deployment of highly functional artificial assemblies of designed bioregulators and regulatory circuits in combination with redesigned genes, with clearly specified technical and functional requirements for effective and highly controlled bioproduction of natural products, biochemicals and xenobiotica [74] [80].

The intended applications of certain *in vitro* Synthetic Biology products are aiming on are fascinating. All those applications need to use parts, building blocks or compounds to be provided by *in vivo* Synthetic Biology. Only bioambitioned nanotechnology approaches which use parts and building blocks from artificial biologic production can be classified accordingly *in vitro* Synthetic Biology. *In vivo* Synthetic Biology therefore is an indispensable prerequisite for providing materials like artificial designed molecules and material with desired function for *in vitro* Synthetic Biology applications.

Synthetic Biology is the deployment of an engineering discipline that is objective driven. It is not primarily a discovery science, as it builds on our current understanding while simplifying some of the complex interactions characteristic of natural biology. Also, it is intentional design based engineering of systems based on biological functions and rules aimed at obtaining new functions which are not present in nature.

Thus, our working definition is as follows: *Synthetic Biology is the engineering of biological components and systems that do not exist in nature and the re-engineering of existing biological elements; it is determined on the intentional design of artificial biological systems, rather than on the understanding of natural biology.*

3. STATISTICAL ANALYSIS OF CURRENT SYNTHETIC BIOLOGY RESEARCH

This section provides a statistical analysis of Synthetic Biology research. Continual development of this analysis is a key component of future project activities, including the interviews with key Synthetic Biology stakeholders. Thus, the work described in this section should be treated as the first version of the analysis, based on the data collected until September 2005.

The statistical analysis focuses on the type and number of publications in the field since 1970, the characteristics of the publication authors and the sources of finance for Synthetic Biology research.

3.1. Identification of Publications and Activities

The Consortium has developed a search and identification mechanism that identifies journal publications, research activities and institutions in Synthetic Biology. These publications, activities and institutions are classified into seven fields:

- Concepts and political strategy
- Theoretical bio-engineering *in silico*
- Biological inspired nanotechnology *in vitro*
- Practical engineering *in vivo*
- Applications of Synthetic Biology (related and enabling technologies)
- Products
- Others

More details of this classification are illustrated in Figure 3 below.

Figure 3: Synthetic Biology classification details

1. Concepts and political strategy

2. Theoretical bio-engineering *in silico*
   - *Modeling of natural systems*
     - *Genome, Proteome, Metabolone analysis*
     - *Analysis and modelling of molecular networks*
     - *Metabolic profiling*
   - *Modeling of synthetic systems*
     - *Design principles of systems and networks*
     - *Noise in systems and components*
     - *Information processing and control theory*

3. Biological inspired nanotechnology *in vitro*
   - *Biomimetics, Nanobionics, Evolutionary Nanotechnology*
     - *Computation using biological components and principles*
     - *Selfassembling, biomimetic, biomaterials, bioelectronics*
     - *Single molecule manipulation and/or measurement methods*
     - *Reporters and sensors*
     - *Molecular machines, actuators and device*
   - *Artificial Life*

4. Practical engineering *in vivo*
   - *Engineering of structural function*
     - *Molecular engineering (rational design)*
       - *DNA/RNA/PNA*
       - *Proteins*
     - *Artificial evolution and evolutionary optimization strategies (irrational design)*
       - *DNA/RNA/PNA*
       - *Proteins*
     - *Semisynthetic design (rational + irrational design)*
   - *Engineering of regulatory function*
     - *Biochemical or genetic network design*
     - *Riboswitches*
   - *Parts fabrication, characterization, assembly*
     - *The BioBricks strategy*
     - *Programmable organisms or systems*

5. Applications of Synthetic Biology (related and enabling technologies)
   - *Molecular Biology Methodology in general*
     - *Genome-, Chromosome-, Genetic Engineering, Molecular Evolution methodologies*
     - *DNA-, Gene synthesis*
   - *Analytics*
     - *Diagnostics*
     - *Microarrays, Biochips, Microfluidic devices, Nanotechanalytic*
       - *Microfluidics*
     - *Analytical chromatography, spectroscpical methodologies, bioimaging, high throughput bioassays*
     - *Chromatography for molecule and cell enrichment, purification, isolation*
   - *Computing*
     - *Biocomputing, Bioinformatic, Systems Biology*
     - *System Sciences, Informatics, Computing Technologies*
   - *Biological chemicals*
     - *Building blocks, fine chemicals*
     - *Biocatalysis, biotransformations*
   - *Biopharmaceuticals*
     - *Small molecule and Macromolecule drugs*
     - *Delivery systems*
   - *Biomaterials*
     - *Biopolymers, colloids and nanoparticles*
     - *Biocomposites*
   - *Cell technology*
     - *Cell culture, Transfection*
     - *Stem Cell technology*
   - *Tissue and Organ engineering, Transplantation*
   - *Reproduction Technologies, In Vitro Fertilisation*
   - *Transgenic plants and animals*
   - *Bio-energy sources*
     - *Bio-fuels, biogas*
     - *Bioelectricity*

6. Products
   - *Small molecular drugs, bio-drugs, bio-agents*
   - *Flavors, fragrances, colors, pigments, commodities*
   - *Biopolymers, biocomposites*
   - *Cell culture, Stem Cells*
   - *Tissues, organs, organisms*
   - *Bio-fuels, bio-electricity*
   - *Biomimetic, biocomputers*

7. Others

This research will form the basis of the Project Database. The database will be one of the key outputs from the project and will contain information about the structure, activities and participants in the Synthetic Biology sector. The database will be fully searchable, so that the user can identify relevant information according to their stated search parameters. The search parameters for the project database include the following:

- Field (as described in Figure 3 above)
- Institute/Firm/Project/Organization
- Author and Co-Authors
- Country
- Journal
- Funding source
- Keyword search of abstract
- Date of publication/activity

Below we provide the current list of active individuals and organizations under the seven field headings. The list thus provides details of the actors (both individuals and organizations), that are currently providing Synthetic Biology research in Europe and North America. It should be stressed that the development of knowledge and understanding of this research, and thus the development of the project database, is an ongoing task in the project. Thus, although the project has already identified in excess of 200 scientists, organizations and funding bodies this should be regarded as the analysis at this stage of the project.

