The new ‘omics era
Editorial overview
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Currently, David Ward’s research focuses on the identification of genes implicated in the pathophysiology of neuropsychiatric diseases and the development of techniques for the quantification of gene expression in living cells and whole organisms. Dr Ward is a member of the US National Academy of Sciences.

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DC White took his research direction from O Warburg who counselled from the back of his white horse “making unique measurements secures resources” and has utilized analytical chemistry and an early involvement with wonderful extractable lipids to monitor interactions in the microbial world. Unfortunately, tandem mass spectroscopy for amateurs is a most expensive but rewarding hobby.

It has been 18 months since the widely acclaimed announcement that a draft sequence of the human genome had been completed. The development and implementation of new techniques to exploit this sequence information has spawned a new generation of ‘omics enterprises with an increasing emphasis on comparative and functional versions of genomics, proteomics, metabolomics, cellomics, and organomics coupled with a non-‘omics glue, bioinformatics. Regardless of how much the reader is irked by the ‘omics suffix, novel technologies are rapidly emerging to enhance the acquisition of data in these fields in a multiplex and highly parallel fashion and to mine such datasets for diagnostic or therapeutic leads. In this issue dedicated to analytical biotechnology, several review articles are presented that highlight some of the technical advances that will drive ‘omics activities forward.

Array technology is still booming. Although the status of gene expression profiling chips with oligonucleotide or cDNA arrays from medium- to high-density is now relatively mature, the production of high-density chips for quantitative protein analysis is less advanced. The review by Schweitzer and Kingsmore (pp 14–19) describes some of the recent advances in protein array technology and highlights technical challenges that still need to be resolved. A second review by Phelps, Palumbo and Beliaev (pp 20–24) focuses on the use of microarrays to analyse metabolic alterations and phenotypic changes induced by both genetic and environmental factors. Array analysis of shifts in DNA and mRNA sequences that define genetic changes are correlated with potential metabolic consequences. The analyses focus on those mutations that effect specific pathways in complex metabolic networks. The combination of rapid methodology with time-of-flight mass spectrometry to detect ^{13}C-labeled metabolites and NMR to define their positions during flux measurements, can yield flux maps and metabolic control points. Such information represents the phenotypic equivalent of microarrays, reflecting changes in gene expression in response to environmental parameters, electron donors, stressors and temperature changes.

The analysis of ^{13}C in microbial lipids as a geochemical metabolic tracer is reviewed by Zhang (pp 25–30). A whole new anaerobic methane-oxidizing system, long known by geologists, has now been defined as a consortium of tightly linked archaea and sulfate-reducing bacteria that even the most conservative microbiologist can appreciate. Interactions between these methane oxidation processes and the methane hydrate reservoirs might have had great consequences on global temperatures in the past and could possibly induce runaway warming in the future.

The diversity of the biological universe is increasingly demanding the development of biosensors with high specificity yet great versatility in analyte detection. In addition to the challenge of characterizing unique bioorganisms or their cognate nucleic acids and proteins, societal and environmental issues raise the need to detect a plethora of small chemical compounds with cost-effectiveness and sensitivity. The directed engineering and selected evolution of DNA

and RNA molecules that can perform a diverse range of molecular recognition and catalytic functions is one approach to the creation of new types of biosensor. In his review on allosteric ribozymes (pp 31–39), Breaker describes the latest advances in the engineering of nucleic acids that function as true molecular switches which trigger catalytic (or signal-generating) events only when bound to a specific target molecule. Targets detected to date, range from proteins to oligonucleotides, cyclic AMP and metal ions; additional target-type diversification surely lies in the near future.

Chan and colleagues (pp 40–46) describe recent developments with highly fluorescent, nanometer-sized particles, termed quantum dots, which can be readily coupled to various biorecognition molecules and used as reagents for the ultrasensitive detection and imaging of a broad spectrum of biological analytes. One of the interesting features of quantum dot nanocrystals is that their emission wavelength is dependent on particle size; thus, by judicious selection of different nanocrystal sizes it is possible to analyse multiple target molecules simultaneously using a single excitation light source. Combining quantum dot technology with other advances, such as microfluidics, microarrays or flow cytometry, should further enhance the rapid and sensitive visualization of proteins, genes and cells in various analytical formats.

