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Review

Another side of genomics: Synthetic biology as a means for the exploitation of whole-genome sequence information

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Abstract

The successful completion of the Human Genome Project and other sequencing projects opened the door for another quantum jump in science advancement. The most important public sequence databases are doubling in size every 18 months. By revealing the genetic program of many organisms, these efforts endow biologists with the ability to study the basic information of life in toto as an initial step toward a comprehensive understanding of the complexity of entire organisms. We review the area of synthetic biology, defined as the making and use of biosystems founded on the chemical synthesis of the coding DNA (and potentially RNA). The recent developments discussed here introduce a rich source of oligonucleotides to the field: in situ synthesised microarrays, which in fact represent nothing else but matrix nucleic acid synthesisers. With this new way of producing the oligonucleotides used in the making of synthetic genes in a very cost-effective manner, the field of synthetic biology can be expected to change dramatically in the next decade. Synthetic genes will then be the tools of choice to obtain any sequence at any time in any laboratory.

Keywords: Synthetic biology; Synthetic gene; In situ synthesised microarrays; Matrix nucleic acid synthesiser; Array-derived oligonucleotide

Contents

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1. Introduction

The successful completion of the Human Genome Project and many other sequencing projects opened the door for another quantum jump in science advancement. New genome sequences are being finished almost daily, and many more will be forthcoming as we continue to add species from the evolutionary tree. This dynamic development already reminds some (Myhrvold, 2005) of Moore's law governing information technology. Moore's law is the empirical observation that at our rate of technological development, the complexity of an integrated circuit with respect to minimum component cost will double in about 24 months.

The most important public sequence databases are doubling in size every 18 months.

With all this information in hand, researchers have only just begun to think about new biological questions they can ask. By revealing the genetic program of many organisms, biomedical science has been transformed, endowing biologists with the ability to study the basic information of life in toto as an initial step toward a comprehensive understanding of the complexity of entire organisms. To work on the systems biology level will lead to a deeper understanding of life and have many important implications for the health care sector, the biotechnology industry and our environment.

2. A definition of synthetic biology

The purpose of this review is a discussion of another side of genomics: synthetic biology or "Synbio", with special emphasis on recent developments that promise a major breakthrough. We define synthetic biology as the making and use of biosystems founded on the synthesis of the coding DNA (and potentially RNA) based upon chemically synthesised nucleic acids oligonucleotides of programmable sequences. The recent developments discussed here make use of a rich source of oligonucleotides: in situ synthesised microarrays, which in fact represent nothing else but matrix nucleic acid synthesisers.

Synthetic biology is older than recombination technology. While the latter has been developed in the early 1970s (Smith and Wilcox, 1970; Jackson et al., 1972) after the successful discovery and use of sequence specific restriction enzymes and ligases, the making of synthetic genes goes back another decade. The first functional synthetic gene was made and published in 1964 by a research team led by H.G. Khorana, as part of their work on the elucidation of the genetic code (Khorana, 1968; Agarwal et al., 1974; Khorana, 1965). The gene carried the code for the tyrosine transfer RNA and was successfully tested in bacteria after being built from basic chemicals.

Others have later optimised and perfected the chemical synthesis of nucleic acids (Beaucage, 1993) and automated the complete process (Lashkari et al., 1995). For the two decades from 1980 to 2000 the predominant applications of the vast majority of the synthesised oligonucleotides were use as primers for PCR (Mullis et al., 1986) and sequencing (Sanger et al., 1977) as well as site-directed mutagenesis (Flavell et al., 1975; Gillam and Smith, 1979). During the 1990s, a growing number of biochip applications was added, (Schena et al., 1995; Fodor et al., 1991).

DNA recombination technology, at some point increasingly supported by PCR, mutagenesis and related methods, was faster and more cost effective then the creation of synthetic genes, and shaped the field of molecular biology. Synthetic genes played a minor role in the molecular biology laboratories, though they were always recognised as valuable tools. They sometimes might be the only accessible source for the desired DNA, as in cases where the natural DNA may be unavailable to the experimenter or the desirable DNA has never existed. Also, sequences that are deduced rather than experimental (e.g. resulting from protein sequencing or representing a new fusion of gene domains) can be made that way. Generally, synthetic genes are especially useful, if it is desired to re-engineer the target sequence, either the coding region or regulatory signals of importance (protein initiation, ribosome binding sites, promoters, and the like), and to alter the codon usage for a particular host or model organisms. Last but not least, synthetic genes allow the efficient construction of a family of related, but different constructs, with permutations at special regions of interest. Ultimately, synthetic genes allow complete flexibility of target sequence design and obviate intermediate steps often needed to get to a desired sequence by cloning and recombination technology.

The creation of synthetic genes is based on a simple concept: the target DNA is produced by programmed chemical synthesis of short oligonucleotides (typically