Table 1: Individuals, Organizations and Activities in Synthetic Biology

First Name	Surname	Institute / Firm / Project / Organization
1. Concepts and political strategy		
Ronald	Breslow	Michigan State University, USA
Barbara	Hobom	Freie Journalistin, Freiburg, Germany
Gerd	Hobom	Institut fur Mikrobiologie und Molekularbiologie, Univerity of Giessen, Germany
Eric	Drexler	Foresight Nanotech Institute, California, USA
Leland	Hartwell	Fred Hutchinson Cancer Center, Seattle, USA
Marco	Piccolino	Dipartimento di Biologia, Università di Ferrara, Ferrara, Italy
Philip	Ball	Nature, London, UK
Eduard	Mirzoian	Institute of History of Natural Science and Technology, Russian Academy of Sciences
Mihail	Roco	National Science Foundation, Virginia, USA
Harold	Craighead	School of Applied and Engineering Physics and The Nanobiotechnology Center, Cornell University, USA
Wayt	Gibbs	Scientific American, New York, USA
Dan	Ferber	Popular Science, Florida, USA
Eors	Szathmary	Research Group of Theoretical Biology and Ecology, Eotvos University and Collegium Budapest, Hungary
Garath	Belovsky	University of Notre Dame, Indiana, USA
Chappell	Brown	EE Times, New York, USA
Oliver	Morton	Wired and Newsweek International, USA
Stephan	Herrera	Nature Biotechnology, New York, USA
Sydney	Brenner	The Salk Institute for Biological Studies, California, USA
Paul	Rabinow	University of California, USA
Michael	Savageau	Department of Biomedical Engineering University of California Davis, Genome and Biomedical Sciences Building, USA
Lauren	Clark	MIT School of Engineering, Laboratory for Information and Decision Systems, USA
Tara	O'Toole	Center for Biosecurity, University of Pittsburgh Medical Center (UPMC), USA
George	Poste	The BioDesign Institute, Arizona State University, USA
Christian	Krassnig	European Commission, DG Research, Brussels, Belgium
Hubert	Bernauer	ATG:biosynthetics GmbH, Germany

First Name	Surname	Institute / Firm / Project / Organization
2. Theoretical bio-engineering *in silico*		
Modeling of natural systems		
	Genome, Proteome, Metabolone analysis	
Eugene	Koonin	National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Maryland, USA
Janusz	Bujnicki	Bioinformatics Laboratory, International Institute of Molecular and Cell Biology, Warsaw, Poland
Edward	Marcotte	Center for Systems and Synthetic Biology, Institute for Molecular Biology, University of Texas at Austin, USA
Shailesh	Date	Center for Systems and Synthetic Biology, Institute for Molecular Biology, University of Texas at Austin, USA
Vishwanath	Iyer	Center for Systems and Synthetic Biology, Institute for Molecular Biology, University of Texas at Austin, USA
	Analysis and modelling of molecular networks	
Ulrich	Gerland	Physics Department, University of California at San Diego, USA
Amos	Tanay	Deptartment of Computer Science, Tel-Aviv University, Israel
Ron	Shamir	School of Computer Science, Tel Aviv University, Israel
Terence	Hwa	Department of Physics and Center for Theoretical Biological Physics, University of California, USA
Vincent	Hakim	Département de Physique - Ecole Normale Supérieure, Laboratoire de Physique Statistique, Paris, France
Alvis	Brazma	European Bioinformatics Institute, Cambridge, UK
Marta	Cascante	University of Barcelona, Spain
Duncan	Davidson	MRC Human Genetics Unit, Edinburgh, UK
Joaquin	Dopazo	CNIO-Spanish National Cancer Center, Madrid, Spain
Marcelle	Kaufman	Center for Nonlinear Phenomena and Complex Systems, Campus Plaine - CP 231, Université Libre de Bruxelles, Belgium
Jan	Komorowski	Norwegian University of Science and Technology, Norway
Victor	de Lorenzo	CNB-National Center of Biotechnology, Madrid, Spain
Christos	Ouzounis	European Bioinformatics Institute, Cambridge, UK
Vincent	Schachter	Hybrigenics SA, Paris, Spain
Giulio	Superti-Furga	Cellzome & EMBL, Heidelberg, Germany
Alfonso	Valencia	CNB-National Center of Biotechnology.
Hans	Westerhoff	Vrije Universiteit Amsterdam, Netherlands
Shoshana	Wodak	Université Libre de Bruxelles, Belgium

First Name	Surname	Institute / Firm / Project / Organization
	Metabolic profiling	
Richard	Beger	Center for Metabolomics of Division of Systems Toxicology, UAMS NCTR
Rima	Kaddurah-Daouk	Duke University Medical Center, Cambridge, USA
Andy	Nicholls	GlaxoSmithKline R&D, UK
Istvan	Pelczer	Dept. of Chemistry, Princeton University, Princetown, USA
Steven	Watkins	Lipomics Technologies, Inc, California, USA
Gustavo	Caetano-Anolles	University of Illinois, USA
Jerry	Chandler	Krasnow Institute for Advanced Study, George Mason University, Virginia, USA
David	Janero	Research & Development, NitroMed, Inc, Massachusetts, USA
Yvonne	Will	Safety Sciences Department, Pfizer Inc.
John	Montana	Paradigm Therapeutics Ltd, Cambridge, UK
Alfred	Ajami	Xanthus Life Sciences, Inc., Montreal, Canada
Malcolm	McConville	Department of Biochemistry, University of Melbourne, Victoria, Australia
Ana	Soria	Chemistry, University of York, UK
Jules	Griffin	The Department of Biochemistry, University of Cambridge, UK
Arno	Krotzky	Metanomics Health GmbH, Metanomics GmbH & Co. KGaA, Berlin, Germany
John	Ryals	Metabolon Inc, North Carolina, USA
Alfonso	Bellacosa	Population Sciences, Fox Chase Cancer Center, Philadelphia, USA
Michael	O'Connell	Life Science Solutions, Insightful Corporation
Dean	Jones	Core Lab, Emory University, Atlanta, USA
Modeling of synthetic systems		
	Design principles of systems and networks	
Uri	Alon	Weizmann Institute of Science, Rehovot, Israel
Luca	Cardelli	Microsoft Research, Cambridge, UK
Aviv	Regev	BioSPI Project, Weizmann Institute of Science, Rehovot, Israel
Nicolas	Buchler	Center for Studies in Physics and Biology, The Rockefeller University, New York, USA
Jim	Schaff	Virtual Cell, University of Connecticut Health Center, USA
Paul	François	Laboratoire de physique statistique, Ecole Normale Superieure, Paris, France
Farren	Isaacs	Department of Biomedical Engineering, Boston University, USA

