Biomolecular Computing Devices in Synthetic Biology

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ABSTRACT

Synthetic biology and biomolecular computation are disciplines that fuse when it comes to designing and building information processing devices. In this chapter, we study several devices that are representative of this fusion. These are three gene circuits implementing logic gates, a DNA nanodevice and a biomolecular automaton. The operation of these devices is based on gene expression regulation, the so-called competitive hybridization and the workings of certain biomolecules like restriction enzymes or regulatory proteins. Synthetic biology, biomolecular computation, systems biology and standard molecular biology concepts are also defined to give a better understanding of the chapter. The aim is to acquaint readers with these biomolecular devices born of the marriage between synthetic biology and biomolecular computation.

INTRODUCTION

Molecular biology, biochemistry and genetics have been and are the most important drivers of cellular biology. However, new disciplines examining biological processes have emerged. They have ventured new viewpoints and offered a wide range of possibilities for both generating and applying knowledge in other areas. Most of these new fields are multidisciplinary. They feed off different areas like physics, chemistry, mathematics or computing. Of these new disciplines, this chapter will examine synthetic biology and biomolecular computation, but not separately, together, linking the two fields. The goal of this union is to study, design, simulate and implement new biomolecular systems capable of making computations *in vivo*, that is, able to process information inside living systems.

In this chapter, we will look at several simple examples that will give readers an overview of this marriage. These examples will be biomolecular devices based on biological principles that process information. In fact, we will look at NOT and AND logic gates built using genetic circuits (Weiss, 2003); the logic AND built using just nucleic acids that works thanks to competitive hybridization and toeholds (Fontana, 2006; Seelig, 2006), and a nanodevice composed of a DNA hairpin that opens and closes through genetic regulation. Finally, we will consider an automaton that

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diagnoses disease by checking for the presence of different RNA molecules associated with the disease in question and releases the drug if the diagnosis is positive (Benenson, 2004). This is a beautiful example of the marriage of biomolecular computation and synthetic biology with a promising application in biomedicine.

Other devices, noteworthy because they were the first to merge biomolecular computing and synthetic biology, are a genetic toggle switch with two stable states (Gardner, 2000), and the repressilator, which is an oscillatory gene network composed of three repressors (Elowitz, 2000). Both of these devices were designed *in vivo*. Another circuit with two stable states was designed *in vitro* (Kim, 2006). Being extracellular, this circuit achieves better control of the circuit parameters.

SYNTHETIC BIOLOGY, BIOMOLECULAR COMPUTATION AND SYSTEMS BIOLOGY

The definition of synthetic biology is changing and the borders of this discipline are fuzzy. In the following, we will try to give a comprehensive definition that includes the most relevant research that is being developed and could be considered to be part of this field. We will also describe biomolecular computation and systems biology. Systems biology is also a relative new and emerging field that can help to move synthetic biology and biomolecular computation forward.

Synthetic biology: is a discipline halfway between science and engineering (Benner, 2005; De Lorenzo, 2006; ETC group, 2007). It is concerned with:

- The design, construction and modification of biomolecular systems and organisms to perform specific functions.
- To get a better understanding of biological mechanisms.

The operation of these synthetic biomolecular systems is based on the processes of the central dogma of molecular biology, that is, DNA replication, and especially DNA transcription and translation. But there are also designs that are based on more specific biological processes like the competitive hybridization of nucleic acids, the operation of certain enzymes, etc.

There are at present two trends, bottom-up and top-down, in synthetic biology projects (Benner, 2005):

- The bottom-up trend takes the form of a hierarchy inspired by computer engineering (Andrianantoandro, 2006). The building blocks are DNA, RNA, proteins, lipids, amino acids and the other metabolites. These building blocks interact with each other through biochemical reactions to form simple devices. The devices are linked to form modules that can do more complex tasks. These modules are connected to set up biomolecular networks. These networks can be integrated into a cell and change the cell's behaviour. The DNA sequences with special functions, like the operator, the promoter, etc., are called BioBricks in synthetic biology. And there are proposals for recording standard biological parts (http://parts.mit.edu). The bottom-up trend emerged because synthetic biology focuses on creating genetic circuits. The operation of these circuits is based on gene expression regulation through transcription control that primarily involving genes and proteins (Benner, 2005; Hasty, 2002). Therefore, these biomolecules play the key role in device design and construction. However, recent studies on RNA's important cell regulating functions are encouraging its use in the design and construction of synthetic biology devices (Isaacs, 2006; Rinaudo, 2007).
- The top-down trend isolates or reduces parts of the biological systems to a minimum. Its objective is to be able to understand these parts and use them to build more complex