Chapter XX
Systems Biology Applied to Cancer Research

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ABSTRACT

Complex diseases such as cancer have multiple origins and are therefore difficult to understand and cure. Highly parallel technologies such as DNA microarrays are now available. These provide a data deluge which needs to be mined for relevant information and integrated to existing knowledge at different scales. Systems Biology is a recent field which intends to overcome these challenges by combining different disciplines and provide an analytical framework. Some of these challenges are discussed in this chapter.

INTRODUCTION

Systems Biology is emerging as a promising answer to the increasing need for analytical approaches in molecular medicine. Its goal includes modeling interactions, understanding the behavior of a system from interplay of its components, inferring models from data, data integration, confronting the prediction of the model to data, proposing most promising experiments. Solutions to these challenges are often interdisciplinary, and Systems Biology intends to provide such a framework beyond scientific communities 'dialects' or differences in approaches (Lazebnik, 2004). Cancer is too complex a disease to be solely and completely described by the existing clinical variables (e.g.: age of the patient, size of the tumor, histological grade, etc.) which are currently used in practice. It is therefore necessary to identify new biomarkers which will provide additional information about the cancer type, origin, or aggressiveness for instance. Within a decade, high-throughput assays have revolutionized biology and are now being introduced in the clinic. Among these techniques, we focus on DNA microarrays which can monitor the expression of tens of thousands of genes in parallel and offer a means to individualize treatment. This should contribute to guide clinicians toward tailored therapies which will lead to reduced over treatments and costs by an improved prognosis, the design of targeted drugs, as well as more accurate application of drugs. Since this is quite a recent field where each analysis requires a large number of steps, consensus has not yet been reached. Furthermore, researchers involved come from various backgrounds (e.g.: Statistics, Engineering, Biology …). Applying tools from all these fields result in a wide spectrum of approaches that may be confusing at first. Nevertheless there are some trends in the biomedical research community that we review in this chapter in the context of cancer. The outline of the chapter is meant to follow a practical analysis pipeline and URLs for accessing resources (i.e.: softwares and data) are provided in Table 1.

WHAT IS A MICROARRAY?

Quite suited to monitor many genes at once, a DNA microrarray is an inert, solid, flat and transparent surface (e.g.: a microscopic slide) onto which 20,000 to 60,000 short DNA reporters (often called probes) of specified sequences are orderly tethered. Each reporter on the microrarray corresponds to a particular short section of a gene. More and more, a single gene (e.g.: VEGF) is covered by several reporters which span different parts of the gene sequence. Firstly available in the mid 1990's, companies are nowadays developing micorarrays with increased feature density (i.e.: the number of molecular detectors per array) to scan the genome at regular intervals ('tiling' arrays) that are re-usable for instance.

A MICROARRAY EXPERIMENT

After a careful experiment design (Kerr & Churchill, 2001; Y. H. Yang & Speed, 2002) to start with, biological samples are collected either from an *in vitro* or an *in vivo* experiment. Then, the RNA is extracted and labelled (e.g.: with a fluorescent dye). The central reaction is when the labelled RNA is hybridized (bound) to the microarray reporters. Unbound RNA is subsequently washed out so that the amount of bound and labelled RNA can be measured. The intensity of the signal of the reporter is indicative for the relative expression of the corresponding gene. DNA microarrays measure a surrogate