First Name	Surname	Institute / Firm / Project / Organization
Herschel	Rabitz	Department of Chemistry, Princeton University, Princeton, USA
Masaru	Tomita	E-Cell project, Institute for Advanced Biosciences, Keio University, Yamagata ,Japan
Hiroaki	Kitano	The Systems Biology Institute, Yokyo, Japan
Radhika	Nagpal	Harvard University, Massachusetts, USA
Richard	Murray	Division of Engineering and Applied Science, California Institute of Technology, USA
Adam	Arkin	BioSpice, University of California, USA
3. Biological inspired nanotechnology *in vitro*		
Biomimetics, Nanobionics, Evolutionary Nanotechnology		
	Computation using biological components and principles	
Leonard	Adleman	Department of Computer Science, University of Southern California, USA
Julia	Khodor	Laboratory for Computer Science, D279
Masami	Hagiya	Department of Biophysics and Biochemistry, Graduate School of Science, University of Tokyo, Hongo, Japan
Echud	Shapiro	Department of Computer Science & Applied Math and Department of biological chemistry, Weizmann Institute of Science, Rehovot, Israel
Bernard	Yurke	Bell Laboratories, Lucent Technologies, New Jersey, USA
Laura	Landweber	Department of Ecology and Evolutionary Biology, Princeton University, USA
Grzegorz	Rozenberg	Leiden Center for Natural Computing, Leiden University, CA Leiden, The Netherlands
Milan	Stojanovic	Division of Clinical Pharmacology and Experimental Therapeutics, Columbia University, USA
Jean-Louis	Mergny	Laboratoire de Biophysique, Museum National d'Histoire Naturelle, Institut National de la Sante et de la Recherche Medicale Unite 565, Centre National de la Recherche Scientifique Unite Mixte de Recherche 8646, Paris, France
Yaakov	Benenson	Laboratory for Biomolecular Computers, Rehovot, Israel
Ehud	Keinan	Department of Chemistry Technion - Israel Institute of Technology, Haifa, Israel
Darko	Stefanovic	Department of Computer Science, University of New Mexico, USA
	Selfassembling, biomimetic, biomaterials, bioelectronics	
Nadrian	Seeman	Department of Chemistry, New York University, USA
Bernard	Erlanger	Department of Microbiology, Columbia University, USA
Erez	Braun	Department of Physics - Israel Institute of Technology, Haifa, Israel
Mehmet	Sarikaya	Biomimetic and NanoComposite Materials Research Group, University of Washington, USA
Trevor	Douglas	MSU Dept. of Chemistry and Biochemistry, Massachusetts, USA

First Name	Surname	Institute / Firm / Project / Organization
Hao	Yan	Department of Computer Science, Duke University, North Carolina USA
Huajian	Gao	Max-Planck-Institut für Metallforschung, Stuttgart, Germany
Angela	Belcher	Department of Materials Science and Engineering, Massachusetts Institute of Technology, USA
Stephen	Mann	School of Chemistry, University of Bristol, UK
Arun	Majumdar	Department of Mechanical Engineering, University of California, USA
Tijana	Rajh	Chemistry Division, Materials Science Division, Argonne National Laboratory, Illinois, USA
Viola	Vogel	Eidgenössische Technische Hochschule (ETH), Hönggerberg, Switzerland
Matthew	Francis	Department of Chemistry, University of California, USA
Reza	Ghadiri	Department of Chemistry, MB-9; Scripps Research Institute, California, USA
	Single molecule manipulation and/or measurement methods	
Carlos	Bustamante	Howard Hughes Medical Institute and the Department of Molecular and Cell Biology, University of California, USA
Jurgen	Rabe	Department of Physics, Humboldt UniVersity Berlin, Newtonstr. 15, D-12489, Berlin, Germany
Jan	Liphardt	Lawrence Berkeley National Laboratory, Physical Biosciences Division, California, USA
	Reporters and sensors	
Homme	Hellinga	Department of Biochemistry, Nanaline H. Duke, North Carolina, USA
Hagan	Bayley	Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Oxford, UK
David	Walt	Max Tishler Laboratory for Organic Chemistry, Department of Chemistry, Tufts University
Milan	Mrksich	Department of Chemistry and Institute of Biophysical Dynamics, The University of Chicago, USA
Vladimir	Didenko	Baylor College of Medicine, Texas, USA
Dariusz	Górecki	School of Pharmacy and Biomedical Sciences, Institute of Biomedical and Biomolecular Sciences, University of Portsmouth, UK
Jun-Ichi	Kikuchi	Graduate School of Materials Science, Nara Institute of Science and Technology, Nara, Japan
	Molecular machines, actuators and device	
Chengde	Mao	Department of Chemistry, Purdue University, Indiana, USA
Carlo	Montemagno	Biomedical Engineering IDP, UCLA Henry Samueli School of Engineering and Applied Science, California, USA
Michael	Simpson	Molecular-Scale Engineering and Nanoscale Technology Research Group, The Oak Ridge National Laboratory, Tennessee, USA
Christopher	Jarzynski	Theoretical Division, T-13, MS B213, Los Alamos National Laboratory, New Mexico, USA
George	Bachand	Biomolecular Materials and Interfaces, Chemical Synthesis and Nanomaterials, and Center for Integrated

