

## Computational Methods in Drug Development: From Discovery to Functional Genomics

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Genomics technology promises to enhance the development of new drugs through rapid identification of new small molecule and antibody targets, the direct use of gene products (and their derivatives) as pharmaceuticals, and through gene therapy, in which nucleic acid itself becomes the therapeutic agent. Until recently, the majority of work being performed at both academic centers and private corporations fell into the category of gene discovery, that is, identifying and sequencing novel genes. With the assembly of large cDNA/EST databases (at Human Genome Sciences, Incyte, NCBI, and others) and the completion of an initial human genome sequence, the work of finding new genes is nearing completion. However, merely having a genome (or its associated proteome) is not sufficient to develop new therapeutic agents; for this, the function of each gene/gene product must be determined. Furthermore, therapeutic agents must also be specific; thus its cellular action(s) must be determined to a high degree of resolution both spatially and temporally. This information cannot be completely derived *ab initio* from sequence information; a new field, functional genomics, is being developed to solve this problem.

The type of information required for effective functional genomics is not new to biology; it is just needed on a larger scale than conventional biological analysis. Thus, gene expression arrays such as those manufactured by Affymetrix and others can be thought of as being analogous to the Northern blot technique that has been in use for decades, just on a vastly larger scale. Similarly High-Throughput Screening merely seeks to automate and scale assays that had previously been done in smaller scale. In addition new technologies (real-time PCR, differential display, *in silico* expression profiling, etc.) that are derived from the genomics revolution are adding new types of data that can be used to study cellular function.

The challenge facing scientists in both academia and industry is thus twofold. First, the biological techniques must be made fast, reliable and inexpensive. Second, computational techniques must be devised to store, correlate, and mine this data. In particular it is necessary to determine the system-wide effects of effector molecules. Examples of current functional genomics technology (as practiced at Human Genome Sciences) as well as open problems in the functional genomics field will be discussed.