Get familiar with the pico-Newton (pN). It represents the magnitude of the breakaway forces between biomolecules and folding–unfolding forces within single protein molecules. Allison, Hinterdorfer and Han (pp 47–51) explore the burgeoning use of the atomic force microscope in measuring forces between molecules. One-half of a test pair can be attached to the silicon nitride microcantilever and used to probe specific bonds in the other component on the surface. Use of antibodies on the tip results in molecular recognition force microscopy, which adds a further dimension to quantum dot technology.

One of the important end products of functional proteomic endeavours will be the identification and validation of proteins of therapeutic utility. Although many such proteins may be expected to elicit effective biological responses upon intravenous injection, the majority will need to access intracellular compartments to have their pharmacological potential fully realized. The delivery of biomodulating proteins or peptides across the plasma membrane of cells in tissues or through the dermal layers of living organisms has been a perennial problem for the pharmaceutical industry. Recently, however, several small peptides, variously termed protein transduction domains (PTDs), Trojan peptides (TPs) or penetratins, have been shown to efficiently transduce cargo (peptides, proteins, nanoparticles or certain drugs) through cellular plasma membranes via a mechanism(s) independent of endocytosis, surface receptors or transporters. The review by Wadia and Dowdy (pp 52–56) summarizes some of the exciting observations on the intracellular uptake of PTDs fused or cross-linked to proteins or other cargo. The authors highlight the significant promise for this cellular delivery system both *in vitro* and *in vivo*.

Proteomics is a daunting prospect even in a single cell. Each cell contains a lot of proteins potentially able to do a lot of things; there are two ways to find a protein in this mess. The classical way is to use 'hand-grenade' biochemistry. Smash the cells, digest the proteins, separate them as best you can, apply matrix-assisted laser desorption/ionization, quadrupole time-of-flight or your very own Fourier-transform mass spectrometry, and with a huge computer hopefully fish out the unique sequence you are after. This is the 'bottom-up' procedure and it can take an interdisciplinary army with pharmaceutical house budget. Stephenson and colleagues (pp 57–64) propose an elegant new way to find which mosquito contains the West Nile virus with an analytical system we could all possibly afford. This is the 'top-down' approach and is the best way to quickly find a protein of known sequence. Starting with intact proteins from the cell, multicharged ions are generated that are successively neutralized to the +1 charge state and the specific protein (and all its isomers) selected. The rest are discharged. The specific protein amongst the isomers is identified from a short portion of its sequence after fragmentation by tandem mass spectrometry. The identifying sequence is readily determined from major dissociation channels corresponding to the few preferential cleavage sites found under these conditions. This can happen in milliseconds, which is a little better than your average two-dimensional gel.

A common lament often expressed by molecular biologists in both academia and commercial biotechnology firms is 'I wish I had a larger sample of DNA so I could do all the genetic studies required to make an unambiguous conclusion'. Over the past few years, several groups have attempted to address this issue. The short review of Hawkins, Detter and Richardson (pp 65–67) summarizes the various strategies used to date and hints that a new technique, called multiple displacement amplification, may be capable of extensively amplifying genomic DNA from both prokaryotic and eukaryotic organisms without genetic bias. Validation of such a method would have tremendous utility in fields such as forensic medicine, genetic and infectious disease diagnostics, pathology and microbial biology.

Bioinformatics, an essential component of the 'omics era, encompasses the development of new computational methods and their application to the solution of biological problems, often via the mining of information databases. As bioinformatics occupies a central role in a broad spectrum of biological research, its analytical toolkits are equally diverse. The review by Goodman (pp 68–71) focuses on bioinformatic applications in two major areas of research: genome sequencing of higher organisms and gene expression profiling using DNA microarrays. A second review by Almeida (pp 72–76) follows a different track and explores the application of artificial neural networks (ANN) to the analysis of complex datasets. Biology, sad to say, is essentially nonlinear and the distribution of results does not often follow the

bell-shaped curve. ANN, if properly applied, provides insights independent of these constraints in classical multivariate analyses. The uneven quality of ANN software, some of which is faulty, and a lack of well-accepted exploratory techniques for nonlinear dependencies when no mechanistic model is at hand, has led to uneven application in peer-reviewed literature. Knowing when to stop the regression is the key to prevent loss of flexibility or overfitting with a higher validated error.

Analytical chemistry is now inexorably committed to biotechnology for its resources. This commitment will continue to provide excitement as 'we go where no one has gone before' with ever smaller, ever faster, ever more automated, ever more comprehensive, and, sometime in the future, more affordable analyses of the most critical cellular processes. These insights and their therapeutic benefits should grow ever-faster with new technology from the revolution that the genome has just begun.