First Name	Surname	Institute / Firm / Project / Organization
		Nanotechnologies, Sandia National Laboratories
Henry	Hess	Dept. of Bioengineering, Center for Nanotechnology, Seattle, USA
Peixuan	Guo	Purdue University, Indiana, USA
Artificial Life		
Thomas	Ray	Department of Zoology, University of Oklahoma, USA
Chris	Adami	Digital Life Laboratory 136-93, California Institute of Technology, USA
Pier	Luigi Luisi	Dipartimento di Biologia, Università degli Studi di Roma Tre, Rome, Italy
David	Deamer	Deamer Research Group, Department of Chemistry, University of California, USA
Fredric	Menger	Chemistry Building, Department of Chemistry, Emory University, Atlanta, USA
Steen	Rasmussen	Self-Organizing Systems EES-6, MS-T003, Los Alamos National Laboratory, New Mexico, USA
Nicholas	Hud	Center for Fundamental and Applied Molecular Evolution, School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, USA
Albert	Libchaber	The Rockefeller University, New York, USA
Norman	Packard	Protolife S.r.l., Venice, Italy
Stehen	Rasmussen	ProtoCell (www.protocell.org)
John	McCaskill	European Center for Living Technology (ECLT), Venice, Italy
4. Practical engineering *in vivo*		
Engineering of structural function		
	Molecular engineering (rational design)	
Peter	Dervan	Division of Chemistry and Chemical Engineering, California Institute of Technology,USA
Peter	Nielsen	Center for Biomolecular Recognition, IMBG, Laboratory B, The Panum Institute, University of Copenhagen, Denmark
Walter	Gilbert	Biological Laboratories, Harvard University, USA
Sidney	Altman	Department of Biology, Yale University, USA
Susan	Freier	Isis Pharmaceuticals, California, USA
Alfred	Pingoud	Institut für Biochemie, FB Biologie, Justus-Liebig Universität, Copenhagen, Denmark
Jesper	Wengel	Center for Synthetic Bioorganic Chemistry, Department of Chemistry, University of Copenhagen, Denmark

First Name	Surname	Institute / Firm / Project / Organization
Alexander	Rich	Department of Biology, Massachusetts Institute of Technology, USA
Arghya	Ray	Department of Physical Chemistry, Chalmers University of Technology, Gothenburg, Sweden
Cynthia	Wolberger	Department of Biophysics and Biophysical Chemistry and the Howard Hughes Medical Institute, Johns Hopkins University School of Medicine, Baltimore, USA
Martin	Egli	Department of Biological Sciences, Vanderbilt University, Tennessee, USA
John	SantaLucia	Department of Chemistry, Wayne State University, Michigan, USA
George	Church	Harvard Medical School, Massachusetts, USA
Shuguang	Zhang	Center for Biomedical Engineering, Massachusetts Institute of Technology, USA
William	DeGrado	Department of Biochemistry and Biophysics, The Johnson Research Foundation, University of Pennsylvania School of Medicine, USA
Emil Thomas	Kaiser	Laboratory of Bioorganic Chemistry and Biochemistry, Rockefeller University, New York, USA
Michael	Smith	Biotechnology Laboratory and Department of Biochemistry, The University of British Columbia, Canada
David	Tirrell	Division of Chemistry and Chemical Engineering, California Institute of Technology, USA
David	Richardson	Department of Biochemistry, Duke University Medical Center, North Carolina, USA
Jack	Dounitz	Organic Chemistry Laboratory, Swiss Federal Institute of Technology, Zurich, Switzerland
Kathleen	Matthews	Department of Biochemistry and Cell Biology, Rice University, Texas, USA
Srinivasan	Chandrasegaran	Department of Environmental Health Sciences, School of Public Health, Baltimore, USA
Kevin	Mayo	Department of Biochemistry, Molecular Biology and Biophysics, and the Biomedical Engineering Center, University of Minnesota, USA
Eric	Kool	Department of Chemistry, Stanford University, Cailfornia, USA
Padmanabhan	Balaram	Molecular Biophysics Unit, Indian Institute of Science, Bangalore, India
Alan	Kennan	Departments of Chemistry and Molecular Biology and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, California, USA
Reza	Ghadiri	Departments of Chemistry and Molecular Biology and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, California, USA
Tracy	Handel	Department of Molecular and Cell Biology, University of California, USA
Fujie	Tanaka	Departments of Chemistry and Molecular Biology and the Skaggs Institute for Chemical Biology, The Scripps

First Name	Surname	Institute / Firm / Project / Organization
		Research Institute, California, USA
Wendell	Lim	University of California, USA
Rudolf	Allemann	School of Chemistry, University of Birmingham, UK
Sam	Gellman	University of Wisconsin, Madison, USA
Albert	Mildvan	Department of Biological Chemistry, The Johns Hopkins School of Medicine, Maryland, USA
Stephen	Mayo	Howard Hughes Medical Institute and Divisions of Biology and Chemistry, California Institute of Technology,USA
Barbara	Imperiali	Departments of Chemistry and Biology, Massachusetts Institute of Technology, USA
Carlos	Barbas III	The Scripps Research Institute, California, USA
Katja	Arndt	Department of Biology III, University of Freiburg, Germaqny
Ronald	Zuckermann	Chiron Corporation, California, USA
	Artificial evolution and evolutionary optimization strategies (irrational design)	
Stanley	Miller	Department of Chemistry and Biochemistry, University of California, USA
Albert	Eschenmoser	Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule (ETH), Zürich, Switzerland
Luc	Van Meervelt	Biomolecular Architecture, Department of Chemistry, Katholieke Universiteit Leuven, Leuven (Heverlee), Belgium
Thomas	Spratt	Institute for Cancer Prevention, American Health Foundation Cancer Center, New York, USA
Michael	Sismour	Departments of Chemistry and Anatomy and Cell Biology, University of Florida, USA
Hiroshi	Yanagawa	Mitsubishi Kasei Institute of Life Sciences, Tokyp, Japan
Willem	Stemmer	Avidia Research Institute, California, USA
Peter	Schultz	Department of Chemistry, The Scripps Research Institute, California, USA
James	Wells	Department of Protein Engineering, Genentech, Inc., California, USA
Sachdev	Sidhu	Department of Protein Engineering, Genentech, Inc., California, USA
Andreas	Plückthun	Biochemisches Institut, Universitat Zurich, Switzerland
Jack	Szostak	Department of Molecular Biology, Massachusetts General Hospital, USA
Frances	Arnold	Division of Chemistry and Chemical Engineering, California Institute of Technology, USA
Philipp	Holliger	Medical Research Council Laboratory of Molecular Biology, Cambridge, USA
Kazunari	Taira	Gene Discovery Research Center, National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba Science City, Japan

First Name	Surname	Institute / Firm / Project / Organization
Stanislas	Leibler	Laboratory for Living Matter, The Rockefeller University, New York, USA
Mikhail	Soloviev	School of Biological Sciences, Royal Holloway, University of London, UK
David	Liu	Department of Chemistry and Chemical Biology, Harvard University, USA
Andrew	Griffiths	MRC Laboratory of Molecular Biology, Cambridge, UK
Kristian	Müller	Department of Biology III, University of Freiburg, Germany
	Semisynthetic design (rational + irrational design)	
Alan	Fersht	MRC Centre for Protein Engineering, Cambridge, UK
Charles	Richardson	C2 Building, Room 219, BCMP, Harvard Medical School, USA
Engineering of regulatory function		
	Biochemical or genetic network design	
Chaitan	Khosla	Department of Chemical Engineering, Stanford University, California, USA
Mark	Ptashne	Department of Molecular Biology, Memorial Sloan-Kettering Cancer Center, New York, USA
Michael	Elowitz	Biology and Applied Physics Bren Scholar, Michigan, USA
Timothy	Gardner	Center for BioDynamics and Department of Biomedical Engineering, Boston University, USA
Jeff	Hasty	Department of Bioengineering, University of California San Diego, USA
Yohei	Yokobayashi	Division of Chemistry and Chemical Engineering, California Institute of Technology, USA
Yoshiharu	Doi	Polymer Chemistry Laboratory, RIKEN Institute, Saitama, Japan
Jay	Keasling	Department of Chemical Engineering, 201 Gilman Hall, University of California, USA
Tony	Pawson	Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Canada
Alexander	Ninfa	Department of Biological Chemistry, University of Michigan School of Medicine, USA
Måns	Ehrenberg	Department of Cell and Molecular Biology, Uppsala University, Sweden
Lingchong	You	Department of Biomedical Engineering, Duke University, North Carolina, USA
Martin	Fussenegger	Institut fuer Biotechnologie, Zurich, Sweden
Thomas	Schneider	Laboratory of Experimental and Computational Biology, Maryland, USA
Sven	Panke	Institute of Process Engineering, Zürich, Switzerland
James	Liao	Department of Chemical Engineering, University of California, USA
Luis	Serrano	European Molecular Biology Laboratory, Heidelberg, Germany
James	Collins	Center for BioDynamics and Department of Biomedical Engineering, Boston University, USA
Charles	Cantor	Center for Advanced Biotechnology, Boston University, USA

First Name	Surname	Institute / Firm / Project / Organization
Katia	Vancompernolle	Molecular and Metabolic Signalling, Department of Medical Protein Research, Flanders Interuniversity Institute for Biotechnology, Gent, Belgium
	Riboswitches	
Thomas	Steitz	Department of Molecular Biophysics and Biochemistry, Yale University, USA
Robert	Batey	Department of Chemistry and Biochemistry, 215 UCB, University of Colorado, USA
Laising	Yen	Department of Genetics, Harvard Institute of Human Genetics, Harvard Medical School, and Division of Molecular Medicine, Children's Hospital, Massachusetts, USA
Christina	Smolke	Division of Chemistry and Chemical Engineering, California Institute of Technology, USA
John	Mulligan	Blue Heron Biotechnology, Inc, Washington, USA
Parts fabrication, characterization, assembly		
	The BioBricks strategy	
Frank	Seela	Laboratory of Bioorganic and Biophysical Chemistry, Center for Nanotechnology (CeNTech), Münster, Germany
Drew	Endy	Biological Engineering Division, Massachusetts Institute of Technology, USA
Alejandro	Colman-Lerner	The Molecular Sciences Institute, California, USA
Gerry	Sussman	Computer Science and Artificial Intelligence Laboratory (CSAIL), The Stata Center, Massachusetts, USA
Roger	Brent	The Molecular Sciences Institute, California, USA
Pamela	Silver	Department of Systems Biology at Harvard Medical School, USA
Malcolm	Campbell	Davidson College, Biology Department, North Carolina, USA
Tom	Knight	MIT CSAIL, The Stata Center, Massachusetts, USA
Randy	Rettberg	Electrical Engineering and Computer Science Division, Massachusetts Institute of Technology, USA
Rob	Carlson	Electrical Engineeering Department, the University of Washington, USA
Joerg	Stelling	Institute of Computational Sciences, ETH Zentrum, Zurich, Switzerland
	Programmable organisms or systems	
Steven	Benner	Department of Chemistry, University of Florida, USA
Andrew	Kuznetsov	Institute of Biology III, Freiburg University, Germany
Peter	Glazer	Departments of Therapeutic Radiology and Genetics, Yale University School of Medicine, USA
Craig	Venter	9704 Medical Center Drive, Mayland, USA

First Name	Surname	Institute / Firm / Project / Organization
Eckard	Wimmer	Department of Molecular Genetics and Microbiology, School of Medicine, State University of New York at Stony Brook, USA
Peter	Quail	Department of Plant and Microbial Biology, University of California, Berkeley, USA
David	Corey	Departments of Biochemistry and Pharmacology, University of Texas Southwestern Medical Center, USA
Jay	Keasling	Berkeley Center for Synthetic Biology, University of California, USA
Frederick	Blattner	E.coli Genome Project Laboratory of Genetics University of Wisconsin, USA
Ron	Weiss	Departments of Electrical Engineering and Molecular Biology at Princeton University, USA
Thomas	Bulter	Department of Chemical Engineering, University of California,USA
5. Applications of Synthetic Biology (related and enabling technologies)		
Molecular Biology Methodology in general		
Analytics		
	Diagnostics	
Mark	Collins	Chiron Diagnostics, California, USA
Tarek	Elbeik	Department of Laboratory Medicine, University of California, USA
	Microarrays, Biochips, Microfluidic devices, Nanotechanalytic	
Stephen	Quake	Department of Bioengineering, Stanford University, California, USA
Xiaolian	Gao	Department of Chemistry, University of Houston, Texas, USA
Heinz-Bernhard	Kraatz	Department of Chemistry, University of Saskatchewan, Canada
R.	Bashir	Department of Biomedical Engineering, Purdue University, Indiana, USA
Luke	Lee	Berkeley Sensor & Actuator Center, Department of Bioengineering, University of California, USA
Robert	Austin	Departments of Physics and Molecular Biology, Princeton University, USA
Computing		
	Biocomputing, Bioinformatic, Systems Biology	
Niles	Pierce	Department of Bioengineering and Department of Applied and Computational, Mathematics, California Institute of Technology, USA
Biomaterials		

First Name	Surname	Institute / Firm / Project / Organization
	Biopolymers, colloids and nanoparticles	
Quentin	Pankhurst	Department of Physics and Astronomy, and London Centre for Nanotechnology, University College London, UK
Wolfgang	Parak	Department of Chemistry, University of California, Berkeley, USA
Oleg	Salata	Sir William Dunn School of Pathology, University of Oxford, UK
M. G.	Finn	The Scripps Research Institute, California, USA
Amy Szuchmacher	Blum	Center for Bio/Molecular Science and Engineering, Naval Research Laboratory, Washington DC, USA
Cell technology		
	Cell culture, Transfection	
Timothy	McKnight	Molecular Scale Engineering and Nanoscale Technologies Research Group, ORNL, University of Tennessee, USA
Bio-energy sources		
	Bio-fuels, biogas	
	Bioelectricity	
Shuguang	Zhang	Center for Biomedical Engineering, Room 56-341, Massachusetts Institute of Technology, USA
6. Products		
Small molecular drugs, bio-drugs, bio-agents		
Flavors, fragrances, colors, pigments, commodities		
Biopolymers, biocomposites		
Cell culture, Stem Cells		
Tissues, organs, organisms		
Bio-fuels, bio-electricity		
Biomimetic, biocomputers		
7. Others		
John	Koza	Stanford Biomedical Informatics, School of Medicine, Stanford University, California, USA
Jim	Shapiro	Department of Biochemistry and Molecular Biology, University of Chicago, USA

First Name	Surname	Institute / Firm / Project / Organization
Lila	Kari	Canada Research Chair in Biocomputing, Department of Computer Science, University of Western Ontario, Canada
David	Prescott	Department of Biology, Bryn Mawr, Philadelphia, USA
Jim	Crutchfield	Computational Science and Engineering Center, Physics Department, University of California, Davis, USA
George	Church	Harvard Medical School and Center for Computational Genetics, USA
David	Baker	Howard Hughes Medical Institute Investigator at the University of Washington, USA
Jim	Collins	Applied BioDynamics Laboratory, Center for Advanced Biotechnology, Center for BioDynamics, Boston University, USA
Michael	Elowitz	Division of Biology, California Institute of Technology, USA
Drew	Endy	Department of Biology, Massachusetts Institute of Technology, USA
Michael	Hunkapiller	Alloy Ventures, California, USA
Joseph	Jacobson	MIT Media Lab, Massachusetts, USA
Jay	Keasling	Department of Chemical Engineering, University of California, Berkeley, USA
Paul	Modrich	Howard Hughes Medical Institute Investigator at Duke University, North Carolina, USA
Christina	Smolke	Department of Chemical Engineering, California Institute of Technology, USA
Ron	Weiss	Electrical Engineering Department, Princeton University, USA

3.2. Summary

In this sub-section we provide a summary of the publications and activities identified in Section 3.1 above.

The figure shows number of publications per year – identified as either *in vivo*, *in vitro*, *in silico* or concepts/political strategy within Synthetic Biology activities. The publications are all written by the individuals identified in Table 1.

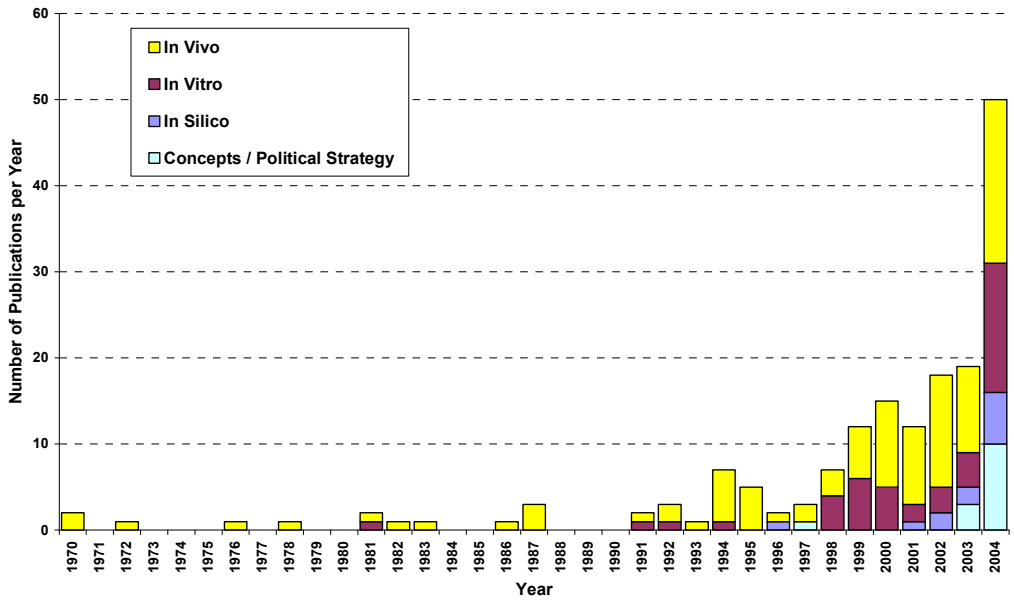

Figure 4: Synthetic Biology Publications per Year

As expected, the number of publications per year increases from 1997 onwards, with a large increase in 2004. The figure also indicates that most publications can be classified as *in vivo*, although there is also a significant number of publications on the overall concepts and political strategy of Synthetic Biology in 2003 and 2004.

These results are further highlighted in Figure 5, which shows the cumulative number of publications in the field of Synthetic Biology since 1970.

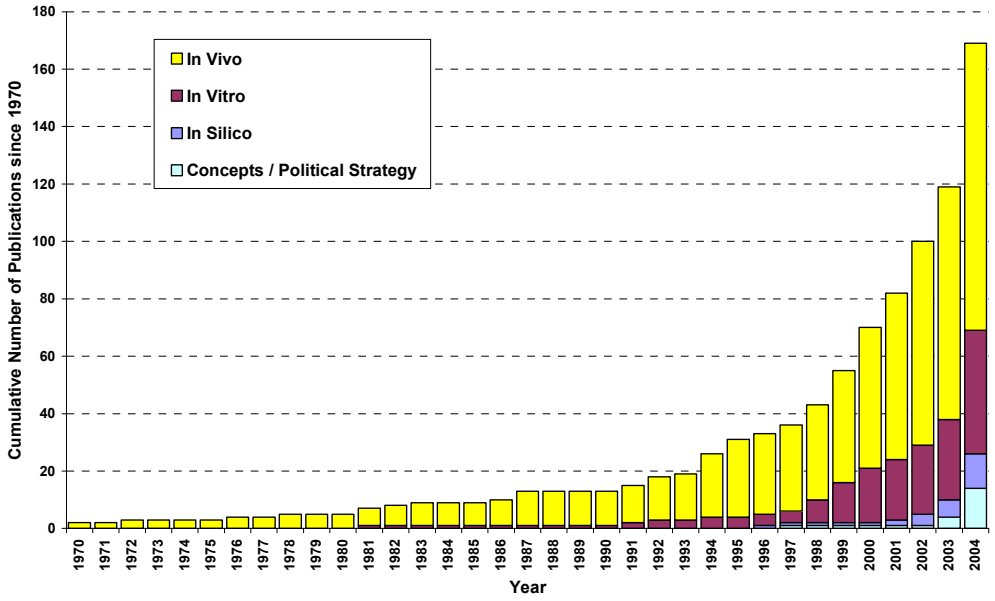

Figure 5: Synthetic Biology Cumulative Publications per Year

As discussed above, publications in the Synthetic Biology field can also be assessed by country of (first) author. Figure 6 below shows that the majority (over two-thirds) of the publications so far identified by the project are provided by US authors. About one quarter are provided by authors from the EU, with a smaller number by Japanese and Israeli authors.

It should be noted that at this stage of the project, no attempts has been made to rank the importance of individual publications. During the project, the quality of the data base will be increased by structured read outs. Use will be made by the citation frequency or type, such as review article, of certain publications to provide a measure for the importance of publications and authors classified in topics of different fields of Synthetic Biology.

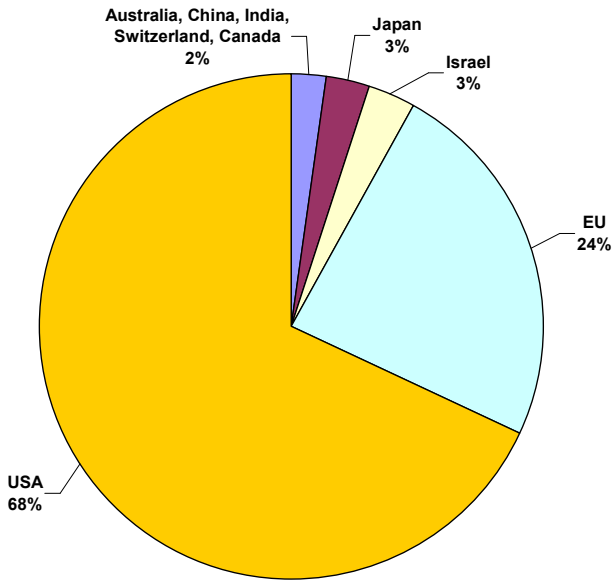

Figure 6: Synthetic Biology Publications by Country

Figure 7 illustrates that within the USA the majority of publications are provided by those based in California (Stanford, Berkley, Caltech, Scribbs, UCLA), Massachusetts (MIT; Harvard, Howard Hughes), New Jersey (Princeton), Florida (University of Florida) New York (Columbia, Rockefeller, Sloan-Kettering Institute), and Maryland (John Hopkins).

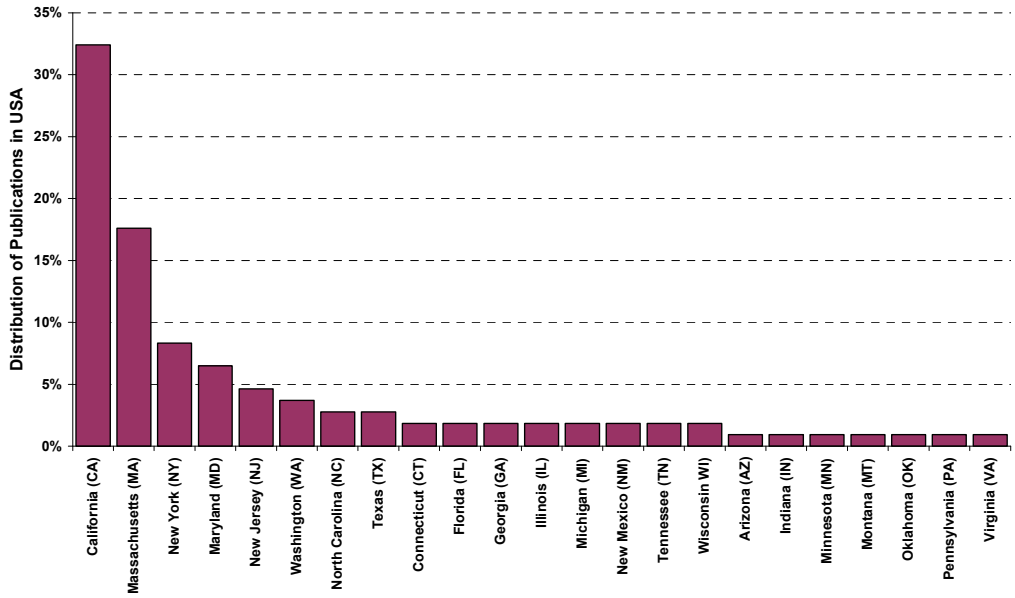

Figure 7: Publications by State - USA

Identifying and assessing the importance of funding sources for Synthetic Biology is an essential element of the project. At this stage a number of funding organizations in the USA and other countries have been identified. Figure 8 below shows the proportion of the number of projects/activities in Synthetic Biology that the identified organizations fund.

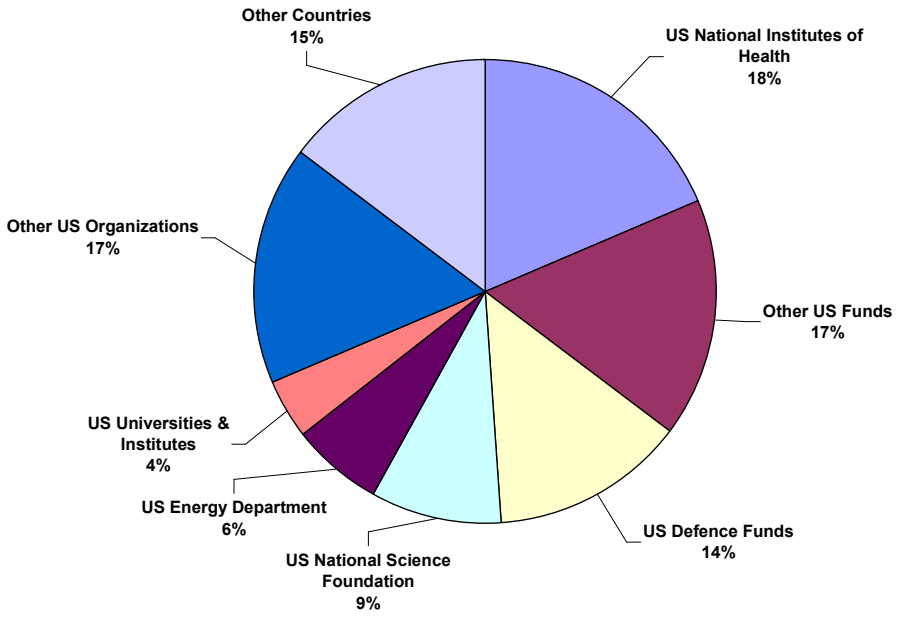

Figure 8: Sources of Funding for Synthetic Biology Research

The category "Other Countries" in the Figure includes the following organizations:

- AMGEN and L'Association Francaise contre les Myopathies (AFM) - http://www.amgen.com/ and www.afm-france.org
- Association pour la Recherche sur le Cancer - www.arc.asso
- Austrian Science Foundation (Fonds zur Förderung der wissenschaftlichen Forschung) - http://www.fwf.ac.at
- Canadian Institutes of Health Research - http://www.cihr-irsc.gc.ca
- Centre National de la Recherche Scientifique - http://www.cnrs.fr/
- Danish International Development Agency - http://www.um.dk/en
- Danish Natural Science Research Council - www.forsk.dk/eng/fnu
- Danish Technical Research Council - www.forsk.dk
- Department of Biotechnology, Government of India - http://dbtindia.nic.in/
- Deutsche Forschungsgemeinschaft - http://www.dfg.de/
- European Molecular Biology Laboratory - http://www.embl-heidelberg.de/
- Engineering and Physical Sciences Research Council - http://www.epsrc.org/

- European Commission - http://europa.eu.int/
- European Molecular Biology Network - http://www.embnet.org
- Fonds der Chemischen Industrie - http://fonds.vci.de/default.asp
- Fund for Scientific Research (Flanders) - http://www.fwo.be/
- German Academic Exchange Service (DAAD) - http://www.daad.org/
- German-Israeli Project Cooperation (DIP) - http://www.internationales-buero.de/de/787.php
- Humboldt Foundation - http://www.humboldt-foundation.de/en/
- Institut National de la Santé et de la Recherche Médicale - http://www.inserm.fr/fr/home.html
- Institute of Biomedical and Biomolecular Sciences - http://www.port.ac.uk/research/ibbs/
- Israel Academy of Sciences - http://www.academy.ac.il/
- Israel Ministry of Health - http://www.health.gov.il/
- Israel Science Foundation - http://www.isf.org.il/
- Japan Society for the Promotion of Science Postdoctoral Fellowship - http://www.jsps.go.jp/english/
- Justus-Liebig Universität - http://www.uni-giessen.de/uni/
- National Science and Engineering Research Council of Canada (NSERC) - http://www.nserc-crsng.gc.ca/
- Raymond and Beverly Sackler Chair for Bioinformatics at Tel Aviv University - http://www.tau.ac.il/exact_sciences/site/
- Swiss National Science Foundation (Schweizerischer Nationalfonds) - http://www.snf.ch/default_en.asp

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